Western-style diet and its impacts on hippocampal-dependent processes

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Statement of Originality and Ethical Accordance

The work presented in this thesis is, to the best of my knowledge and belief, original. I hereby declare that I have not submitted this material, in full or in part, for a degree at this or any other institution.

All human research carried out in this thesis was approved by the Macquarie University Human Research Ethics Committee and in accordance with the American Psychological Association guidelines for research with human subjects.

Tuki Nii Attuquayefio

Signature: …… Date: ...../...../.....

Thesis by Publication Statement

This thesis has been prepared following the 'thesis by publication' guidelines format outlined by Macquarie University. The contributions by myself and co-authors are outlined in the chapters that have been published. Chapters three, four and six have been written and prepared as independent publications. As such, there is some overlap in the arguments and literature cited leading to some repetition across chapters, although I have attempted to minimise this as much as possible. The formatting in this thesis conforms to the American Psychological Association's Publication Manual 6th edition, and published chapters have been formatted accordingly, while the content remains unchanged.

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List of Original Publications

Chapter 3: **Attuquayefio, T. N.,** Stevenson, R. J., Boakes, R. B., Yeomans, M. E., Mahmut, M., Francis, H. M., & Oaten, M. (2016). A high-fat high-sugar diet predicts poorer hippocampal-related memory and a reduced ability to suppress wanting under satiety. *Journal of Experimental Psychology: Animal Learning and Cognition, 42*, 415-428. doi:10.1037/xan0000118

Chapter 4: **Attuquayefio, T. N.,** & Stevenson, R. J. (2015). A systematic review of longer-term dietary interventions on human cognitive function: Emerging patterns and future directions. *Appetite*, *95*, 554-570. doi:10.1016/j.appet.2015.08.023

Chapter 6: **Attuquayefio, T. N.,** Stevenson, R. J., Francis, H. M., & Oaten, M. (2017). A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE* (Accepted for publication).

General Abstract

Based mainly on animal data it has been argued that a Western-style diet impairs hippocampal functions involved in regulating ingestive behaviour – including hippocampal-dependent learning and memory (HDLM), sensitivity to interoceptive signals of hunger and satiety, and the use of such signals to inhibit eating. This thesis has three specific aims, all of which examine whether dietary-induced impairments in animals are evident in humans: (1) To determine if greater consumption of saturated fats and refined sugars (HFS) prevalent in a Western-style diet is associated with impaired hippocampal inhibitory processes for ingestive behaviour; (2) To review any published causal evidence that manipulating energy intake and macronutrient content impacts cognitive function; and (3) To empirically test if an HFS diet causes impairments in hippocampal functions related to ingestive behaviour. Study 1 used a correlational design revealing that greater intake of an HFS diet was associated with poorer HDLM, poorer ability to inhibit wanting (relative to liking) of palatable foods based on physiological state, with the latter being hippocampally-mediated. Study 2 was a systematic review of human experimental studies, revealing that long-term verbal memory tasks were most impacted by changes in energy and fats. Study 3 used an experimental design to show that lean individuals given an HFS diet-intervention for 4 days revealed poorer HDLM and ingestive interoception, relative to a control group. Additionally, greater HDLM impairment was related to larger changes in blood glucose, suggesting one potential pathway by which diet affects the brain. Overall, these findings are consistent with those from animals, providing novel translational findings and the first causal evidence that an HFS diet impairs HDLM.

Chapter 1: Introduction

Recent evidence suggests that consumption of a Western-style diet may have adverse consequences for weight gain and cognitive function (Francis & Stevenson, 2013; Hargrave, Jones & Davidson, 2016). This introductory chapter briefly outlines the effects of a Western-style diet on bodily and brain functioning, and especially the hippocampus, in animals and humans. This introductory chapter also serves as a brief outline of the overall aims of the thesis, with further exploration of particular aims in each subsequent chapter.

1.1 Nutrition Transition

Humans generally consume a varied diet (Drewnowski & Popkin, 1997), with a preference for energy dense foods containing sugars (Scott, 1992) and fats (Dransfield, 2008). For instance, fat content in meats is considered a strong predictor of appearance, texture and flavour and affects consumer choice (Dransfield, 2008). From an evolutionary standpoint, the detection and consumption of fats and sugars in foods is beneficial when such resources are scarce, but is less desirable when these resources are freely available (Drewnowski & Popkin, 1997). Recent technological advances have made fats and sugars easier to produce and process and they are therefore more readily available for consumption (Drewnowski, 2007). For instance, the introduction of animal husbandry and large-scale dairy farming has dramatically augmented total dietary saturated fat intake (Cordain et al., 2005). Many developed countries appear to be shifting away from diets high in complex carbohydrates, fruits, vegetables and fibre to diets rich in saturated fat and refined sugars – a so-called ‘Western-style diet’ (Cordain et al., 2005). This rapid shift in dietary composition has been termed ‘The Nutrition Transition’ (Popkin & Gordon-Larsen, 2004). Specifically, there have been increases in the consumption of saturated fats sourced mainly from animal fats, edible oils such as sunflower, soybean and rapeseed oils, as well as caloric sweeteners such as sucrose and high-fructose corn syrup. At the same time, there has been a decrease in

fruit and vegetable intake, with fibre intake (15.1g/day) up to 50% lower than the recommended values (25-30g/day).

Global energy intake has changed from an average of 2411kcal per person per day in 1969 to 2789kcal in 2001 (a 15.7% increase). Additionally, developing countries show a much sharper increase in daily energy intake from 2111kcal to 2654kcal (a 25.7% increase) compared to developed countries, which have a 13.1% increase from 3046kcal to 3446kcal per person per day during the same time period (Alexandratos et al., 2006). Likewise, between 1961 and 2009, the world total food energy supply has steadily increased by approximately 600kcal/capita per day, with the supply of sugars and sweeteners accounting for 5% of this increase (~30kcal/capita per day) (Wittekind & Walton, 2014). Similarly, global sugar consumption has tripled over the past 50 years, and the intake of sugar-sweetened beverages has increased from 235kcal/day in the 1970s to 318kcal/day in 1990s (Espinel & Innes-Hughes, 2010). For instance, in the United States, per capita intake of all refined sugars was 55.5 kg in 1970, but had increased 69.1 kg by 2000 (USDA, 2002). Similar trends in sugar intake are observed in other developed nations including the United Kingdom (Gibson, 2010) and Australia (Rikkers, Lawrence, Hafekost, Mitrou, & Zubrick, 2013), and in developing countries such as China, India, Southeast Asia, South America and Central America and various regions in Europe (Ismail, Tanzer, & Dingle, 1997; Kearney, 2010; Rugg-Gunn et al., 2007).

Many processed foods, especially fast foods (e.g. pizza) have refined sugars and saturated and trans-fatty acids added to improve palatability. Likewise, the portion size of fast foods such as burgers, fries, pizza, fried chicken and soft drinks has increased 2-5 fold over a 50 year period (Young & Nestle, 2003), and currently the energy density of the typical fast food meal (~1100kJ/100g) is approximately twice the energy density of recommended healthy diets (~525kJ/100g) (Stender, Dyerberg & Astrup, 2007). The increased affordability of sugar-sweetened beverages, carbonated drinks, sugars, refined sugars, and vegetable oils,

along with the generally higher cost of fresh fruits and vegetables has shifted global food consumption towards a Western-style diet (Drewnowski, Darmon & Briend, 2004), which appears to have negative impacts on health outcomes and cognitive function. The persistent and prolonged exposure to excessive amounts of calorie-rich foods, often presented in the form of saturated and trans-fats and simple carbohydrates may be a contributing factor to recent trends in obesity (e.g., Hu, van Dam & Liu, 2001) and neurodegenerative diseases (e.g., Berrino, 2002).

1.2 Impact of a Western-style diet on excess weight gain

Animals show rapid changes in body weight and white adipose tissue following shifts in diet from a standard lab chow to a diet rich in sucrose (e.g., Jurdak & Kanarek, 2009), fats (e.g., Morrison et al., 2010), saturated fat (e.g., Greenwood & Winocur, 1996) and both sucrose and fat (e.g., Beilharz, Maniam & Morris, 2016). The shift from low-fat high-fibre lab chow to a high-fat high-sugar diet draws many parallels with recent shifts in humans from a traditional diet to a Western-style diet (i.e., the Nutrition Transition). Recent trends in obesity prevalence in humans are linked with greater intake of dietary fats (Bray & Popkin, 1999), sugars (Popkin & Nielsen, 2003) and fast foods (Duffey, Gordon-Larsen, Jacobs, Williams, & Popkin, 2007). Epidemiological analysis of dietary patterns in Brazil showed that Western diet consumption was significantly associated with body mass index (Sichieri, 2002) and was a significant predictor of central adiposity in Japanese immigrants in Brazil (Ferreria, Lerario, Gimeno & Sanudo, 2002). Furthermore, data from the United Nations and Food and Agriculture Organization reveal a significant association between the increase in the proportion of energy from fat and the global prevalence of overweight and obesity (Bray & Popkin, 1998). Meanwhile, a meta-analysis of randomised controlled trials and cohort studies reveals that intake of refined sugars or sugar-sweetened beverages are associated with increases in body weight, and the consumption of sugar-sweetened beverages put children at a higher risk of being overweight when tested one year later (Te Morenga, Mallard & Mann,

2013). Thus, it appears that consumption of energy from fats, in particular saturated fats, and refined sugars may be a significant factor in recent obesity trends.

1.3 Impact of a Western-style diet on neurodegenerative diseases

Neurodegenerative disease is an umbrella term describing conditions characterised by the progressive onset in old age of central nervous system dysfunction (e.g., Alzheimer's disease (AD), Parkinson's disease, Mild cognitive impairment). This results in loss of cognitive ability and capacity for self-care and independent living. Evidence for a link between diet and neurodegenerative disease comes from many studies that have been pooled using a meta-analysis, showing a strong positive relationship between the prevalence of AD and caloric intake and fat intake (Grant, 1997).

A Western-style diet may be a risk factor for cognitive impairment and neurodegenerative disease (Francis & Stevenson, 2013). For example, a systematic review of prospective longitudinal studies revealed that (although findings were mixed) saturated fat intake increases risk of AD, mild cognitive impairment and cognitive decline (Barnard, Bunner & Agarwal, 2014). That is, saturated fat intake is associated with greater cognitive decline over 6 years in a population of adults 65 years and older (Morris, Evans, Bienias, Tangney & Wilson, 2004). Saturated fat intake is also associated with poorer global cognitive function and prospective memory in individuals aged 65-79 years, with an increased risk of mild cognitive impairment over a 21 year follow-up period (Eskelinen et al., 2008). The risk of developing AD increases with increasing dietary intake of saturated fats (Kalmjin et al., 1997), saturated fats, and refined sugars (Berrino, 2002). Similarly, the rising prevalence of AD in Japan is linked to the transition from a traditional diet rich in complex carbohydrates and fish to a Western-style diet. It has been observed that rates of AD in Japan are directly related to meat supply and inversely related to rice supply (Grant, 2014). On the other hand, dietary patterns with lowest risk of AD were characterised by low intake of foods high in saturated fats, high-fat dairy products, red meat, organ meat and butter (Gu, Nieves,

Stern, Luchsinger & Scarmeas, 2010) and high in fish consumption (Grant, 1997; Morris et al., 2003). Based on such evidence, greater consumption of a Western-style diet high in saturated fats and refined sugars appears to have adverse longer-term consequences for cognitive function. The relationship between Western-style diet and cognitive function will be explored in greater details later in Chapter of this thesis.

1.4 Impact of a Western-style Diet on Hippocampal Functioning

The previous sections briefly described how a Western-style diet is associated with increased body weight and an increased risk of developing a neurodegenerative disease. In the latter case, a Western-style diet may facilitate disease progression by affecting a brain area known to be susceptible to environmental insult – the hippocampus. Support for this claim comes from both animal and human evidence showing that a diet rich in fats and sugars impairs hippocampal integrity in rats (Goldbart et al., 2006), and greater intake of a Western-style diet is linked to smaller hippocampal volume in older adults (Jacka, Cherbuin, Anstey, Sachdev & Butterworth, 2015).

Importantly, one influential account argues that a Western-style diet impairs the ability of the hippocampus to regulate appetite (see Figure 1.1.). Davidson, Kanoski, Walls and Jarrard (2005) argue that food cues encountered in the *absence* of satiety signals predict the occurrence of rewarding post-ingestive consequences, thereby exciting the association between food cues and their positive post-ingestive consequences (i.e., its memory). After homeostasis has been achieved, food cues should no longer predict rewarding post-ingestive outcomes. That is, satiety should act as an inhibitory gate to the excitatory association between food cues and food, thereby inhibiting appetitive behaviours.

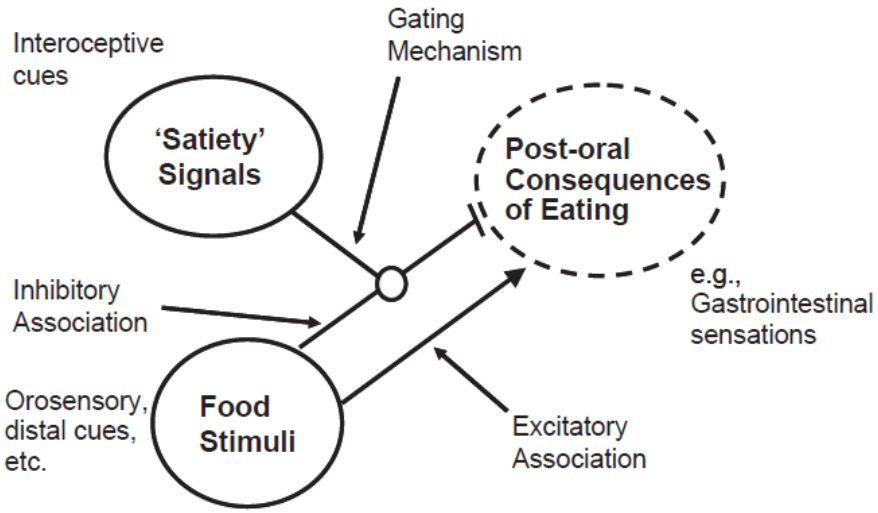

Figure 1.1. The inhibitory account of food intake proposed by Davidson et al. (2005).

This inhibitory model of energy regulation draws support from a wealth of animal research (for a review, see Hargrave, Jones & Davidson, 2016). However, to date, there has been no research in humans on diet-related impairments in the inhibitory regulation of food intake related to the hippocampus.

The inhibitory processes described above are modulated by interoceptive cues of satiety. This may be coordinated by the hippocampus (Lathe, 2001), with it forming inhibitory associations between food cues and their consequences to guide appetitive behaviour (Davidson & Jarrard, 2004). Disruption of hippocampal function may therefore affect the ability of an animal or person to accurately sense energy state cues, and to use such cues to control the ability of food cues to evoke eating behaviours beyond homeostasis. Thus it is argued that a Western-style diet disrupts the ability of the hippocampus to use satiety to appropriately gate the activation of food-related memories that may drive food intake.

An important consequence of this model is that disruption of hippocampal inhibitory control over behaviours directed at obtaining food can heighten the risk of further overconsumption of the same foods that contributed to hippocampal dysfunction. That is, a Western-style diet may interfere with hippocampal functioning, thereby impairing the ability of satiety to inhibit appetitive behaviours. This then increases the likelihood that food cues

would evoke the appetitive behaviour and intake of highly palatable foods irrespective of hunger state, giving rise to further hippocampal impairments (see Figure 1.2). This complex relationship between Western-style diet and hippocampal function has been termed the "vicious cycle" model (Davidson et al., 2005; Kanoski & Davidson, 2011). Repeated failure to inhibit intake during satiety leads to excess energy intake, weight gain and ultimately obesity.

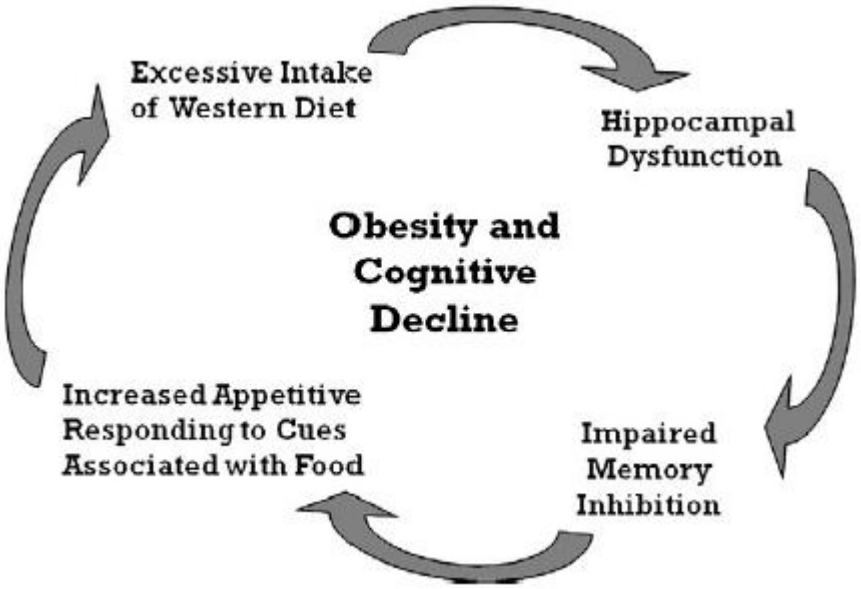

Figure 1.2. A summary of the 'vicious cycle' model taken from Kanoski and Davidson (2011).

This inhibitory model of energy regulation draws support mainly from animal research (for a review, see Hargrave, Jones & Davidson, 2016). The animal findings in support of this model are reviewed in Chapter 2 of this thesis. However, to date, there has been no research in humans on diet-related impairments in the inhibitory regulation of food intake related to the hippocampus. Therefore, the first study in this thesis aims to address this issue by investigating whether inhibitory processes related to food intake are impaired in individuals with a diet richer in saturated fats and refined sugars. Such evidence in humans would strengthen the validity of the inhibitory model of energy regulation put forward by Davidson et al. (2005) by demonstrating its translation to humans.

While human evidence of diet-related impairments in inhibitory processes has yet to be established, there is considerably more robust animal and human evidence showing that a Western-style diet also impacts interoceptive sensitivity to satiety and hippocampal-dependent learning and memory processes. The majority of evidence for these claims comes from animals showing that a diet rich in saturated fats and refined sugars impairs performance on learning and memory tasks that are hippocampally-based (e.g., Beilharz, Maniam & Morris, 2016), and the ability to respond to cues based on physiological state (e.g., Davidson & Jarrard, 1993). In humans, there is correlational evidence showing that habitual consumption of an HFS diet is linked to poorer performance on hippocampally-based memory tasks (e.g., Francis & Stevenson, 2011) and reduced sensitivity to hunger, thirst and satiety signals (e.g., Brannigan, Stevenson & Francis, 2015).

One important difficulty in interpreting these findings relates to the direction of causality. Currently, there appears to be no published review bringing together the current human causal evidence that diet (in general) influences cognition in humans. That is, the arguments for a causal effect of diet on cognition in chiefly based on animal evidence, with no clear picture of causal evidence in humans. Thus, the second aim of this thesis is to review evidence from peer-reviewed journal articles that manipulating energy intake and macronutrient content impacts cognitive function. Finally, it is not known whether a Western-style diet affects cognitive function, as it does in animals. That is, it is unclear if a Western-style diet causes these hippocampal impairments or whether existing differences in hippocampal functioning result in consumption of a Western-style diet. Animal research clearly implies the former, but there is no experimental evidence to support this claim in humans. Moreover, the limited human studies investigating the impact of an HFS diet on hippocampal functions have been correlational in nature, which are limited in their explanatory power. Therefore, the third aim of this thesis is to address this gap in the human

literature by determining whether an HFS diet *causes* impairments in hippocampal-dependent learning and memory and reduced interoceptive sensitivity in humans.

1.5 Thesis Aims and Overview

Evidence in both humans and animals suggests that a Western-style diet, high in saturated fats and refined sugars may impair a key brain region that is implicated in the regulation of ingestive behaviour, namely the hippocampus. While the animal evidence supporting this claim is extensive, the limited human literature is correlational in nature and lacks experimental evidence. Therefore, to determine whether diet-induced impairments in hippocampal functioning in animals are evident in humans, this thesis has three specific aims: (1) to determine if a diet richer in saturated fats and refined sugars (HFS) is associated with impaired hippocampal inhibitory processes for ingestive behaviour; (2) to systematically review empirical evidence showing that manipulations of energy intake or macronutrient content alter cognitive function; and (3) to empirically test if an HFS diet causes impairments in hippocampal functions related to ingestive behaviour, namely memory and interoception. In order to achieve these aims, the research chapters for this thesis are presented as follows:

- Chapter 2 reviews evidence of the impacts of a Western-style diet on the hippocampus and its associated functions believed to regulate ingestive behaviour – hippocampal-dependent learning and memory, interoceptive signals of satiety, and inhibition.
- Chapter 3 draws on animal and human research from the previous chapter to design a correlational study examining the relationship between habitual consumption of an HFS diet and inhibitory processes related to appetite regulation (Aim 1). Further, this study aims to provide additional support for previous findings of the impact of HFS intake on hippocampal-dependent learning and memory and sensitivity to changes in fullness in humans.

- Chapter 4 systematically reviews the experimental diet intervention literature in humans to determine which cognitive functions, if any, are impacted by dietary manipulations of energy intake or macronutrient content (Aim 2). Findings from this chapter are used to explore which cognitive domains may be most sensitive to dietary shifts.
- Chapter 5 describes methodological considerations for designing nutritional intervention studies in humans. Importantly, these considerations are addressed within the framework of designing the parameters for an empirical study of a diet intervention reported in Chapter 6.
- Chapter 6 presents an experimental diet intervention to provide causal evidence that shifting lean adults to an HFS diet impairs hippocampal-dependent learning and memory and interoceptive sensitivity relevant to long-term energy regulation (Aim 3). Potential physiological mechanisms known to be related to hippocampal function are also explored.
- Chapter 7 discusses the major findings of this thesis and its implications for cognitive function, neurodegenerative diseases, as well as the wider implications for the regulation of food intake and weight.

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Chapter 2: The Effects of a Western-style diet on hippocampal function

The primary focus of this chapter is to provide an overview of research on the effects of a Western-style diet on the hippocampus. The rationale for focusing on the hippocampus is based on the fact that it has a number of roles in the regulation of appetite, including: (1) recalling what, when and how much food was consumed (i.e., episodic learning and memory); (2) the ability to accurately sense interoceptive signals of hunger and fullness, and; (3) the utilisation of such signals in the inhibition of ingestive behaviour. Thus, in this chapter, it will be argued that the hippocampus regulates ingestive behaviour via these three functions (i.e., hippocampal-dependent learning and memory, interoception and inhibition), and so if a Western-style impairs hippocampal functioning it will then impair appetitive control. As the effects of a Western-style diet in animals and humans have been comprehensively reviewed elsewhere (Francis & Stevenson, 2013; Hargrave, Jones & Davidson, 2016), this chapter provides only a general overview of the relevant literature. Therefore, the themes and articles in this chapter are used to represent the general findings in this research area. In addition, as the vast majority of research in this area comes from animals, the review draws primarily upon this literature with additional support from available human correlational data.

2.1 Adverse Impacts of a Western-style Diet on the Hippocampus

The hippocampus is located in the medial temporal lobe and is particularly susceptible to environmental insults (Walsh & Emerich, 1988). The hippocampus may therefore manifest variability in functioning depending on a number of factors (e.g., stress, sleep quality, epilepsy etc.), of which a Western-style diet may be one. A Western-style diet, typically high in saturated fats and refined sugars (HFS) appears to disrupt hippocampal functioning at the physiological level. The evidence showing hippocampal disruption by a Western-style diet comes primarily from experimental evidence in animals, with limited correlational evidence in humans. In animals, a high saturated fat diet leads to impairments

in hippocampal morphology (Granholm et al., 2008), and hippocampal neurogenesis critical for learning and memory (Lindqvist et al., 2006). A high-sugar diet also impacts hippocampal insulin signalling (Agrawal & Gomez-Pinilla, 2012; Soares et al., 2013) and hippocampal inflammation (Beilharz et al., 2014). Likewise, diets high in fats or sugars result in decreased proliferation of hippocampal neurogenesis (for a more comprehensive review, see Zainuddin & Thuret, 2012), which is argued to be mediated (at least in part) by neurotrophins such as brain-derived neurotrophic factor (BDNF). Indeed, animals show reduced expression of hippocampal BDNF following a high-fat diet (Wu, Ying & Gomez-Pinilla, 2004) or an HFS diet (Kanoski, Meisel, Mullins & Davidson, 2007; Molteni, Barnard, Ying, Roberts & Gomez-Pinilla, 2002; Martire et al., 2014). Meanwhile, the integrity of the CA1 field of the hippocampus – an area critical for learning and memory – is impaired by a 90 day HFS diet (Goldbart et al., 2006), and an 8 month HFS diet reduces hippocampal dendritic spine density and impairs long-term potentiation in the CA1 field of the hippocampus (Stranahan et al., 2008). In humans, there is limited evidence that supports the animal data. One imaging study demonstrated that elderly adults with greater consumption of a Western-style diet have a smaller hippocampal volume, independent of age, gender, education, smoking status, physical activity and diabetes (Jacka, Cherbuin, Anstey, Sachdev & Butterworth, 2015). Thus, based principally on animal evidence, exposure to an HFS diet – a major feature of a Western-style diet – appears to have negative consequences for neurological function at the site of the hippocampus.

2.2 Hippocampal-related Functions of Appetite Impacted by Diet

The previous section established that the hippocampus is adversely impacted by a Western-style diet at the neurological level. This is important as Western-style diet-related changes to hippocampal functioning may have adverse consequences for appetite regulation. Therefore, the aim of the following section is to outline the role of the hippocampus in ingestive behaviour and the impact of diet-related changes to hippocampal functioning on

ingestive behaviour. It is believed that there are at least three regulatory roles of the hippocampus in ingestive behaviour – hippocampal-dependent learning and memory (HDLM), interoception and inhibition. This chapter is therefore organised into three sections covering these three functions, and information within each section is presented in the following manner. First, evidence of the link between the relevant function and the hippocampus is provided. Second, the role of this hippocampal function in ingestive behaviour is outlined. Third, an overview of the animal and human evidence of the detrimental impacts of a Western-style diet on this hippocampal function is presented. Finally, the consequences of these diet-related changes to hippocampal function for subsequent ingestive behaviour is discussed.

2.2.1 Hippocampal-dependent Learning and Memory and Ingestive Behaviour

2.2.1.1 Hippocampal-dependent learning and memory (HDLM).

The hippocampus is considered an important substrate for the encoding and retrieval of both spatial and several non-spatial forms of memory in animals and long-term episodic memory in humans (Squire & Dede, 2015). Extensive animal research has shown that hippocampal damage severely impairs the ability of rodents to learn and remember a task based on spatial orientation (Kim & Frank, 2009; Martin & Clark, 2007; Morris, Garrud, Rawlins & O'Keefe, 1982; Winocur & Olds, 1978), and lesions of the hippocampus selectively impair performance on spatial memory and discrimination tasks in mice (Dillon, Qu, Marcus & Dodart, 2008). Rats with hippocampal lesions are also impaired on another hippocampally-dependent spatial memory task – the novel object recognition task, consistently failing to recognise objects when object place or context is manipulated (Mumby, Gaskin, Glenn, Schramek & Lehmann, 2002). Furthermore, such impairments on hippocampal-dependent memory tasks are evident after a three hour delay (Broadbent, Gaskin, Squire, & Clark, 2010) or a 24 hour delay between learning and testing trials (Clark,

Zola & Squire, 2000), suggesting that the integrity of the hippocampus is important for long-term memory processes.

In humans, the hippocampus plays a critical role in long-term episodic memory – our capacity to recall everyday events and facts (Eichenbaum, 2004). A commonly cited example of the role of the hippocampus in memory comes from the case study of Henry Molaison, typically referred to as 'H.M.' (Scoville & Milner, 1957). In an attempt to treat severe epilepsy, H.M. underwent surgery to remove his medial temporal lobe, including the hippocampal formation. Although some elements of his memory remained intact (i.e., procedural memory and semantic memory), H.M. presented significant impairments in his recall of autobiographical events (i.e., episodic memory). Scoville and Milner (1957) concluded that the extent of bilateral hippocampal damage was directly related to the specific memory impairments. This was based on the observations that H.M. (and other amnesic patients with similar hippocampal damage) were impaired on formal tests of memory, while patients with damage to the amygdala or uncus were not impaired on these measures. However, due to the broad nature of H.M.'s brain lesions, it was only presumed that such deficits were due to hippocampal damage. Post-mortem 3D imaging techniques combined with histological slices later revealed that some hippocampal tissue remained (Annese et al., 2014), obscuring the relationship between hippocampal integrity and memory.

A later study showed that another amnesic patient (R.B.) with lesions specific to the hippocampus presented with similar episodic memory impairments mostly in the form of anterograde amnesia, while other cognitive functions were spared (Zola-Morgan, Squire & Amaral, 1986). In agreement with these findings, recent brain imaging studies reveal that performance on episodic memory measures correlates with hippocampal activation, while non-episodic memory performance does not (Travis et al., 2014) and structural MRI scans show that bilateral hippocampal volume is strongly linked to improved HDLM performance (Monti et al., 2015). Likewise, the hippocampus is activated during recall of

autobiographical memories, but not semantic memory recall (Maguire, 2001). The level of hippocampal activation of autobiographical memories is associated with the vividness and details (Sheldon & Levine, 2013), and with the level of emotionality and personal significance of a recalled autobiographical event (Addis, Moscovitch, Crawley & McAndrews, 2004). Based on this evidence, it is therefore reasonable to contend that the hippocampus is involved in long-term learning and memory processes, especially in declarative tasks.

2.2.1.2 The utilisation of HDLM in ingestive behaviour.

An early example of the role of memory in the regulation of food intake comes again from patient H.M., who was unable to remember consuming lunch (Scoville & Milner, 1957), and readily consumed a second meal presented one minute after his first meal was removed (Hebben, Corkin, Eichenbaum & Shedlack, 1985). Two other densely amnestic patients with bilateral hippocampal damage, R.H. and B.R., who were similarly impaired on hippocampal-dependent learning and memory tasks, also readily consumed the same meal, multiple times in rapid succession, with no explicit knowledge that they had eaten (Rozin, Dow, Moscovitch & Rajaram, 1998). The authors concluded that memory of what and how much was consumed probably played a role in meal onset and termination.

Following on from this idea, recent research has explored the role of episodic memory in intact individuals by manipulating the level of memory encoding or retrieval via distraction (Higgs, 2008). A meta-analysis of 24 human studies experimentally manipulating memory, distraction and awareness found that enhancing the memory of consumed foods reduces later intake to a moderate degree. Meanwhile, distraction (i.e., preventing the encoding of memory) moderately increases immediate food intake, and greatly increases later food intake (Robinson et al., 2013). Other studies show that enhancing pleasurable food-related memories increases subsequent food intake (Robinson, Blissett & Higgs, 2012), eating rate moderates later portion size recall (Ferriday et al., 2015), and visually-presented portion size,

not actual portion size, influenced memory for that meal portion size (Brunstrom et al., 2012). Similarly, episodic memory of a meal is a better predictor of hunger hours later than the actual amount of food consumed (Brunstrom et al., 2012), all suggesting that memory-related processes play a role in ingestive behaviour.

One interpretation of these findings is that episodic memory of food consumed acts to inform subsequent decisions about how much to eat (Higgs, 2002), and that learned control over this process is hippocampally-mediated (Higgs Williamson, Rotshtein & Humphreys, 2008). In other words, the ability to encode or retrieve memories to regulate ingestive behaviour may rely on an intact hippocampus, as patients with hippocampal damage who present with severe episodic memory impairments, also consume multiple meals with no recollection of previous consumption (Higgs, Williamson, Rotshtein & Humphreys, 2008). Importantly, recent work shows that among overweight and obese prepubescent children, total abdominal adiposity is negatively associated with HDLM, while this pattern of results is not evident in non-overweight children (Khan et al., 2014). This suggests that hippocampal function might be predictive of weight-related outcomes. It is therefore plausible that factors known to alter hippocampal functioning, such as diet, may explain variance in weight-related outcomes.

2.2.1.3 Impact of a Western-style diet on HDLM.

Animal and human studies suggest that the high intake of saturated fats, refined sugars or a combination of both may be a driving factor of the adverse consequences for HDLM and obesity associated with a Western-style diet (e.g., Davidson, Kanoski, Walls & Jarrard, 2005; Francis & Stevenson, 2011). It should be noted that some human studies focus on saturated fat and refined sugar intake (e.g., Francis & Stevenson, 2011), while others assess some or all of the aforementioned characteristics of a Western-style diet (e.g., Jacka et al., 2015). Thus, while animal research focuses on HFS intake, the human research may assess HFS intake or the more comprehensive dietary profile of a Western-style diet. The

following subsections therefore provide an outline of the HDLM impairments associated with increased intake of: (1) saturated fats; (2) refined sugars; and (3) saturated fats and refined sugars or a Western-style diet.

2.2.1.3.1. Saturated fat

Fatty acids fall into three major categories: polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), and saturated fatty acids (SFAs). The relative intake of fat, especially saturated fats, has serious implications for cognitive impairments in both animals and humans. There is extensive evidence in rodents that high-fat feeding impairs memory tasks known to be hippocampally-based, including the 8-arm radial maze (Valladolid-Acebes et al., 2011), the 14-arm T-maze (Morrison et al., 2010; Pistell et al., 2010), the water radial maze (Boitard et al., 2012; Boitard et al., 2014; Granholm et al., 2008), and the Morris water maze (White et al., 2009; Wu et al., 2004). Furthermore, fat type may be an important factor in diet-induced changes in cognition. In particular, rats given a diet high in saturated fats (40%) for 3 months are impaired on hippocampal-dependent tests of spatial memory (Olton's radial arm maze), general learning ability (Hebb-Williams maze) and memory function (variable-interval delayed alternation task) relative to rats given a diet high in polyunsaturated fats or standard chow (Greenwood & Winocur, 1990; Winocur & Greenwood, 1999). Likewise, a 10% saturated fat diet leads to deficits in conditional discrimination and working memory (Winocur & Greenwood, 1993), and the degree of impairment on these learning and memory tasks is directly related to the levels of saturated fats (Greenwood & Winocur, 1996).

The impacts of saturated fats on hippocampal-related cognitive function in animals are well supported in human research. Epidemiological and longitudinal studies show that a high intake of saturated fats increases the risk of dementia in middle-aged individuals (Kalmijn et al., 1997) and increases the risk of impaired mental flexibility, speed and memory (Kalmijn et al., 2004). A later study found that greater intake of saturated fats is associated

with increased risk of mild cognitive impairment and poorer prospective memory over a 21-year period (Eskelinen et al., 2008). Furthermore, in young women, greater intake of saturated fats is associated with increased errors and poorer memory recall and recognition on hippocampal-related memory tasks (Gibson, Barr & Jeanes, 2013). Meanwhile, after adjusting for differences in body mass index, Baym et al. (2014) found a negative association between performance on hippocampal-related memory tasks and habitual intake of saturated fats in children aged 7-9 years. Thus, greater intake of saturated fats is linked to poorer performance on HDLM tasks in humans, and this effect is evident across the lifespan.

2.2.1.3.2. Refined sugars

Carbohydrates are classified into complex carbohydrates such as polysaccharides (e.g., starches) or simple carbohydrates such as monosaccharides (e.g., glucose) and disaccharides (e.g., sucrose). Increased intake of simple carbohydrates (i.e., refined sugars) may have long-term implications for obesity and learning and memory processes. In a transgenic mouse model of Alzheimer's disease, chronic exposure to 10% sucrose solution over 25 weeks impairs spatial memory on the Morris water maze (MWM), with an accompanying 2-3 fold increase in insoluble amyloid-β proteins prevalent in Alzheimer's disease (Cao, Lu, Lewis & Li, 2007). Similar impairments on the MWM have been found following consumption of a 10% sucrose solution (Kendig, Boakes, Rooney & Corbit, 2013). Another study showed that adolescent rats given 30-day access to a diet either high in sucrose or high in fructose are impaired on spatial memory tasks, but not non-spatial learning (Hsu et al., 2015). Meanwhile, rats fed a 32% sucrose solution over 6 weeks show impairments on the MWM after ten days (Jurdak, Lichtenstein & Kanarek, 2008), and a 32% sucrose diet over 8 weeks impairs performance on another hippocampal-dependent task (i.e., the object recognition task), where animals were unable to differentiate between a novel and a familiar object (Jurdak & Kanarek, 2009).

In humans, ingestion of a high glycaemic meal containing refined sugars impairs hippocampally-dependent delayed memory recall in healthy adults (Benton et al., 2003; Nabb & Benton, 2006). While human research has yet to establish the longer-term impacts of refined sugars on HDLM, it is known that excessive sugar consumption leads to insulin resistance (e.g., Gross, Li, Ford & Liu, 2004), and greater sugar consumption has been linked to impairments in delayed verbal memory recall on HDLM tasks (e.g., Gold et al., 2007).

2.2.1.3.3. Saturated fat and refined sugar intake

Recent research has focused on the combination of refined sugars and saturated fats (i.e., an HFS diet), as this combination appears to have the most robust effects on HDLM (e.g., Beilharz, Maniam & Morris, 2014). The majority of findings showing that an HFS diet adversely impacts HDLM come from animal research, that show quite clear impairments in HDLM when they are fed an HFS diet (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Darling, Ross, Bartness, & Parent, 2013; Francis, Mirzaei, Pardey, Haynes & Cornish, 2013; Goldbart et al., 2006; Hoane, Swan & Heck, 2011; Kanoski & Davidson, 2010; Kanoski, Zhang, Zheng, & Davidson, 2010; Messier, Whately, Liang, Du & Puissant, 2007; Molteni et al., 2002; Tran & Westbrook, 2015). Interestingly, such HFS diet-related impairments on HDLM tasks are apparent even after only relatively short exposure (3-5 days) to this highly palatable diet (Beilharz, Maniam & Morris, 2014; Kanoski & Davidson, 2010). Longer exposures (3-8 months) to an HFS diet also results in deficits in hippocampal-dependent spatial memory tasks (Goldbart et al., 2006; Stranahan et al., 2008) and a negative discrimination task (Kanoski et al., 2010). Importantly, this diet-related impairment in HDLM appears to be specific to the hippocampus, since an HFS diet selectively impairs performance on learning and memory tasks that are dependent on the hippocampus, but spares hippocampal-independent tasks (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Molteni et al., 2002).

While the findings in animals are extensive, only a handful of studies have investigated the relationship between an HFS diet and HDLM in humans. Despite this, the findings in humans are consistent with animal research. One key study showed that higher self-reported dietary HFS intake is associated with impaired performance on HDLM tasks in young healthy adults, while performance on hippocampal-independent measures of attention, working memory and cognitive flexibility show no relationship to HFS diet (Francis & Stevenson, 2011). A later study also found a negative association between performance on the HDLM task and dietary HFS intake in young healthy adults, after controlling for body mass index (BMI) and age, while non-hippocampal measures were not linked to HFS diet (Brannigan, Stevenson & Francis, 2015). Consistent with these findings, elderly adults with a greater intake of a Western-style diet are impaired on global cognitive tests, which include hippocampal-based memory tasks (Devore et al., 2009; Gardener et al., 2014; Granic et al., 2016). The fact that a Western-style diet impairs HDLM is important since a key feature of neurodegenerative disease is the progressive loss of memory and hippocampal damage, and diet-related changes to HDLM may contribute to this progressive decline in neurodegenerative disease. Indeed, there is good evidence that greater intake of a Western-style diet increases risk of cognitive impairment from Alzheimer's disease (Berrino, 2002; Gardener et al., 2014; Granic et al., 2016; Grant, 1997; Grant, 2014; Gu, Nieves, Stern, Luchsinger & Scarmeas, 2010; Morris et al., 2003; Torres et al., 2012). Taken together, the animal and human research indicate that consumption of a Western-style diet, high in HFS intake, impairs learning and memory tasks known to be hippocampally-based.

2.2.1.4 Impact of Western-style diet-related impairments in HDLM on ingestive behaviour.

Impairments in HDLM associated with Western-style diet intake may have adverse impacts on ingestive behaviour. One way that a Western-style diet may affect ingestive behaviour is by disruption of learning and memory processes. This idea is exemplified in the

findings from Francis and Stevenson (2011), showing that, relative to those with a lower intake, healthy young adults with a diet richer in saturated fats and refined sugars: (1) are impaired on HDLM tasks; (2) consume more snack items and more energy from snacks; (3) consume more energy during a lunch meal, and; (4) are less accurate in recalling previously consumed snack items. Importantly, the poorer recall accuracy for previously consumed snack items is significantly associated with poorer HDLM performance, suggesting that learning and memory processes controlled by the hippocampus may also mediate the former. Another important finding from this study is that snack item recall accuracy is negatively correlated with amount consumed in a subsequent lunch meal (Francis & Stevenson, 2011). While this finding is consistent with the idea that accurate recall of prior food intake impacts the amount consumed in subsequent meals (e.g., Higgs, Williamson & Attwood, 2008), it also highlights that such memory-related processes involved in ingestive behaviour may be impaired in individuals that habitually consume a Western-style diet.

2.2.2 Interoception and Ingestive Behaviour

2.2.2.1 Interoception.

Interoception is the ability to perceive internal body states, including temperature and pain, as well as hunger, thirst and satiety (Cameron, 2001). There is consistent evidence in animals and humans that surgical, genetic or hormonal disruption of the hypothalamus has profound effects on eating behaviour and weight-related outcomes. Early work by Burton, Rolls and Mora (1998) showed that single neurons in the lateral hypothalamus decreased and increased their firing rates when hungry monkeys tasted food. Further, disruption of the ventromedial hypothalamus produces hyperphagia (excessive consumption), while hypophagic responses are evident from lateral hypothalamus disruption (Flier & Maratos-Flier, 1998). One study found that lesions of the pathway between the basolateral amygdala and the lateral hypothalamus promoted eating in sated animals, when they were presented with food cues previously paired with stimuli that predicted its delivery when the animal was

hungry (Petrovich, Setlow, Holland & Gallagher, 2002). This is consistent with previous literature showing the role of the hypothalamus in interoception. However, the vast majority of animal literature (experimental, surgical, lesion, and genetic) and human (observational and imaging) suggest that the integration of such interoceptive signals to regulate eating behaviour may rely on other brain areas. Importantly, recent work in both animals and humans suggests that the hippocampus plays a key role in processing interoceptive cues and may be particularly vulnerable to environmental insult (e.g., Hsu & Kanoski, 2014). In animals, lesions of the hippocampus disrupt the ability to effectively discriminate between stimuli based on physiological state (Davidson & Jarrard, 1993; Davidson et al., 2010). A recent study in humans showed that poorer performance on a measure of HDLM is associated with poorer interoceptive awareness on the Multidimensional Assessment of Interoceptive Awareness questionnaire, as well as an insensitivity to gastric emptying on a water load task (Dudley & Stevenson, 2016). The fact that a well-established hippocampal memory task is positively associated with interoceptive sensitivity measures suggests that the hippocampus may also be involved in interoceptive processing in humans.

2.2.2.2 Interoception and Ingestive Behaviour.

The medial temporal lobe, which includes the hippocampus, is important in mediating interoceptive signals of hunger and satiety (Berriman et al., 2016), and its function may be a significant factor in ingestive behaviour. Indeed, lesions studies in animals and neuropsychological evidence in humans indicate that the hippocampus may mediate interoceptive cues of hunger and satiety to regulate eating behaviour. In animals, damage to the hippocampus increases food intake, body weight gain and disrupts the relationship between meal size and latency to start next meal (Davidson et al., 2009; Henderson, Smith & Parent, 2013). Likewise, lesions of the hippocampus impair appetitive conditioned responding (Tracy, Jarrard, & Davidson, 2001). Lesions of the dorsal, ventral or complete hippocampus impact ingestive behaviour, leading to increases in meal frequency (Clifton,

Vickers & Somerville, 1998) meal size (Davidson et al., 2009) and increased body weight gain compared to control rats (Forloni, Fisone, Guaitani, Ladinsky & Consolo, 1986; Davidson et al., 2009).

Consistent with this idea, case studies of amnesic patients reveal that damage to hippocampal brain areas leads to severe interoceptive agnosia and impact ingestive behaviour. Patient H.M., who had a medial temporal lobe resection, appeared to be insensitive to interoceptive satiety signals, as his ratings of hunger and thirst did not change from before to after a meal, even after consuming a second meal (Hebben et al., 1985). One interpretation of this finding is that H.M. consumed this second meal because he was unable to remember consuming the first meal, as discussed earlier. Another equally plausible interpretation is that H.M. had no interoceptive awareness of the first meal, and so consumed the second meal. A third possibility is that both of these functions adversely influenced H.M. What this suggests is that food-related changes to appetite may be cognitively mediated, requiring an intact hippocampus to integrate memories of internal state cues, sensory properties of the food and post-ingestive consequences (Baker, Booth, Duggan & Gibson, 1987). Other amnesic patients with an intact hippocampus do not show these impairments in interoception (i.e., impaired changes in hunger) and food intake, suggesting that these functions rely on the hippocampus (Hebben et al., 1985). This claim is supported by a later study from Rozin et al. (1998). Two densely amnestic patients with bilateral hippocampal damage, R.H. and B.R., who also presented with memory impairments, consumed multiple meals and showed little change in hunger ratings across successive meals (Rozin et al., 1998). Likewise, more recent studies reveal that, relative to controls, amnesic patients with medial temporal lobe damage show little change in hunger and fullness following a lunch meal, tend to consume more energy at lunch, and consume more food than controls when presented with another meal 15 minutes later (Higgs et al., 2008).

2.2.2.3 Impact of a Western-style diet on interoception.

In animals, exposure to an HFS diet impairs the ability to use interoceptive cues of hunger and fullness (Davidson et al., 2009; Davidson et al., 2010; Sample, Martin, Jones, Hargrave & Davidson, 2015). Likewise, in humans, greater consumption of saturated fats and refined sugars is associated with a reduced sensitivity to changes in hunger and fullness (Francis & Stevenson, 2011), and thirst (Brannigan, Stevenson & Francis, 2015). Cooling and Blundell (1998) also showed that individuals with different habitual fat consumption present with different profiles of hunger in response to test meals high in fats or carbohydrates. Specifically, individuals with a diet high in fat reported a higher baseline hunger rating and a more rapid return to hunger following a high-fat or high-carbohydrate meal relative to low-fat consumers. These findings suggest that a Western-style diet may interfere with the ability to accurately sense signals of satiety, which has been argued to gate the activation of food-related memories (Davidson et al., 2005).

2.2.2.4 Impact of Western-style diet-related impairments in interoception on ingestive behaviour.

Findings from both humans and animals indicate that consumption of a Western-style diet impairs hippocampal function, which may have downstream effects on the control of ingestive behaviour. One such ingestive control concerns the ability to perceive internal states such as hunger and satiety (i.e., interoception). The ability of the hippocampus to use interoceptive cues to regulate ingestive behaviour may be compromised by the consumption of a Western-style diet (Davidson et al., 2005). Individuals with a high-fat diet not only show different hunger profiles to meals high in fat or carbohydrates, but also consume significantly more energy from high-fat meals based on meal volume, relative to low-fat consumers (Cooling & Blundell, 1998). That is, while the low-fat consumers vary their food intake based on energy density, high-fat consumers fail to do this, leading to greater energy intake. Likewise, habitual consumers of an HFS diet eat more food but show similar shifts in hunger

and fullness relative to low consumers of this diet (Francis & Stevenson, 2011). The authors concluded that this represents a reduced interoceptive sensitivity, with habitual consumers of an HFS diet requiring significantly more energy to generate a one unit change in hunger and fullness (Francis & Stevenson, 2011). Consistent with this argument, habitual consumers of an HFS diet show smaller changes in thirst after intake of salted snacks, along with smaller changes in thirst per volume of water consumed. The thirst ratings prior to water intake are also a poorer predictor of later water intake, suggesting that these individuals have a reduced awareness of interoceptive signals (Brannigan, Stevenson & Francis, 2015).

One question raised by such findings in humans relates to how an HFS diet impairs interoceptive sensitivity. One possibility may be that a high intake of salt (also characteristic of an HFS diet) may impair the ability of salt to elicit in-mouth changes (i.e., dry mouth) that would lead to interoceptive changes such as thirst. However, given that salt thirst/appetite appears to be related to the activation of non-hippocampal areas including the amygdala, insula and orbitofrontal cortex (Daniels & Fluharty, 2004; Saker et al., 2014), the relationship of salt to impairments in hippocampal-dependent processes associated with a Western-style diet remains unclear. Another possibility is that highly palatable foods prevalent in a Western-style diet may upregulate hunger signals, blunt satiety signals and activate reward pathways (Erlanson-Albertsson, 2005). For example, rats fed an HFS showed enhanced learning of the association between a flavour and its post-ingestive consequences, where sensitivity to this association was correlated with obesity (Wald & Myers, 2015). While evidence of HFS-related changes to learning are robust in animals, human evidence has been less reliable. Indeed, flavour-nutrient learning – associating the orosensory properties of a food with its caloric post-ingestive consequences – and flavour-taste learning – associating a flavour with an already liked taste – have been difficult to demonstrate in humans (Yeomans, 2012), and a Western-style diet appears to have no impact on flavour-nutrient learning (Brunstrom, Rogers, Myers & Holtzman, 2015). A third possibility, and one that is argued

throughout this thesis, is that interoceptive processing supported by the hippocampus (Berriman et al., 2016), is impaired by consumption of a Western-style diet. In other words, a Western-style impairs the ability to use interoceptive signals to inhibit post-ingestive associations or memories and therefore inhibit ingestive behaviour (Davidson et al., 2005). Indeed, there is substantial evidence for the involvement of the hippocampus in the use of interoception in appetite regulation. Impairments in hippocampal function associated with a Western-style diet, therefore, imply that the ability of interoception to regulate ingestive behaviour may also be impaired by this diet.

2.2.3 Inhibition and Ingestive Behaviour

2.2.3.1 Inhibition.

Inhibition is an important construct in psychology as successful behaviour depends on the ability to focus attention on relevant cues, to inhibit responses to irrelevant cues, and to suppress habitual responses when appropriate (Dillon & Pizzagalli, 2007). One form of inhibition that is a focal point in this chapter, and throughout this thesis, involves the ability to inhibit learned responses in the presence of an appropriate cue (Chan, Morell, Jarrard & Davidson, 2001), a process which appears to be subserved by the hippocampus, and to a lesser extent by the prefrontal cortex. Several researchers have suggested that the hippocampus is important for inhibition (e.g., Davidson & Jarrard, 2004; Kimble, 1968). For instance, forming the inhibitory link between an excitatory conditioned stimulus and the memory of the rewarding event with which the stimulus is associated relies on the hippocampus (Davidson & Jarrard, 2004). In line with this idea, damage to the hippocampus interferes with the formation of linking an unconditioned stimulus and an inhibitory conditioned context in animals (Benoit, Davidson, Chan, Trigilio & Jarrard, 1999) and the ability to inhibit responses on a hippocampal-dependent spatial alternation task is impaired following lesions to the hippocampus (Kim & Frank, 2009). The neural pathways linking the hippocampus and the ability of satiety cues to inhibit food intake have been identified in

animals. For instance, glucagon-like-peptide-1 signalling in the hippocampal-to-prefrontal cortex pathway appear to underlie inhibition of food intake (Hsu et al., 2017), while the inhibitory effects of satiation on food intake are subserved by the hippocampal-to-lateral septum pathway (Sweeney & Yang, 2015).

Recent neuroimaging data in humans points to similar conclusions of the role of the hippocampus in inhibitory processes. In humans, inhibition is typically measured by assessing whether individuals are able to appropriately suppress learned responses in a task. Indeed, recent evidence shows that the hippocampus is not only in involved in memory encoding and recall, but also the suppression of memories when appropriate (Anderson, 2001; Anderson & Green, 2001; Anderson et al., 2004). That is, inhibiting recall of previously learned word pairs reduces subsequent memory recall (Anderson et al., 2004), and inhibited words are associated with increased activation in the dorsolateral prefrontal cortex and decreased activation in the hippocampus, with greater activation in these brain areas in individuals better able to inhibit memories (Anderson, 2004; Benoit & Anderson, 2012). That is, if hippocampal activation signals the retrieval of an inappropriate memory, then this information is transferred to the dorsolateral prefrontal cortex where it exerts a negative influence over the hippocampus to inhibit the memory (Benoit & Anderson, 2012). What this suggests is that these brain areas, as in animals, are involved in inhibition, and the ability to inhibit responses or associations is dependent on the functional integrity of these brain areas.

2.2.3.2 Inhibition and ingestive behaviour.

Long-term energy regulation requires balancing food seeking behaviours and consumption in modern obesogenic environments, with the ability to suppress or inhibit those behaviours. Based on this premise, Davidson et al. (2005) propose a model of energy regulation based on the ability of an organism to inhibit responses when appropriate. Specifically, upon encountering food cues in a hungry state, pleasant food-related memories associated with the cue are excited or retrieved, but such associations are inhibited when

sated. The formation of this inhibitory association in the presence of satiety requires an intact hippocampus. In other words, when a stimulus excites the memory of an event/stimulus, the process by which the activation of the memory is inhibited requires an intact hippocampus. Therefore, inhibitory processes involved in energy regulation and ingestive behaviour likely call upon the hippocampus (Davidson et al., 2005). It has been shown in animals that hippocampal neurons inhibit meal onset in young rats (Henderson, Smith & Parent, 2013), and lesions to the hippocampus impair the ability to use satiety as an inhibitory cue (Davidson & Jarrard, 1993). Likewise, lesions of the hippocampus impair the ability of animals to solve a feature negative discrimination task, where interoceptive satiety cues (X) signal that food-related target cues (A) are not followed by a rewarding post-ingestive outcome (XA−) (Holland, Lamoureux, Han, & Gallagher, 1999).

Generally speaking, a higher BMI in human subjects is also associated with poorer inhibitory control to pictures of highly palatable foods (Houben, Nederkoorn & Jansen, 2014). Neuroimaging data also show that reduced activation of the parahippocampal gyrus and the dorsolateral prefrontal cortex is associated with an impaired ability to control the hyperconsumption of food, especially in the obese (Brooks, Cedernaes & Schiöth, 2013), and reduced activation of the dorsolateral prefrontal cortex predicts subsequent intake of palatable foods (Cornier, Salzberg, Endly, Bessessen & Tregellas, 2010). Meanwhile, non-obese men asked to suppress food desires show increased activation in orbitofrontal portion of the PFC and hippocampus (Wang et al., 2009), suggesting a role of these brain areas in inhibition and energy regulation.

2.2.3.3 Impact of a Western-style diet on inhibition.

Based on animal evidence, it has been argued that the inhibitory gating process in inhibition tasks such as the feature negative discrimination task may also occur in energy regulation. Here, satiety acts as the feature negative stimulus to inhibit the excitatory association between a food cue and its rewarding post-ingestive outcome (Davidson, Sample

& Swithers, 2014). In this way, a Western-style diet may impair hippocampal function and therefore the ability of the inhibitory gating mechanism to work effectively. Compelling evidence for the impact of a Western-style diet on hippocampal-related inhibition comes from studies using feature negative discrimination tasks. In this task, animals are presented with a 5 second stimulus (e.g., a tone) followed by the presentation of two sucrose pellets (Tone +). However, if the tone is preceded by a 5 second presentation of another stimulus (e.g., a light), then no sucrose pellets are presented (Light → Tone -). Animals learn to respond appropriately by seeking the sucrose pellets when presented with the tone, but inhibit responses when presented with the light. The feature negative discrimination task suppresses conditioned responding by promoting the activation of an inhibitory association between the target (tone) and the unconditioned stimulus (sucrose pellet). The feature negative discrimination task is considered hippocampally-dependent, since neurotoxic lesions to the hippocampus impair performance (Holland et al., 1999). Importantly, consumption of an HFS diet for 90 days impairs hippocampal-dependent feature negative discrimination performance, but spares hippocampal-independent simple discrimination performance (Davidson et al., 2013; Kanoski, Zhang, Zheng & Davidson, 2010). Rats with HFS-diet impairments on this task also show reduced levels of BDNF in the hippocampus and medial PFC, again supporting the notion that the hippocampus is involved in inhibitory processes (Kanoski, Meisel, Mullins & Davidson, 2007).

While the role of the hippocampus in inhibition is well-supported by animal studies, there is only emerging evidence in humans that a Western-style diet impacts inhibition processes related to the hippocampus. Poorer performance on inhibitory control tasks is significantly associated with increased saturated fat intake (Allom & Mullan, 2014), and lower self-report ratings of self-control (i.e., inhibitory control) are associated with poorer diet quality (Sproesser, Strohbach, Schupp & Renner, 2011). Likewise, consumption of an HFS diet, especially from sugar-sweetened beverages and take-away foods, is linked with

greater trait impulsivity, independent of BMI and gender (Lumley, Stevenson, Oaten, Mahmut & Yeomans, 2016), suggesting that this consumption of an HFS diet is related to poorer inhibitory control. Evidence for this claim comes from the fact that inhibitory control of eating behaviour via dietary restraint has been linked to increased sugar and fat intake (Rideout, McLean & Barr, 2004), and habitual HFS intake is negatively associated with restraint (Brannigan et al., 2015; Francis & Stevenson, 2011), implying that inhibitory control may be impaired in habitual consumers of an HFS diet.

2.2.3.4 Impact of Western-style diet-related impairments in inhibition on ingestive behaviour.

One role of the hippocampus is to regulate food intake via inhibitory control mechanisms. An important consequence of hippocampal dysfunction associated with consumption of a Western-style diet may be the impaired ability to inhibit responses to food-related stimuli when appropriate. Indeed, it has previously been argued that highly palatable foods may weaken inhibitory control (Lumley et al., 2016). It may be that diet-related changes to hippocampal function may be contributing to deficits with inhibitory control, making it more difficult to inhibit a food-related memory or association, and increasing ingestive behaviour. Animal data show that an HFS diet impairs performance on the food-related feature negative discrimination task, but not on hippocampal-independent simple discrimination problems (Davidson et al., 2012). That is, animals fed an HFS diet are unable to inhibit responding to food in this task. Likewise, appetitive responding for non-rewarding trials on this task is increased in animals fed an HFS diet (Kanoski et al., 2010). Importantly, diet-induced impairments in inhibition to food are linked to blood-brain permeability and hippocampal integrity, as well as excessive weight gain (Davidson et al., 2012; Davidson et al., 2013; Kanoski et al., 2010). What this suggests is that an HFS diet may facilitate weight gain by disrupting effective hippocampal function, and therefore inhibitory control of food intake.

The human data showing that a Western-style diet impacts ingestive behaviour via changes in inhibitory control is limited. Francis and Stevenson (2011) show that: (1) an HFS diet is negatively associated with restraint; (2) restraint scores are negatively associated with snack intake; (3) lower restraint scores are associated with poorer hippocampal-dependent memory recall; and (4) that poorer accuracy in recall of food intake, relative to actual amount consumed (which is larger in those with an HFS diet) is associated with lower restraint scores. What this suggests is that individuals with a greater intake of a Western-style diet have poorer inhibitory control over eating behaviour – a notion consistent with the inhibitory model of appetite regulation proposed by Davidson et al. (2005). Based on the evidence reviewed in this section, it is evident that no human study has as yet examined links between Western-style diet intake and poorer inhibitory control. Consequently, the following chapter of this thesis aims to determine if such inhibitory processes related to ingestive behaviour are impaired in habitual consumers of an HFS diet.

2.3 Summary and Conclusions

Based on the animal and human research reviewed in this chapter, functions of memory, inhibition and the utilisation of interoceptive signals appear to be subserved by the hippocampus, and to a lesser extent, the prefrontal cortex. There are three important findings that come from this chapter: (1) a high intake of saturated fats and refined sugars – a common feature in a Western-style diet – impairs HDLM in animals, and this is supported by correlational studies in humans; (2) an HFS diet is also linked with reduced sensitivity to interceptive signals of hunger and satiety and poorer regulation of food intake based on such signals, with the ability to such satiety signals to regulate ingestive behaviour relying on the hippocampus; and (3) animal studies show that an HFS diet impairs inhibitory learning important for food regulation and body weight maintenance. While there is emerging evidence in humans to support the findings from (1) and (2), there is no human evidence to support (3). This therefore forms the basis for the study in Chapter 3 – to investigate whether

a Western-style diet is associated with impaired hippocampal-dependent inhibitory processes related to ingestive behaviour.

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Chapter 3: A high-fat high-sugar diet predicts poorer hippocampal-related memory and a reduced ability to suppress wanting under satiety

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A high-fat high-sugar diet predicts poorer hippocampal-related memory and a reduced ability to suppress wanting under satiety

The rise in obesity in many countries has been linked to the increased consumption of a Western-style diet, one rich in saturated fats and refined sugars, and low in fibre, fruit and vegetables (Drewnowski, 2007). While this type of diet may contribute to weight gain via its palatability and energy density, it may have other effects as well. A recent animal-based model of obesity proposes that such a diet adversely impacts certain centrally controlled aspects of food intake regulation via memory and inhibition processes, which then directly contribute to weight gain (Davidson, Kanoski, Walls & Jarrard, 2005). Specifically, diets rich in saturated fat and refined sugar impair the ability of the hippocampus to appropriately inhibit food-related memories under a sated physiological state, which subsequently promotes energy regulation and thus obesity (Davidson et al., 2005). Animals consistently show robust impairments in hippocampal-related learning and memory following a shift from standard lab chow to a diet high in fat (e.g., Morrison et al., 2010; Greenwood & Winocur, 1996), sucrose (e.g., Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney & Corbit, 2013), and both saturated fat and refined sugars (e.g., Beilharz, Maniam & Morris, 2014; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Tran & Westbrook, 2015). While the animal data are substantial, there has been relatively little translation into human research. So far, it has been established that greater consumption of a saturated fats and refined sugars – a HFS diet – is associated with poorer performance on hippocampal-related measures of learning and memory in children (Baym et al., 2014) and adults (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011) and with smaller hippocampal volume in the elderly (Jacka, Cherbuin, Anstey, Sachdev & Butterworth, 2015). These correlational findings suggest that as in animals, such a diet may impair hippocampal function across the lifespan.

The hippocampus may mediate several different regulatory functions in respect of food intake. These include: (1) explicit retrieval of what has been eaten to aid conscious

modulation of food intake (Higgs, 2002; Robinson et al., 2013); (2) integration of physiological signals of hunger, fullness and thirst, with memory for what has recently been eaten and drunk, to generate interoceptive states (Brannigan, Stevenson & Francis, 2015; Brunstrom et al., 2012); and (3) state-dependent retrieval and inhibition of pleasant food-related memories (Davidson et al., 2005; Davidson, Sample & Swithers, 2014). It is this last proposed mechanism that is of principal interest here, because of its apparent importance in modulating appetite according to hunger state.

It has been suggested, again based on animal data, that upon encountering food cues when hungry, pleasant food-related memories associated with the cue are excited or retrieved, thereby motivating the animal to eat that food. However, when sated, such associations are inhibited, thus reducing the incentive to consume. The regulation of appetitive behaviour is therefore based on the ability of satiety cues to inhibit this association, and this ability depends on the functional integrity of the hippocampus (Davidson et al., 2005; Davidson, Sample & Swithers, 2014). It follows then that successful long-term energy regulation involves integrating physiological states (hunger/satiety) with these memory-driven motivational states, so as to facilitate or retard energy intake when encountering food cues in the environment. According to Davidson et al. (2005), diets high in fats and refined sugars disrupt this process by impairing hippocampal function. The latter would then impair the ability of satiety to inhibit pleasant food-related memories in the presence of palatable food cues, and hence the ability to modulate the incentive salience of food based upon physiological state. While animal data supports this type of model (e.g., Davidson et al., 2012; Murray et al., 2009), there is as yet no test of it in humans. The main focus of this current study is to provide such a test.

Liking a food when eating it (i.e., palatability) and wanting a food on seeing it (i.e., incentive salience) are key drivers of human eating behaviour (Finlayson, King & Blundell, 2007a). Wanting is hypothesised to be the consequence of an active process whereby internal

cues to bodily state and external cues to food are transformed into representations with an assigned motivational value (Berridge, 1996). Generating a 'want' is therefore highly dependent upon memory, with each food cue leading to the retrieval of its own particular sensory and hedonic attributes. While wanting may be heavily dependent upon memory, liking is likely to be far less dependent, because here *consumption* directly activates sensory-driven pleasure circuits (i.e., for sweetness, saltiness, fatty mouthfeel). Accordingly, wanting for a food should be strongly linked to hippocampal-related memory processes, while liking should not.

Another important consequence of this definition of wanting by Berridge (1996) is that the motivational value of a food should vary as a function of physiological state – a phenomenon termed 'alliesthesia' (Cabanac, 1971). While Cabanac (1971) defined this phenomenon using pleasantness (i.e., liking), others have since shown that changes in internal state induce greater decreases in wanting than liking when exposed to olfactory stimuli (Jiang et al., 2008) and visual stimuli (Finlayson, King & Blundell, 2007b). According to Davidson et al., (2005), the presence a food cue activates the stored representation of that food when hungry, but is inhibited when sated. Therefore, wanting should be more sensitive than liking to changes in physiological state, since wanting is driven by the integration of physiological state *and* by the activation of a food-related memory (Berridge, 1996), while liking involves only the former. To see then if wanting is less effectively modulated by state in habitual consumers of a HFS diet (and changes in liking are not), we asked participants to evaluate their desire to consume and their liking for palatable snack foods (Palatable Food Cue task) when hungry and later, after an experimental lunch, when sated. Our major prediction was that changes in wanting from a hungry to a sated state would be smaller in habitual consumers of a HFS diet than comparable changes in liking. In addition to ratings of liking and wanting, we also obtained salivary responses to these foods, which we expected to mirror changes in wanting.

To see if state-dependent effects on wanting and liking in the Palatable Food Cue task were associated with performance on a hippocampal-related task, participants were also given a second test. This involved learning pairs of words - Verbal Paired Associates (VPA) – a task that is known to be dependent upon an intact hippocampus (Baxendale, 1995; Eichenbaum & Bunsey, 1995; Karantzoulis, Scorpio, Borod & Bender, 2012). Not only did we expect VPA performance to be poorer in frequent consumers of a HFS diet as predicted by our earlier work (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011), we also expected that VPA performance would correlate with size of the state-dependent change in wanting but not liking.

Following VPA training and testing, participants were asked to engage in a series of further learning trials, which involved either explicit inhibition of some verbal paired associates and explicit rehearsal of others - the 'Think/No-think' task. It has been claimed that performance on the 'Think/No-Think' task is also related to the hippocampus (Anderson & Green, 2001; Anderson et al., 2004). We thus predicted that performance on this task should also be poorer in frequent consumers of a HFS diet.

A further feature of this study was our attempt to recruit participants of normal body mass index (BMI) ($\leq$25kg/m^2), as well as controlling for variation in BMI, since increased BMI may affect memory recall (De Wit et al., 2016). Several other factors can affect hippocampal function. These include age (e.g., Bouchard et al., 2008), gender (e.g., Cosgrove, Mazure, & Staley, 2007), physical activity (e.g., Erickson et al., 2011), sleep quality (e.g., Reimann et al., 2007), and depression and stress (e.g., Videbach & Ravnkilde, 2004). Furthermore, diet quality, food intake and attitudes to food and eating have been linked with gender (e.g., Northstone, 2012), sleep quality (e.g., Chaput, 2013), physical activity (e.g., Drewnowski & Evans, 2001), and depression and stress (e.g., Appelhans et al., 2012). These possibly confounding factors were also measured in this study.

Assessment of participants' diets used a validated food frequency questionnaire, designed to indicate differences in intake of saturated fat and refined sugar, the Dietary Fat and Sugar questionnaire (DFS: Francis & Stevenson, 2013). In addition, we also assessed skin carotenoid levels using a spectrophotometer to determine fruit and vegetable intake (Stephen, Coetzee & Perrett, 2011). Given that skin carotenoid levels reflect the healthiness of one's diet (Stephen et al., 2011), and that HFS intake is also characterised by lower fruit and vegetable intake (Drewnowski, Darmon & Briend, 2004), this measure was expected to be negatively correlated with scores on the DFS. It also allowed us to test whether the *absence* of fruit and vegetables (rather than the *presence* of saturated fat and refined sugar) was associated with any hippocampal-related effects, on the grounds that a healthy diet may be protective.

In sum, the primary aims of the current study were to determine if more frequent consumption of a HFS diet impairs state-dependent changes in wanting but not liking, and to see if this effect is linked to hippocampal-related processes. Secondary aims were to determine whether a hippocampal-related measure of learning and memory (VPA) was acquired more slowly in frequent consumers of a HFS diet and whether this also extended to the Think/No-Think task.

3.1 Method

3.1.1 Participants.

People differ in the degree to which they eat a HFS diet. As we wished to use a correlational approach in our analyses, we needed to ensure that we had sufficient numbers of people who rarely or frequently consumed a HFS diet. To this end we screened a large sample and recruited people only from the upper and lower quartiles of a measure designed to assess dietary intake of fats and refined sugars (more below). Having sampled in this way - and knowing that there would be some regression to the mean when peoples dietary habits were measured again during the study – we treated the dietary data as a continuous variable

(i.e., a correlational approach) rather than grouping participants into 'highs' and 'lows'. This decision was made because the continuous approach under these circumstances is considerably more powerful than the grouping approach (MacCallum, Zhang, Preacher & Rucker, 2002; Preacher, Rucker, MacCallum & Nicewander, 2005), as it uses all of the available information.

Participants were recruited via two routes. The first involved screening the participant pool maintained by the Department of Psychology at Macquarie University using the DFS, which is a 26-item food frequency questionnaire (score range from 26 to 130) designed to identify variability in intake of saturated fat and refined sugar. The DFS has good test-retest reliability (r = .84 over 22 weeks), and has been validated against a full-length food frequency questionnaire and a 4-day diet diary, for both saturated fat and refined sugar intake (Francis & Stevenson, 2013). Cut-offs for the DFS were similar to Francis and Stevenson (2011), with scores above 70 and below 55 being used to identify potential participants. A total of 651 undergraduates completed the DFS. Of these 267 remained as potentially eligible participants, since they met all of the following criteria: (a) fell above or below the cut-offs; (b) reported a BMI between 17 and 26 (broader than the conventional criteria because this was a self-estimate and as we included people of both Caucasian and Asian descent); (c) were aged between 17 and 35; and (d) consented to be approached.

The second recruitment route drew upon the broader university community. Two types of advertisement were routinely placed around campus, with one featuring fruits and vegetables and the other highly palatable snack foods. When a potential participant phoned to enquire about the advertisements, they were asked to report consumption frequencies for the seven items from the DFS that had the highest item-total correlations (Soft drinks; Cakes & Cookies; Pizza; Fried chicken, or chicken burgers; Doughnuts, pastries, croissants; Corn chips, potato chips, popcorn with butter; French fries, fried potatoes). Participants who met age and BMI criteria were potentially eligible to take part. Additionally, participants that

scored below 16 or above 21 on this short-form DFS were also eligible to take part. The cut-offs of this 5-item short-form of the DFS were used to screen for the low (<16) and high (>21) consumers used in this study, and these groups differences were believed to persist when the full 26 item version was used later in the study.

To determine whether a potentially eligible person was actually able to participate required a telephone screening interview. This assessed any current health issues (physical or mental illness; chronic conditions; recent hospitalisations; any history of eating disorders; any head injuries; food allergies), any past health issues, and spoken English ability (i.e., for participants recruited via adverts this included leaving a voicemail message and undertaking the screening interview). Participants who reported anything beyond minor health complaints (which included asthma) or who could not adequately comprehend the interview were excluded. Eligible participants were instructed to breakfast as normal, and then refrain from eating in the 3 h before testing so as to arrive hungry for lunch, with sessions being booked to start at either 1100 for a 1200 lunch or 1300 for a 1400 lunch. Participants were also told that they could drink water in this period but not caloric beverages and that they were not to exercise beyond their normal pattern.

In total 97 participants completed the study. Of these 56 were from the psychology subject pool and 41 from the broader community. Data from three participants were excluded. One male participant revealed that they were diabetic and epileptic on the health screening questionnaire administered at the start of the study. Two female participants had BMI's < 17 - one of 16.2 and the other of 15.2. Although neither reported having an eating disorder during telephone screening (nor to having a BMI under 17) nor on the health screening questionnaire, we were concerned that this BMI might point to significant under-nutrition, with unpredictable impacts on food-related behaviour. The same pattern of significant findings was obtained even when these three participants were included.

Demographic and other information about the 94 participants whose data were included in the reported analyses are given in Table 3.1.

Table 3.1. *Descriptive statistics and Pearson correlations between participant characteristics, DFS (diet) score and the spectrophotometer measure*

Variable	Descriptive statistics	Variable's correlation with:	
		DFS (Diet)	Spectrophotometry
DFS (diet) score	M = 62.0, SD = 12.8, range 34-88		
Spectrophotometer	M = 15.8, SD = 1.8, range 11.3-20.2	-.21*	
Gender	40 men/54 women	.22*	-.17
Age	M = 20.3, SD = 3.6, range 17-34	-.19	.13
BMI	M = 22.3, SD = 2.6, range 17.2-27.9	-.15	-.02
DASS			
Depression	M = 3.5, SD = 3.6, range 0-18	-.14	.14
Anxiety	M = 2.9, SD = 2.6, range 0-10	-.01	.17
Stress	M = 4.8, SD = 3.6, range 0-16	-.02	.14
Total score	M = 11.2, SD = 8.1, range 0-35	-.05	.19
PIRS (Sleep quality)	M = 4.7, SD = 1.3, range 2-8	-.04	.13
Activity (Mins/day)	M = 79.1, SD = 87.5, range 0-573	.14	.04
TFEQ			
Restraint	M = 7.4, SD = 5.4, range 0-20	-.35*	.23*
Disinhibition	M = 6.5, SD = 3.0, range 1-14	-.06	.19
Hunger	M = 6.6, SD = 3.5, range 0-14	.16	.14

* $p < .05$

3.1.2 Materials.

The experimental lunch served during the study was either 350g of Beef Lasagne (Woolworths select brand: total energy 1930kJ [5.5% protein, 5.5% fat, 15.0% carbohydrate, by weight]) or if they disliked lasagne (prior to consumption), 350g of Spinach and Ricotta Ravioli (Woolworths select brand; 1640kJ [4.6% protein, 3.7% fat, 14.9% carbohydrate, by weight]). Alongside this hot meal, participants were also presented with a plate of cookies, consisting of four chocolate Tim Tam biscuits (total energy 1596kJ [4.6% protein, 26.9% fat,

63.9% carbohydrate, by weight]) and eight Woolworths chocolate chip cookies (total energy 1744kJ [5.0% protein, 22.7% fat, 66.7% carbohydrate, by weight]).

The Palatable Food Cue task used eight snack food items, four savoury and four sweet. These were: (1) a cheese and bacon ball (Fritolay); (2) a 0.5 cm^3 piece of cheddar cheese (Mainland); (3) a BBQ Pringles chip; (4) a salt and vinegar Pringles chip; (5) a piece of Flake chocolate (Cadbury Flake bites); (6) a mini Tim-Tam chocolate biscuit (Arnotts); (7) a mini chocolate chip cookie (Arnotts); and (8) a Malteser (Mars).

The 52 words for the paired associate tasks were selected from the lists in Nørby et al. (2010). All of the selected words were nouns with between 5 and 9 letters, emotionally neutral and occurring in the medium to high frequency range of the Corpus of Contemporary American English. From these 52 words, 26 pairs were formed that were not obviously related, which was achieved by randomly generating word pairs and then having the experimenters check for relatedness (see Appendix 2 for selected word pairs).

3.1.3 Procedure.

The study protocol was approved by the Macquarie University Human Research Ethics Committee and written consent was provided by each participant. The study started with the completion of: (1) a questionnaire to check adherence to the pre-experimental instructions; (2) a health questionnaire to confirm the screening interview and to check for any common chronic diseases, current health, and basic medical history; (3) a brief sleep scale (the Pittsburgh Insomnia Rating Scale 2; Moul et al., 2002); (4) a depression, anxiety and stress scale (DASS-21; Lovibond & Lovibond, 1995); and (5) a physical activity measure (IPAQ-SF; Papathanasiou et al., 2010). To assess skin yellowness and thus carotenoid levels, two readings from the palm of each hand were obtained with a CM-700D Konica-Minolta Spectrophotometer, using the *b** axis measure (Stephen, Coetzee & Perrett, 2011).

Participants were then given the major study tasks in the following sequence: (1) The Palatable Food Cue task while hungry; (2) Verbal Paired Associates training followed by the

Think/No-Think task, and then lunch; and (3) the Palatable Food Cue task while sated. Each of these tasks, and the lunch meal, were accompanied by additional measures (detailed below), most notably ratings of how hungry, thirsty, full, happy, sad, relaxed and alert they were - in that order - on 120mm line rating scales (anchors Not at all and Very). These ratings were repeated at various intervals throughout the session and are referred to as the hunger/mood ratings set.

Palatable Food Cue task (hungry). After completing the hunger/mood rating set, participants were instructed to place two pieces of sterile dental wadding around their submaxillary and sublingual salivary ducts (under the tongue), as well as placing one piece around each parotid duct (one each side of the upper jaw). The time elapsed from when the final piece of wadding was inserted until the time the last piece was removed was recorded. With the dental wadding in place, participants were then asked to touch, sniff and lick (in that order) each of eight snack food items presented in randomised order. Once participants had completed their interaction with all items they removed the wadding from their mouth and placed it into a bag for weighing.

After participants had rinsed their mouth with water they were presented with a fresh set of the eight snack food items, again in randomised order. Starting with the first item, participants were asked to look at it and judge how much they wanted to eat it using a 120mm line rating scale (anchors Not at all and A lot). This formed our measure of food wanting based solely upon viewing the sample.

They were then asked to taste the sample after which they made two further ratings, both on 120mm line rating scales: (1) How much did you like this food? (anchors Not at all and A lot); and (2) How much more of this food would you like to eat now? (anchors None and A lot). The first of these two ratings formed our measure of liking. The second rating assessed immediate desire for more based upon sensory experience (in contrast to the wanting measure obtained prior to sampling the food that must be based upon memory).

Following a water rinse, participants then repeated this process for each of the remaining snack food items.

Verbal Paired Associates (VPA). Before participants started this phase, they were asked to complete a second set of hunger/mood ratings. The VPA task started with an initial presentation block composed of 26 trials. In each trial, a word pair was presented on the computer screen for 5 s (e.g., table legend). Participants were instructed to read each word pair out loud and try to learn it. In the subsequent four training blocks only the first word of each pair was presented for 5 s (e.g., table), and participants were instructed to say out loud the (not shown) associated word. If they failed to respond within 5 s or their response was incorrect, the correct associate was presented (i.e., legend) and participants were instructed to say the pair out loud. The number of errors was recorded for each training block. The presentation order of the 26 trials was randomised in the initial presentation block and in each of the training blocks.

Think/No-think task. Following completion of the VPA task, the Think/No-Think training started. The 26 pairs used in the VPA task were randomly allocated to four sets: 2 'Practice' pairs, 8 'Baseline' pairs, 8 'Think' pairs, and 8 'No-Think' pairs. The two practice pairs were used to familiarise participants with the procedure. Participants were instructed that when they saw an initial word in green, they were to think of its associated word and to say it out loud (Think word). However, if they saw an initial word in red, they were instructed to suppress thinking of the associated word and to remain silent (No-Think word). No feedback was provided. The 8 Think and 8 No-Think initial words were then presented 7 times each (i.e., 112 trials). These 112 trials was organised into 7 blocks each composed of 16 trials, with each block composed of the 8 Think and 8 No-Think initial words, presented in randomised order. On each trial, the initial word was displayed for 5 s, with a 1-s inter-trial interval. Participants then immediately undertook the first Think/no-think test phase. The first word of each of the 26 pairs was presented for 5 s, all in standard black font.

Participants were told to recall out loud its associated word (including the 'No-Think' words). Order of presentation was random and no feedback was given. A second test occurred at the end of the study, as described later.

Lunch. Participants started by completing the third hunger/mood ratings set. They were then instructed to eat as much of the presented food as they wished and to ask for more if they were still hungry. They were also told that all uneaten food would be thrown away. *Ad libitum* access to cold water was provided throughout lunch.

During the lunch period participants were told not to use electronic devices (all belongings etc., being left in the laboratory vestibule), but were allowed to read magazines provided in the test room while eating. The content of these magazines had been screened to avoid any eating-related or upsetting material. After giving participants their food, the experimenter left the test room, returning 10 min later to see if they would like any more food and to ask the participant to call out when they had finished or if they wanted more. Uneaten food was then removed for later weighing.

Palatable Food Cue task (sated). After completing the fourth hunger/mood ratings set, participants undertook the Palatable Food Cue task again. This was identical to the first test in all respects, with salivation to the 8 snack food items measured first, followed by evaluation (want on looking), consumption, and evaluation (like and want on tasting), of each of the 8 snack food items.

Final measures. Participants started by completing the fifth and final set of the hunger/mood ratings. They were then given a delayed test for the 26 pairs learned earlier in the experiment. The test format was identical to that described above, except that a different randomised presentation order was used.

Participants then completed two questionnaires. The first was the 26-item DFS (Francis & Stevenson, 2013), so that a current measure of dietary saturated fat and refined sugar intake was available for the analysis. The second was the 51-item Three-Factor Eating

Questionnaire, which has established reliability and validity (Stunkard & Messick, 1985), and which was used to collect data on participants' eating-related behaviours and attitudes. Finally, participants' height and weight were measured to assess BMI.

3.1.4 Analysis.

Four sets of variables required square-root transformations to enable parametric analysis – the DASS scores (and the total score), participant age, the energy intake measures (and total energy intake), and the activity measure from the IPAQ.

On the VPA task, each participant had a percent correct score for each block and a learning rate score, calculated as percent correct on Block 4 minus percent correct on Block 1 (VPA Learning rate).

On the Think/No-Think task scores were derived from the two test phases, the initial and the delayed test, which took place at the end of the study. On each test, three scores were computed by calculating the percent correct responses for the 8 Think items, the 8 No-Think items and the 8 Baseline items. A further score was also derived, reflecting the overall magnitude of Think/No-Think related inhibition (collapsing across both tests; [[Think + Baseline]/2] – No-Think]).

Two sets of scores were computed for the Palatable Food Cue task, one for when the test was completed hungry and one when it was completed sated. On both occasions four measures were derived: (1) mean wanting on looking; (2) mean food liking after tasting; (3) mean want more scores after tasting; and (4) salivation rate (in grams per sec). For the first three scores, these were all averaged across the 8 snack food items, and for the fourth, only an aggregate score for all items was available.

Three approaches were taken to analyse these data. The first involved descriptive statistics and zero order correlations between the diet-related variables (i.e., DFS score and the spectrophotometer measure) and the demographic, control, interoceptive and eating-related measures. The second approach was to analyse VPA, Think/No-Think, and Palatable

Food Cue task data, with repeated measures ANOVA, to test for changes over time in outcome measures (i.e., VPA learning, Think/No-Think related inhibition, change in wanting/liking ratings with state). The third approach was to examine sources of variability in the VPA, Think/No-Think, and the Palatable Food Cue task using stepwise regression analyses. It is this third approach that directly addresses the primary and secondary aims identified in the introduction of this chapter.

The selection of predictor variables for each regression model was based upon the following criteria. First, all models contained the main predictor of interest; the DFS diet score, along with basic demographic and control variables. Thus all models started with the following predictors: [1] age; [2] gender; [3] DASS total score (as the three sub-components were highly correlated); [4] PIRS sleep score; [5] activity score from the IPAQ; [6] Restraint score from the TFEQ; [7] Hunger score from the TFEQ; [8] Disinhibition score from the TFEQ; [9] BMI; and [10] DFS (diet) score. Second, this initial set of predictors was then included in a further regression analysis alongside the spectrophotometer measure, to establish whether this displaced the DFS (diet) score, indicating whether it was the absence of fruit and vegetables in the diet, rather than the presence of saturated fat and refined sugar, that might be predictive of performance. Third, for the Palatable Food Cue task regressions, amount of lunch consumed (total in kJ) and the change in hunger across lunch were added into all models, as participants varied in how much they ate and in how much hunger ratings changed across the meal. Fourth, on the two regression analyses establishing links between performance on the Palatable Food Cue task and measures of hippocampal-related learning and memory, we included both our primary measure of hippocampal-related functioning, VPA Learning rate, as well as a secondary measure, namely the Think/No-Think related inhibition score. Finally, we note that it is generally advisable in regression to have at least 5-10 cases per predictor variable, and while all our models fell above the lower bound, a higher ratio would have been more desirable.

3.2 Results

3.2.1 Participant Characteristics, Lunch, Interoceptive and Mood Measures.

Participant characteristics are presented in Table 3.1. There was a significant association between the DFS dietary score and the spectrophotometry measure. Participants reporting diets richer in saturated fat and refined sugar tended to have less yellow skin (beta values), indicative of lower fruit and vegetable intakes. There were some significant associations between participant characteristics, and the diet and spectrophotometry measures. Female participants tended to have lower DFS scores than men, and greater dietary restraint, as measured by the TFEQ. For females, the latter was associated with lower DFS score and yellower skin.

Hunger, fullness and the lunch-related measures are detailed in Table 3.2. Both hunger and fullness ratings significantly changed across Time, $F(4,372) = 239.40$, $MSE = 361.32$, $p < .001$, partial eta-squared = .72, and $F(4,372) = 276.52$, $MSE = 380.30$, $p < .001$, partial eta-squared = .75, respectively. In both cases, there were highly significant linear trends across Time for decreasing hunger, $p < .001$ and for increasing fullness, $p < .001$. There were a number of significant associations between hunger and DFS score, and one with fullness, but none involving the spectrophotometer measure. Hunger ratings tended to be higher and fullness ratings lower in participants reporting a higher DFS score (i.e., more refined sugar and saturated fat).

For energy consumed at lunch, both overall, and for each food-type, there was a tendency for this to be higher in participants reporting a higher DFS score (p's from .061 for total energy intake, .078 for biscuits and .42 for lasagne/ravioli intake).

We also assessed changes in thirst and mood across the study. For thirst, ratings changed across the study, $F(4,372) = 61.36$, $MSE = 492.80$, $p < .001$, partial eta-squared = .40, with progressively decreasing thirst (linear trend, $p < .001$). For mood ratings, happiness ratings significantly increased across the study (linear trend, $p < .001$), sadness ratings

decreased (linear trend, $p < .001$), and participants also reported feeling more relaxed (linear trend, $p < .01$). There were no significant changes in alertness ratings.

Table 3.2. *Descriptive statistics for hunger and fullness ratings across the study and for eating-related variables from the study lunch*

Time Variable	Descriptive statistics Mean (SD)	Variable's correlation with: DFS (Diet)	 Spectrophotometry
Start of the study			
Hunger 1 (mm)	68.1 (29.3)	.16	.14
Fullness 1 (mm)	29.9 (25.5)	-.01	-.05
Prior to memory inhibition testing			
Hunger 2 (mm)	64.2 (25.9)	.32*	-.07
Fullness 2 (mm)	44.9 (24.9)	-.28*	.08
Prior to lunch			
Hunger 3 (mm)	74.4 (26.4)	.31*	.00
Fullness 3 (mm)	38.1 (22.8)	-.09	.11
Lunch consumption			
Lasagne/Ravioli kJ	1799.5 (506.5)	.09	.02
Biscuits kJ	772.3 (800.2)	.20*	-.06
Total kJ	2571.8 (974.0)	.21*	-.02
Post-lunch			
Change in hunger across meal (Hunger 3 – Hunger 4)			
	60.0 (30.9)	.19	.00
Hunger 4 (mm)	14.4 (17.7)	.13	-.01
Fullness 4 (mm)	95.7 (22.5)	-.13	.07
End of the study			
Hunger 5 (mm)	13.5 (16.7)	.15	-.14
Fullness 5 (mm)	100.0 (21.9)	-.15	.08

* $p < .05$

3.2.2 Verbal Paired Associates (VPA)

A one-way repeated measures ANOVA, with Block (first, second, third and fourth training block), entered as the within factor, revealed a significant main effect of Block, $F(3,279) = 327.22$, $MSE = 6.07$, $p < .001$, partial eta-squared = .78, with mean percent correct score increasing linearly across blocks (significant linear trend, $p < .001$; also noting a small cubic component, $p < .01$) – see Figure 3.1.

To determine whether VPA learning rate (percent correct on Block 4 minus percent correct on Block 1) was related to diet, we conducted a stepwise regression analysis. The dependent variable VPA learning rate, with predictor variables, DFS (diet) score, BMI, age, gender, IPAQ total activity score, DASS total score, PIRS sleep score, and Restraint, Hunger and Disinhibition scores from the TFEQ. The final model was significant and is presented in Table 3.3, with DFS (diet) score, TFEQ Disinhibition score, and DASS total score, as predictors. We then repeated this model, but now adding in the spectrophotometer score as a further predictor, but the same regression model emerged again (i.e., the spectrophotometer score was not predictive). Overall, these findings suggest a slower VPA learning rate is associated with higher reported intake of saturated fat and refined sugar (see Figure 3.1).

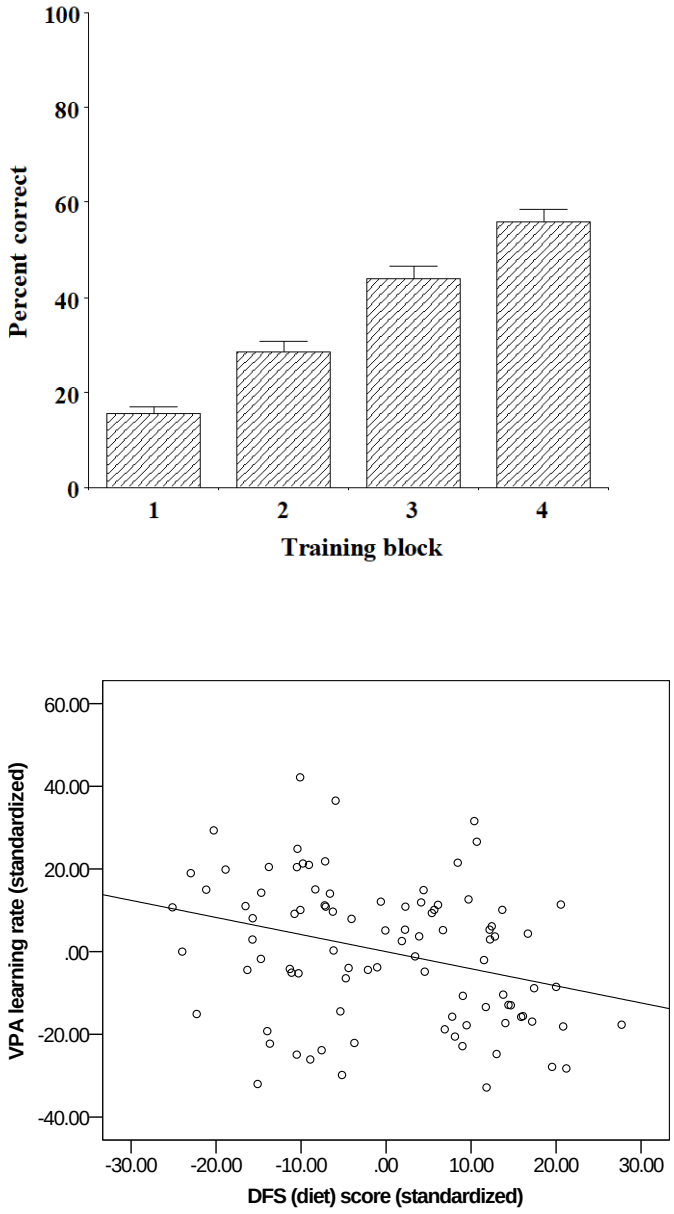

Figure 3.1. Top panel – Mean (and SE) learning rate on the VPA task for all participants (as percent correct) for each of the four training blocks; Bottom panel – Scatter plot of standardised DFS (diet) score and standardised VPA learning rate (Block 4 % correct minus Block 1 % correct) for all participants.

Table 3.3. *Final stepwise regression model predicting Verbal Paired Associates learning rate (final training Block [4] percent correct minus initial training Block [1] percent correct)*

Model Predictor variables	*r* =	S*r* =	Sr^2% =	*p* <
1. (Spectrophotometer included) $F(3,90) = 7.89$, $p < .001$, adjusted $R^2 = .18$				
DFS (diet) score	-.29	-.28	8.1	.005
DASS total	-.21	-.28	7.8	.005
TFEQ Disinhibition score	.23	.28	7.6	.005

3.2.3 Think/No-Think task

A repeated measures ANOVA was conducted with Measure (Baseline vs. Think vs. No-Think) and Time (Immediate test vs. Delayed test) as within factors. The analysis revealed two significant effects. First, Measure, $F(2,186) = 6.59$, MSE = 0.25, $p < .005$, partial eta-squared = .07, with poorest recall in the No-Think condition, relative to the equally trained Think condition, and to the Baseline condition – see Table 3.4. Simple contrasts revealed that the No-Think condition had the poorest recall, relative to the other two conditions (p's < .002), which did not differ. Second, Time, $F(1,90) = 9.22$, MSE = 0.34, $p < .005$, partial eta-squared = .09, with percent correct recall improving slightly from the initial to the delayed test (see Table 3.4).

Table 3.4. *Think/No-Think task testing scores*

Measure	Initial test Mean % correct (SD)	Delayed test Mean % correct (SD)
Think	65.0 (26.3)	66.3 (26.3)
No-think	58.8 (26.3)	61.3 (28.8)
Baseline	65.0 (27.5)	67.5 (27.5)
Inhibition effect*	6.2 (14.5)	5.6 (15.7)

Note: Think/No-Think score was calculated as ((Think + Baseline)/2) – No-Think

We then tested whether performance on the Think/No-Think task (see Table 3.4 – but collapsing across the initial and delayed test), could be predicted by participants dietary self-reports and other variables, again using stepwise regression. The dependent variable was the memory inhibition score derived from the Think/No-Think task, with predictor variables as described above. The final model was significant with just one predictor remaining in the model, IPAQ total activity score – see Table 3.5. Repeating this model by adding in spectrophotometer scores did not change the outcome, which indicated that larger inhibition scores were observed in participants who reported greater levels of physical activity. Finally, we note that participants varied in how much they had learned the word pairs (on the VPA task) before starting the Think/no-think task. However, we could find no evidence that this affected participants' memory inhibition effect.

Table 3.5. *Final stepwise regression model predicting the inhibition effect (collapsing across the initial and delayed tests) from the Think/No-Think task*

Model Predictor variables	*r* =	S*r* =	Sr^2% =	*p* <
1. (Spectrophotometer included) $F(1,92) = 4.25$, $p < .05$, adjusted $R^2 = .03$				
Activity	.21	.21	4.4	.05

3.2.4 Palatable Food Cue task

Self-report measures. Participant evaluations of the palatable foods were analysed using a two-way repeated measures ANOVA, with State as one factor (Tested hungry vs. Tested sated) and Measure as the other (Want to eat [on looking] vs. Liking [after tasting] vs. Want more [after tasting]), with the data illustrated in Figure 3.2. The ANOVA revealed main effects of State, $F(1,93) = 175.96$, MSE = 546.03, $p < .001$, partial eta-squared = .65, and Measure, $F(2,186) = 143.65$, MSE = 109.58, $p < .001$, partial eta-squared = .61, which were qualified by an interaction between State and Measure, $F(2,186) = 54.08$, MSE = 46.72, $p < .001$, partial eta-squared = .37. To determine the source of the interaction effect, the three difference scores across State (Tested hungry minus Tested full) for each Measure (Want to eat [on looking] vs. Liking [after tasting] vs. Want more [after tasting]) were compared. As suggested in the Introduction, want to eat scores on looking at the food fell significantly more with the change of State than liking scores, $p < .001$. Want more scores after tasting the snack also decreased more across State, than liking scores, $p < .001$. Finally, want more after tasting scores fell further across State than want to eat on looking scores, $p < .05$. So while

all evaluations declined when tested sated, this decrease was greater for both wanting ratings than for the liking rating.

We then tested our primary aim, namely whether the state-dependent difference in wanting ratings made when *looking* at the food, relative to the liking rating made after tasting it, could be predicted by dietary variables. In addition to the predictor variables used before, two further predictors were now included: Change in hunger across lunch, and the amount of energy consumed at that meal. The final significant model, which included the DFS (diet) score, is presented in Table 3.6. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model. As illustrated in Figure 3.2, want to eat ratings - relative to liking ratings after tasting - were *less affected* by state in participants who consumed diets richer in saturated fat and refined sugar. To make this effect more vivid, in Figure 3.3 we present data (liking and wanting ratings made when hungry and replete) from just the dietary extremes of our sample – the top and bottom 20% on DFS (diet) score. As can be seen, want to eat on looking scores, relative to liking, change less across state in those who routinely eat the most saturated fat and added sugar. Thus, state may be less able to moderate retrieval of pleasant food-related memories in participants who frequently consume diets rich in saturated fat and refined sugar.

Finally, we examined the sources of variability in the other major component of the Time by Measure interaction, namely the relatively larger decline in wanting more after tasting, relative to liking. The same stepwise regression approach was used with the same predictor variables. The final model was significant, $F(2,91) = 14.10$, $p < .001$, adjusted $R^2 = .22$, with two predictors remaining in the model. These were change in hunger, $Sr = .42$, $Sr^2\% = 18.1\%$, $p < .001$ and sleep quality score, $Sr = .24$, $Sr2\% = 5.5\%$, $p < .02$. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model.

Table 3.6. *Final stepwise regression model predicting the change in liking relative to the change in wanting to eat ratings across state (hungry minus full), on the Palatable Food Cue task*

Model Predictor variables	*r* =	S*r* =	Sr^2% =	*p* <
1. (Spectrophotometer included) $F(3,90) = 15.41$, $p < .001$, adjusted $R^2 = .32$				
Change in hunger	.38	.43	18.5	.001
PIRS (Sleep quality)	.35	.34	11.7	.001
DFS (diet) score	-.19	-.26	6.7	.005

Saliva measure. Salivation rate significantly increased between the hungry and sated tests from a M = 0.038 g/sec (SD = 0.009) to M = 0.049 g/sec (SD = 0.011), $t(93) = 12.21$, $p < .001$, $r^2 = .61$. We tested to see if change in salivation rate between the hungry and sated states could be explained by any of the predictor variables used in the preceding regression analyses, but there were no significant models.

We then checked to see if change in salivation rate across states was associated with the aggregate self-report measures (i.e., main effect of Time), after partialling out the amount of energy consumed at lunch and changes in hunger across the meal. Greater salivation in the sated state (relative to the hungry state) was associated with smaller reductions in liking and wanting (i.e., main effect of Time), $r_{12.34}(90) = -.22$, $p < .05$, providing some validation for the self-report ratings. The three parts of the interaction effect for the self-report data were not significantly associated with change in salivation rate between internal states (*r*'s < .14).

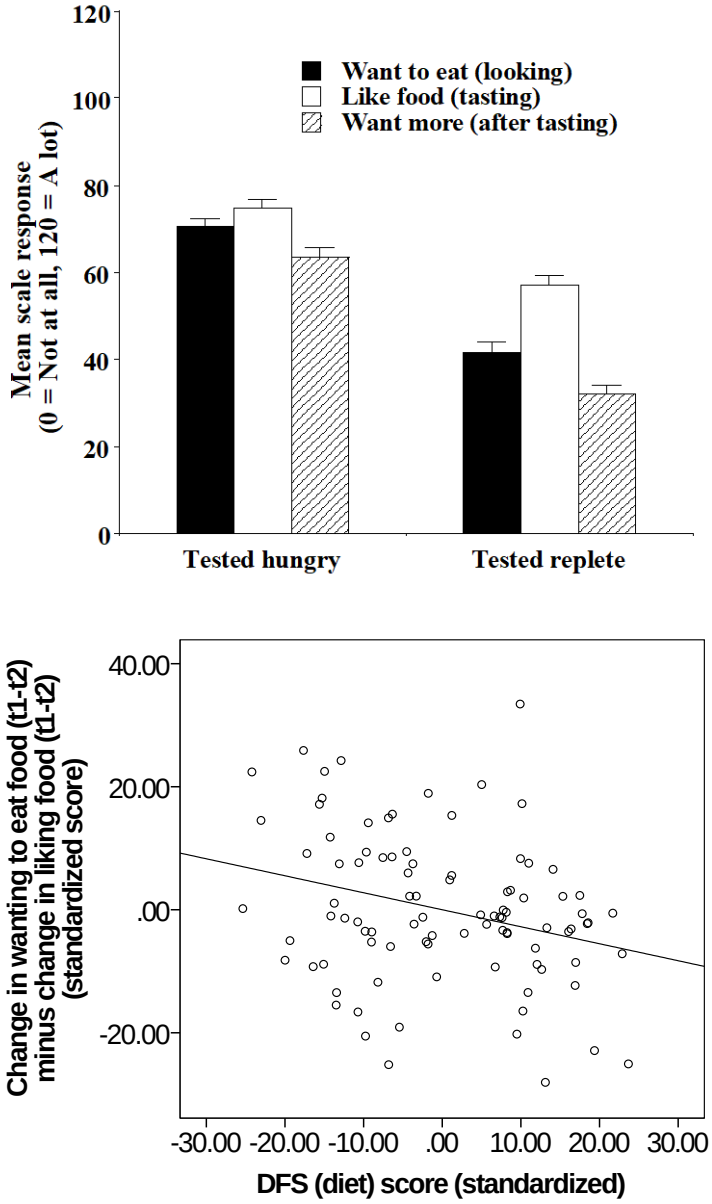

Figure 3.2. Top panel – Mean (and SE) wanting (on seeing), and liking and want more ratings (after tasting) in all participants obtained before and after lunch; Bottom panel – scatter plot of standardised DFS (diet) score and standardised change in wanting relative to liking across state (i.e., Food Memory Inhibition effect) for all participants.

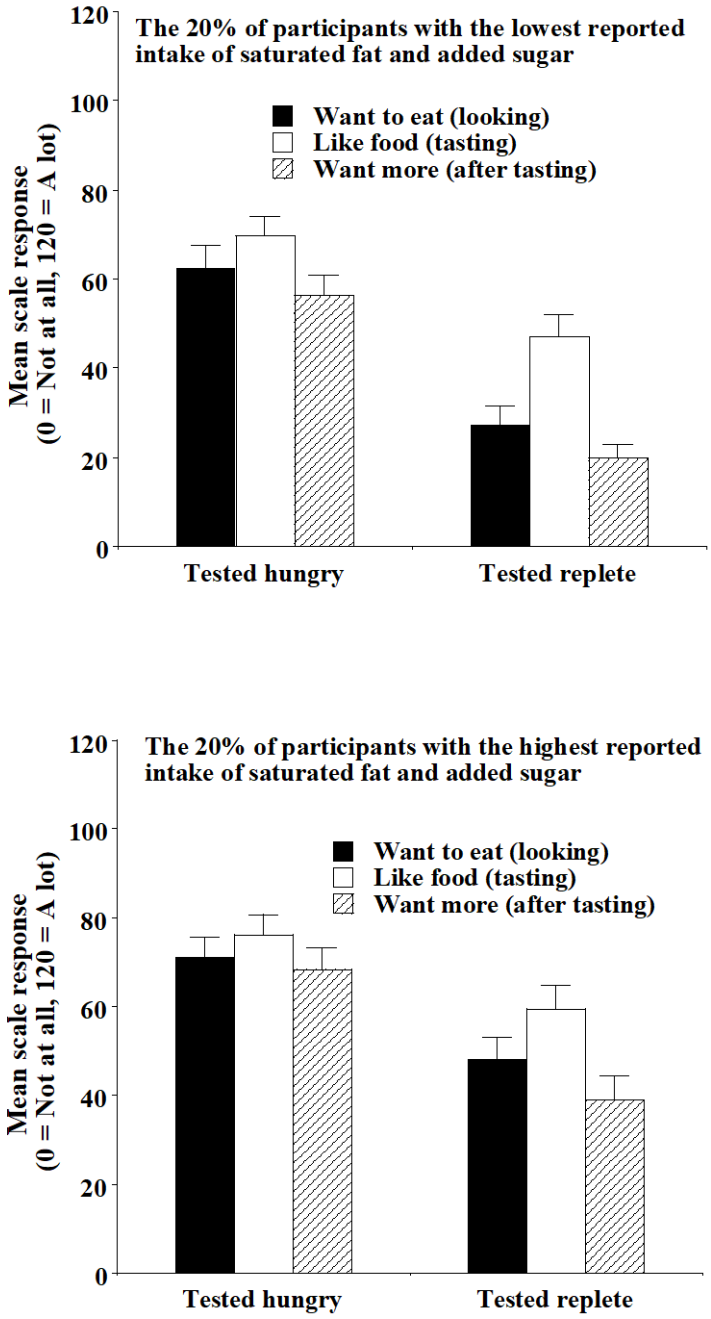

Figure 3.3. Top panel – Mean (and SE) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the *lowest* reported intake of saturated fat and sugar, obtained before and after lunch; Bottom panel – Mean (and SE) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the *highest* reported intake of saturated fat and sugar, obtained before and after lunch.

3.2.5 Relationship between VPA and Think/No-Think tasks and the Palatable Food Cue task

If hippocampal-related processes contribute to participants' desire to consume food via state-dependent inhibition of food-related memories, then performance measures from the VPA and Think/No-Think tasks should explain individual variability in changes in wanting and liking between the hungry and sated states. In addition, to the extent that such measures tap hippocampal process more directly than diet, they should displace diet-related predictors on the Palatable Food Cue task findings. To test this, we conducted two further regression analyses, examining each major component of the Time by Measure interaction from the Palatable Food Cue task. The primary hippocampal-related predictor was VPA learning rate and the secondary predictor being Think/No-Think inhibition score, noting that these two variables did not significantly correlate, r = -.05.

The dependent variable for the first regression was the difference across states between the wanting rating made when looking at the food, relative to the liking rating made when eating it. As can be seen in Table 3.7, VPA learning rate during training was the best predictor, displacing DFS diet score from the model (contrast with Table 3.6). Repeating this model by adding in spectrophotometer scores led to the same outcome. Overall, this suggests that state-dependent changes in wanting scores when just *looking* at palatable food - relative to liking scores when that food is actually consumed – are strongly predicted by how quickly participants learned the verbal paired associates, which in turn was shown earlier to be associated with reported dietary intake of saturated fat and refined sugar.

Table 3.7. *Final stepwise regression model predicting the change in liking relative to the change in wanting to eat ratings across state (hungry minus full), on the Palatable Food Cue task, now including VPA learning rate and the inhibition score from the Think/No-Think task*

Model Predictor variables	*r* =	S*r* =	Sr^2% =	*p* <
1. (Spectrophotometer included) $F(4,89) = 16.10$, $p < .001$, adjusted $R^2 = .39$				
VPA learning rate	.41	.36	13.0	.001
Change in hunger	.38	.36	13.0	.001
PIRS (Sleep quality)	.35	.35	12.0	.001
Age	.07	.17	2.9	.05

Finally, we examined sources of variability in the other major component of the Time by Measure interaction, namely the relatively larger state-dependent decline in wanting more after tasting, relative to liking. This regression analysis produced the same outcome as the one described earlier (an identical model – predictors change in hunger and sleep quality), with no significant involvement of either hippocampal-related performance measure.

3.3 Discussion

The primary question addressed by this study was whether state-dependent reductions in wanting for palatable snack foods (relative to state-dependent reductions in liking for palatable snack foods) were: (1) less affected in consumers of a HFS diet; and (2) mediated by hippocampal-related processes. Consistent with expectation, the difference between wanting and liking responses between the hungry and sated states was smaller for habitual consumers of a HFS diet. We also found, again as predicted, that these diet-related

impairments in wanting according to state were significantly predicted by VPA learning rate but not by the memory inhibition score from the Think/No-Think task.

There were several important ancillary findings: (1) VPA learning rate was associated with greater consumption of a HFS diet, replicating previous findings of associations between tests sensitive to hippocampal-related function and diet in healthy young people (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011); (2) greater consumption of a HFS diet was associated with smaller changes in hunger and fullness, that is reduced interoceptive sensitivity also as observed before (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011); (3) greater energy intake on test lunch tended to be linked with greater HFS dietary intake (Francis & Stevenson, 2011); (4) reduced skin yellowness, indicating lower intake of fruits and vegetables, was associated with greater consumption of a HFS diet; and (5) skin yellowness was not a significant predictor of hippocampal-related processes, suggesting that the *absence* of fruits and vegetables was not a driving factor in diet-related cognitive performance. Finally, while we found that salivation rate was related to overall changes in wanting and liking between the hungry and sated state, it was not associated with diet or hippocampal-related processes.

While the present findings are consistent with evidence linking diet to hippocampal function in humans (e.g., Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011; Jacka et al., 2015), it is the links between diet, hippocampal memory performance and wanting that are of central importance. Specifically, those with a diet richer in saturated fats and refined sugars reported smaller changes in wanting scores across state *relative* to liking scores. Since wanting (i.e., incentive salience) has a memorial component and should vary as a function of physiological state, it is plausible that it is an impairment in this process, which is driving these smaller changes in wanting relative to liking across state in HFS diet consumers. We therefore suggest that, in line with the model proposed by Davidson et al. (2005), this finding reflects poorer inhibition of pleasant food-related memories when sated.

We also predicted earlier that state-dependent changes in liking should be less affected by any adverse impacts to hippocampal-related learning and memory, as liking is driven more by the direct sensory experience of the food (Robinson & Berridge, 2000) rather than by any memories of it. Importantly, the change between states was significantly larger in wanting relative to liking, and this interaction was predicted by dietary intake of fats and sugars (see Table 3.6) and performance on the VPA task (see Table 3.7) – suggesting hippocampal mediation. Future research could include non-hippocampal-dependent cognitive measures to confirm the specificity of this finding exclusively to the hippocampus.

One potential implication of the wanting and liking findings is that in habitual consumers of a HFS diet physiological state should have less regulatory importance, resulting in desire-driven eating whenever palatable food cues are encountered (e.g., Lowe & Butryn, 2007). Another potential implication of these findings relates to the 'vicious circle' model of obesity (Davidson et al., 2005). Here, disruption of hippocampal inhibitory control over food-related behaviours can heighten the risk of further overconsumption of the same foods that initially contributed to hippocampal dysfunction, promoting weight gain. Findings from animals provide support for this model (Davidson, Kanoski, Schier, Clegg & Benoit, 2010; Kanoski, Meisel, Mullins & Davidson, 2007; Kanoski & Davidson, 2010). The present results are consistent with the vicious circle model of obesity and may aid understanding of appetite control and overconsumption. Nonetheless, while we argue here that a diet rich in saturated fat and added sugar impairs, via hippocampal processes, the ability to use satiety to inhibit pleasant food-related memories, an alternative interpretation is also plausible. Individuals more prone to palatable food intake may be more likely to eat when sated and to choose high-fat high-sugar foods. While we suggest this latter possibility is plausible due to the correlational nature of our study, the former interpretation seems more likely given what is known from animal data.

An unexpected finding was that performance on the Think/No-Think task was unrelated to HFS diet intake and to VPA learning rate. Moreover, there was also no relationship between the changes in wanting/liking across state and memory inhibition score from the Think/No-Think test. If these processes are all mediated by the same brain area – and fMRI data suggests that memory inhibition on the Think/No-Think task *is* (Anderson et al., 2004) – we would expect performance on these measures to be related. Since such relationships were not observed, one possibility is that other neural processes may be important in the Think/No-Think task. There are two reasons for this assertion. First, while state-dependent changes in wanting/liking do not require explicit instruction to occur, the Think/No-Think task involves explicit (i.e., strategic) direction to inhibit or rehearse stimuli. Second, the strategic nature of the Think/No-Think task has been illustrated experimentally, as substituting an associated word instead of suppressing it, leads to markedly different memory recall when tested later (Racsmány, Conway, Keresztes & Krajcsi, 2012; del Prete, Hanczakowski, Bajo & Mazzoni, 2015). Nonetheless, a further alternative explanation also needs to be considered in light of the fact that fMRI data indicates that performance on the Think/No-Think task is associated with hippocampal activation (Anderson et al., 2004). It is possible that the Think/No-think task may be insensitive to diet-induced affects relative to other hippocampal-related tasks (i.e., VPA). Indeed, this could be potentially important as it would imply that not all hippocampal-related measures are equally sensitive to diet-induced change.

The spectrophotometer findings suggest that the hippocampal-related memory performance is not linked to reduced intake of fruit and vegetables, but rather to greater consumption of a HFS diet. There are several implications from this finding. First, the inverse association between skin yellowness and scores on the DFS scale provide further external validity, as greater saturated fat and sugar intake is usually associated with reduced fruit and vegetable intake (Cordain et al., 2005; Kearney, 2010). While further research is

required, this points to the potential utility of the spectrophotometer as a simple indirect measure of diet quality. Second, it suggests that it is the presence of saturated fat and added sugar – as in animals – that is problematic, rather than the absence of fruit and vegetables. This implies that a diet containing significant amounts of fruit and vegetables may not be protective against a diet that is also high in saturated fat and added sugar.

Several control variables emerged as significant predictors of either VPA learning rate, the Think/No-Think memory inhibition score or for the Food Memory Inhibition effect. While depression, stress, and anxiety have all been found before to be associated with hippocampal volume and/or function (e.g., Videbach & Ravnkilde, 2004), four associations were more surprising. First, physical activity was associated with the Think/No-Think memory inhibition score. We included a measure of physical activity because this is known to increase hippocampal volume and function (Erickson et al., 2011; Pereira et al., 2007). This in turn would suggest that memory inhibition performance on the Think/No-Think task was in fact supported by the hippocampus, something we argued earlier was not in fact the case. However, physical activity is in fact associated with improvements across many cognitive domains and brain areas, and the largest effects (on meta-analysis) are seen for tasks that involve executive function (Hillman, Erickson & Kramer, 2008).

A second association was observed between TFEQ Disinhibition score and VPA learning rate. TFEQ Disinhibition was positively associated with BMI, TFEQ Restraint and TFEQ Hunger, all of which have been found before to relate to measures sensitive to hippocampal-related measures of learning and memory (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011). Third, we found that both increasing age and poorer sleep were associated with larger reductions in wanting (relative to liking) across state, effects that were unlikely to be related to hippocampal-related processes, since VPA learning rate was also included in this model. Thus, older age and poorer sleep - in the context of a young and

healthy sample - reflect some other as yet unknown factors associated with better food-related memory inhibition.

We have shown here that HFS dietary intake is not only associated with poorer hippocampal-related memory performance as indexed by VPA learning rate, but also with poorer inhibition of food-related wanting when sated. Our findings suggest that hippocampal-related processes are involved in energy regulation apparently in much the same way as suggested by animal models (Davidson et al., 2005; Davidson et al., 2014), irrespective or not of whether habitual consumption of a HFS diet causes (or is a consequence of) poorer hippocampal function. While causality cannot be inferred here, the results from this study provide the first piece of evidence in humans to parallel those from animals linking a HFS diet, impaired hippocampal function, less efficient state-dependent inhibition of food seeking behaviours and hence enhanced susceptibility to excess energy intake.

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Chapter 4: A systematic review of longer-term dietary interventions on human cognitive function: emerging patterns and future directions

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A systematic review of longer-term dietary interventions on human cognitive function: emerging patterns and future directions

Cognitive function describes a variety of processes that allow humans to perceive, evaluate, store, manipulate and respond appropriately to information from internal and external sources. Obesity, independent of its associated medical comorbidities, is significantly associated with impaired cognitive function, especially in elderly adults (Smith, Hay, Campbell, & Trollor, 2011). A review by Fitzpatrick, Gilbert and Serpell, (2013) indicated that obese individuals are impaired on measures of decision-making, planning and problem solving, with fewer difficulties on tasks of verbal fluency and learning and memory. Moreover, important links have been established between midlife obesity and elevated risk for later onset of dementia (Fitzpatrick et al., 2009). While studies are generally supportive of the links between obesity and cognitive impairment and dementia, there are still significant inconsistencies within and across different cognitive domains (Fitzpatrick et al., 2009), suggesting some factor other than obesity might be affecting cognitive function.

While other researchers have focused on other influences on cognition such as physical activity (Hillman, Erickson & Kramer, 2008) or micronutrients (de Jager et al., 2014), there is now accumulating evidence that cognitive function may be influenced as much by diet, as by obesity itself. Diet refers to the habitual pattern of long-term intake of particular foods. Researchers readily extract from this total energy intake and typically fractionate this into energy derived from its macronutrients - fats, proteins and carbohydrates. We acknowledge that while others have emphasised the importance of the effects of micronutrients on cognition over a period of years (e.g. de Jager et al., 2014; Parletta, Milte & Meyer, 2013; Otaegui-Arrazola, Amiano, Elbusto, Urdaneta, & Martínez-Lage, 2014), here we focus solely on the experimental studies that have manipulated either total energy intake, macronutrient content, or both. Since macronutrients differentially affect memory and attention at the post-prandial level (e.g. Jones, Sünram-Lea & Wesnes, 2012), then these

areas of cognition may be affected by the macronutrient profile of a diet over longer periods ranging from days to months. Importantly, diet may act on particular areas of cognition in different ways, with some more important than others. Understanding which areas of cognition are most susceptible to the effects of diet may have important consequences for long-term prevention and treatment of cognitive impairment, including neurodegenerative disease. For instance, a meta-analysis by Grant (1997) on 18 community-based epidemiological studies drawn from the total food supply data of 11 countries found a link between diet and neurodegenerative disease (See Figures 4.1 and 4.2). Despite potential inflation of results due to food supply data not accounting for food wastage, spoilage etc., these figures nonetheless indicate that for every per capita additional gram of fat or calorie consumed daily, one might expect an average increase of 0.03% and 0.003%, respectively, in AD prevalence in the population of adults 65 years or older. For instance, a 0.3% increase in AD prevalence would be associated with a daily increase of either 10g of fat or 100 calories. Regression analyses revealed very strong positive relationships between the prevalence of Alzheimer's disease (AD), and total energy and fat intake (r^2 = 0.932 and 0.880, respectively) in the population of adults 65 years or older, suggesting that certain elements of one's diet (especially total energy intake and fat intake, as the data show) may be one of several contributing factors in the prevalence of neurodegenerative disease. While the findings of Grant (1997) are enticing, there is need for caution as evidence of the relationship between diet and cognition is still emerging.

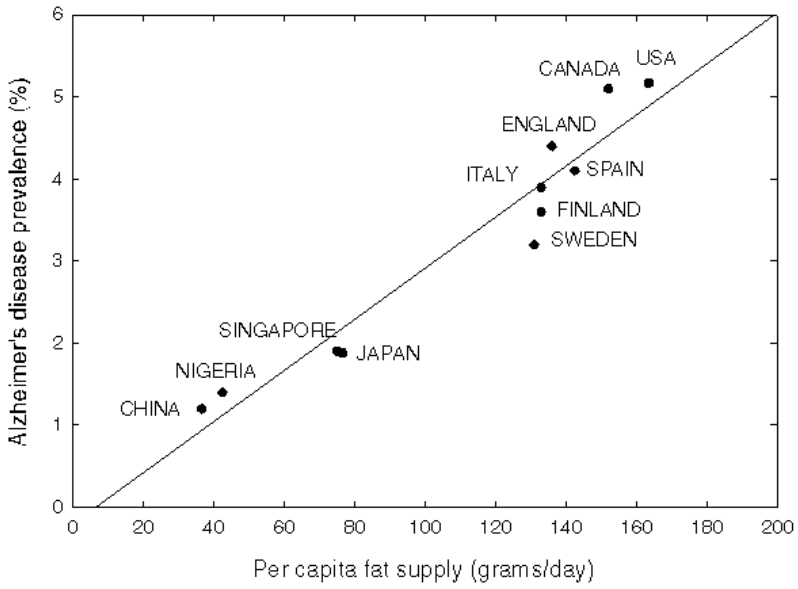

Figure 4.1. Taken from Grant (1997), the scatter plot of Alzheimer's disease prevalence versus fat supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate = -0.203 + (0.0312*fat (grams/day))).

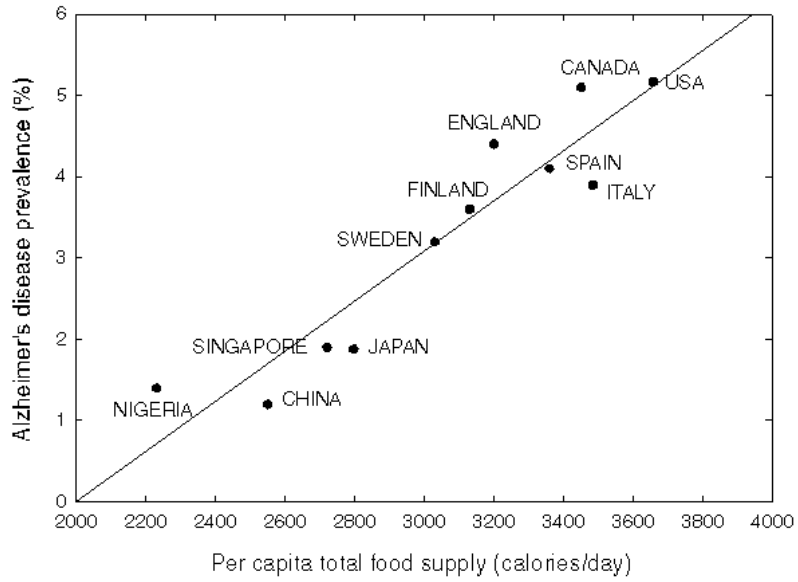

Figure 4.2. Taken from Grant (1997), the scatter plot of Alzheimer's disease prevalence versus total food supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate = -6.178 + (0.00309*(total calories/day))).

Other researchers have similarly concluded that a diet high in saturated fats and refined sugars – the so-called "Western diet" – increases the risk of AD (Berrino, 2002), while a diet low in saturated fats and refined sugars, and high in polyunsaturated (PUFAs) and monounsaturated fats (MUFAs) – the "Mediterranean diet" decreases the risk of AD (Lourida et al., 2013). Indeed the Mediterranean diet - typically high in fish, nuts, and antioxidant-laden fruits and vegetables has been of great interest as it may be effective for weight loss maintenance (Panagiotakos, Chrysohoou, Pitsavos, & Stefanadis, 2006) and because of possibly beneficial effects on cognitive function. That saturated fat may be an independent risk factor for impaired cognition has now emerged in several correlational studies. Higher saturated fat intake is associated with: (1) impairments in speed, mental flexibility and memory in individuals older than 55 years (Kalmijn et al., 2004); (2) poorer global cognitive function and memory in older adults (Eskelinen et al., 2008); and (3) impairments in delayed memory, working memory and verbal fluency in women with type-2 diabetes (Devore et al., 2009).

Part of the reason for interest in saturated fat alone and in combination with added sugar derives from the extensive animal literature examining the impact of these macronutrients on cognition. Diets rich in saturated fat and added sugar (HFS diets) specifically impair cognitive performance associated with brain regions implicated in memory, inhibition and the regulation of food intake – the hippocampus and possibly the prefrontal cortex (Davidson, Kanoski, Walls & Jarrard, 2005). The prefrontal cortex is involved in inhibition and executive function (Anderson et al., 2004), while the hippocampus has a well-established role in memory function, with damage to this structure affecting memory function and interoception (Hebben, Corkin, Eichenbaum, & Shedlack, 1985). Animals show impairments in hippocampal-dependent tasks following a diet high in fat (Morrison et al,. 2010), sucrose (Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney & Corbit, 2013), and both refined sugar and saturated fat (Beilharz, Maniam & Morris, 2014; Molteni,

Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). In humans, cross-sectional studies have revealed that higher reported HFS intake is associated with a reduced sensitivity to internal signals of hunger and satiety and impaired performance on hippocampal-dependent memory tasks in normal-weight adults (Francis & Stevenson, 2011) and young children (Baym et al., 2014). These findings suggest that diet-induced impairments in hippocampal-related interoception and memory may precede weight gain and obesity. Dietary intake of fat and sugar, which is high in the Western diet and low in the Mediterranean diet, could potentially be one factor in explaining the links between obesity and cognitive impairment.

While cross-sectional data have generally shown a positive relationship between consumption of an HFS diet and poorer memory function in humans, there is preliminary evidence showing that other cognitive domains including executive function might also be affected (Nyaradi et al., 2014; Torres et al., 2012). Some experimental studies have shown that performance on measures of executive function improve following short-term (McMillan et al., 2011) and long-term (Martínez-Lapiscina et al., 2013a) adherence to a Mediterranean diet. Similarly, a prospective cohort study of 1410 elderly adults revealed that higher adherence to a Mediterranean diet was associated with slower cognitive decline, as measured by the Mini Mental Status Examination (MMSE) (Féart et al., 2009).

Animal studies of diet-cognition relationships have the major advantage of being able to demonstrate causal links between changes in cognitive performance and diet (e.g. Molteni et al., 2002). While a similar causal route could also apply to humans, most studies investigating the effects of diet on cognition have been cross-sectional (e.g. Baym et al., 2014; Francis & Stevenson, 2011), longitudinal (e.g. Eskelinen et al., 2008) or cohort studies (e.g. Barberger-Gateau et al., 2007). Correlations cannot imply causality since other extraneous factors may be involved, but research that is based on experimental evidence makes a causal inference far more plausible. To date, the relationship between diet and cognition in humans remains causally ambiguous.

The main objective of this manuscript is to review the limited experimental evidence of the link between diet and cognition in humans. We focus solely on human experimental studies that have tested the longer-term effect of diet on cognition. Many of the papers we review here were not motivated to collect cognition-related data because they had strong a priori reasons to do so (i.e., they were not premised on the animal literature referred to here), and indeed, in many cases cognitive-related data seems to have been an auxiliary aim of these studies. This review draws together the highly varied research in an effort to identify potential emerging patterns in the data linking diet to cognitive performance.

4.1 Method

Electronic literature searches were conducted between September 2013 and January 2014 using the following databases; PsycInfo, the Cochrane Central Register of Controlled Trials (CENTRAL), and Medline (PubMed). Manual searches were also run using smaller search engines (e.g. Google Scholar) to update the literature as much as possible. Search words represented terms utilised in other reviews in the area as well as words deemed appropriate by the authors. The following search terms were used in various combinations to find relevant articles: “diet”, “dietary pattern”, “energy”, “macronutrient”, “fat”, “protein”, “carbohydrate”, “intake”, “calori*”, “sugar”, ” intervention”, “cogniti*”, “memory”, “executive function”, “impair*”, “neurocog*”, “psych*”, “attention”, “hippocamp*”, “neurocog*”, “healthy”, “obese”, “overweight”, “lean”, “BMI” and “weight”. Relevant studies cited in review articles or articles identified through the search were also considered and retrieved in a manual search.

4.1.1 Inclusion and Exclusion Criteria

An initial search using the above search terms yielded 4141 articles. An initial screen of title and abstract of each paper was conducted, yielding a total of 87 full text articles retrieved for further review and determination of eligibility. Articles were included if

researchers manipulated or advised on intake of energy and/or macronutrient content (fat, protein, or carbohydrate) for a period longer than 24 hours (i.e. not post-prandial), did not completely deprive participants of food, assessed cognitive function using validated measures, and tested adults only (≥18 years) across the entire adult lifespan. Additionally, only articles written in English were considered while there were no restrictions on publication year. Application of these criteria yielded 32 research articles applying to 30 different dietary interventions (two articles were longitudinal follow-up studies). Three studies included an additional group that altered diet and exercise (Martin et al., 2007; Smith et al., 2010) or deprived energy completely (Lieberman et al., 2008), so only the findings from the appropriate diet manipulation groups were used.

Across the literature, the groups of individuals tested vary significantly (e.g. obese adults, frail elderly, or healthy men only), but these have been grouped together here for practical reasons. We posit that any potential differences between groups in cognitive performance associated with age or health status are of minor importance to the overall pattern since the magnitude, but not the direction, is likely to vary between different groups of individuals. Indeed, some groups may be more vulnerable to dietary changes than others, but the highly varied nature of the current literature makes it difficult to discern any meaningful pattern. Due to the inadequate reporting of cognitive outcomes and their effect sizes, as well as a distinct lack of nutritional breakdown of each diet in some studies, this paper provides a qualitative review of the experimental evidence of the link between diet and cognition. The effect sizes of cognitive outcomes and nutritional information of each diet will be reported when possible. The summary tables in this review were constructed and organised based on intended dietary targets of each study (e.g. low-fat) rather than reported dietary intakes, since in many cases dietary adherence varied. For instance, despite imposing restrictions only on carbohydrate intake, Krikorian et al. (2012) reported significant differences in total energy intake between groups and over the intervention period.

4.2 Findings by cognitive domain

Broadly, the review has been organised into two sections based on cognitive domains: (1) memory (working, long-term verbal, and long-term visual-spatial memory) and (2) other cognitive domains (global cognitive function, executive function, attention, & information processing speed). Of the diet intervention studies reviewed here, 23 assessed memory and 31 assessed other cognitive domains. This split is made on both organisational grounds, but also because memory processes, and especially long-term ones are of special interest, given the human and animal literature mentioned above.

4.2.1 Memory

While it has been established that memory tasks are most sensitive to macronutrient intake at the post-prandial level (Hoyland, Lawton & Dye, 2008), the longer-term experimental evidence has not been reviewed. We have divided the following section into three sub-components – working memory, visual-spatial memory, and long-term verbal memory. Working memory refers to the system used to keep things in mind while performing complex tasks such as reasoning, comprehension and learning (Baddeley, 2012). Visual-spatial memory is responsible for recording information about one's environment and its spatial orientation. While working memory persists only for around thirty seconds, long-term verbal memory involves storage and retrieval of information from several minutes to decades. Additionally, long-term verbal and visual-spatial memory systems appear to be mediated chiefly by the hippocampus (Van Petten, 2004), and may be particularly susceptible to diet-induced damage (Walsh & Emerich, 1988) and thus requires more detailed consideration. The effects of diet on these sub-components of memory have been summarised in Table 4.1.

4.2.1.1 Working memory

To date, research has only studied the impact of decreases in energy intake on working memory (WM), while the impact of increasing energy intake is unknown. Research has yielded mixed findings. A 30% energy-restricted diet (6300kJ – 6600kJ/ day) either high (45%) or low (4%) in carbohydrate content led to improvements in numerical WM (digit span backwards) after 8 weeks (Halyburton et al., 2007) and 1 year (Brinkworth, Buckley, Noakes, Clifton & Wilson, 2009). A common measure of numerical WM storage capacity, digit span backwards requires participants to recall a series of digits in reverse order of initial presentation. Since numerical WM performance did not vary as a function of macronutrient manipulation at both time points, the restriction in energy intake likely explains this improvement. However, in the absence of an appropriate control group, it was unclear whether the improvements in WM were due to the restricted energy intake or due to repeated administration of the test (practice effect).

Martin et al. (2007) found that non-numerical WM performance improved following a six-month 25% energy-restricted diet (6500kJ/day) and a low-energy diet (3700kJ/day, but effect sizes were small *(η^2 <0.07)*. Since there was a significant effect of time and WM performance in the diet group did not differ from the control group, improvement over time likely reflected a practice effect. Indeed, other studies involving similar energy restrictions (Bryan & Tiggemann, 2001 – 20%; Pearce, Noakes, Wilson & Clifton, 2012 – 30%; Witte, Fobker, Gellner, Knecht, & Flöel, 2009 – 30%) and even of longer duration (Cheatham et al., 2009 – 30%) did not find any significant changes in WM performance.

There is only limited evidence that WM performance is influenced by dietary macronutrient content. Working memory is unaffected by changes in protein (Lindseth et al., 2011; Van Der Zwaluw et al., 2014), while there have been mixed findings with carbohydrate intake. The processing of carbohydrates affects short-term glycaemic control and cognition (Benton et al., 2003) and may influence long-term cognition and brain function since some

brain areas, such as the hippocampus, have insulin receptors (Stangl & Thuret, 2009). Glycaemic index (GI) ranks carbohydrates according to their effect on blood glucose levels. Cheatham et al. (2009) found that varying dietary GI did not affect WM in healthy overweight adults over six months [High GI (Energy (E): 7900kJ; Protein (P): 20%; Fat (F): 20%; Carbohydrate (C): 60% (GI = 85.6)) vs. Low GI (E: 7900kJ; P: 30%; F: 30%; C: 40% (GI = 52.4))]. Similarly, Smith et al. (2010) found no changes in WM following adherence to the high-carbohydrate Dietary Approaches to Stop Hypertension (DASH) diet (E: 8209kJ; P: 19%; F: 28%; C: 55%) relative to a usual diet control group.

Severe restriction of carbohydrates may have deleterious effects on WM. Although the nutritional information was not reported, D'Anci, Watts, Kanarek & Taylor (2009) compared a three week low-carbohydrate diet based on *The Atkins* (1998) program to a high-carbohydrate diet based on the American Dietetic Association (ADA) recommendations (E: 8368kJ; P: 18%; F: 29%; C: 55%). Following a week of severe carbohydrate restriction, low-carbohydrate dieters recalled fewer digits on the digit backwards task compared to the ADA dieters, while there were no differences in the less cognitively demanding digit forwards task. Importantly, the difference in WM performance between the energy-matched diets was likely due to the severe restriction of carbohydrate since diet-induced impairments were not evident following the reintroduction of carbohydrates at weeks 2 and 3 of the diet (D'Anci et al., 2009).

Since the low-carbohydrate Atkins-like diet (D'Anci et al., 2009) was also high in total fat, it may be that increasing total fat, rather than decreasing carbohydrate content was responsible for the impairments in WM. However, this seems unlikely since no differences were found in WM performance when comparing a high-fat to a high-carbohydrate diet. Halyburton et al. (2007) compared the effects of a high-fat, low-carbohydrate diet ((E): 6636kJ/day; (P): 33%; (F): 61% (21% Saturated fat (SFA)); (C): 4%) to a high-carbohydrate, low-fat diet (E: 6319kJ/day; P: 23%; F: 26% (5.6% SFA); C: 45%) on WM in overweight

and obese participants over a period of 8 weeks. Improvements in numerical WM were evident in both groups after 8 weeks (Halyburton et al., 2007) and remained stable at 1-year follow-up (Brinkworth et al., 2009). Despite this, the trajectory of cognitive change did not vary between diet groups, suggesting that the restriction in energy intake, and not carbohydrate or fat intake, was likely driving this improvement.

Working memory in other studies was unaffected by increases in total fat intake (Edwards et al., 2011; Lieberman et al., 2008). No changes in WM were reported following 2.5 day diets high in carbohydrates (E: 11784kJ; P: 1%; F: 0%; C: 99%) or carbohydrates and total fat (E: 11796kJ; P: 1%; F: 26%; C: 73%), suggesting that changes in either carbohydrate or total fat intake do not affect WM (Lieberman et al., 2008). Likewise, Edwards et al. (2011) placed twenty men on a ketogenic high-fat low-carbohydrate (Atkins-style) diet (E: not reported; P: 24%; F: 74%; C: 2%) for 7 days, and found no significant changes in numerical WM performance relative to baseline performance following 3 days on a low-fat high-carbohydrate diet (E: not reported; P: 22%; F: 17%; C: 61%). Interestingly, a subsequent study with an improved randomised controlled cross-over design with a 2-week wash-out period in between, as well as 3 days on a standardised diet prior to each 5 day test diet found some changes in WM (Holloway et al., 2011). Speed of memory index, a composite score derived from WM and recognition scores, was significantly slower after healthy men were fed a high-fat diet for 5 days (E: not reported; P: 26%; F: 70%; C: 4%) relative to an isoenergetic low-fat diet (E: not reported; P: 26%; F: 24%; C: 50%). However, caution should be taken since the individual component scores of WM performance were not reported and another related composite score – 'quality of WM' related to the ability to hold information temporarily in the articulatory loop and the visuo-spatial sketchpad – was unchanged following the high-fat diet.

Meanwhile, a comprehensive study by Lindseth et al. (2011) reported that fat may improve WM. Lindseth et al. (2011) gave participants diets either high in fat (E: not

reported; P: 22%; F: 56%; C: 22%), protein (E: not reported; P: 56%; F: 22%; C: 22%), or carbohydrates (E: not reported; P: 22%; F: 22%; C: 56%), or a "balanced" control diet (E: not reported; P: 15%; F: 35%; C: 50%), for four days each in a randomised, counterbalanced cross-over design. Numerical WM performance, as measured by the Sternberg short-term memory test (Sternberg, 1966) varied as a function of diet. Specifically, response times on this memory test were faster for participants fed the high-fat diet, especially for higher memory loads but remained unchanged in other diets. One potential confound in this study was that participants completed the cognitive tests within two hours of their final meal, suggesting participants were tested in a post-prandial state. Improvements in memory performance in the high-fat diet condition may have reflected post-prandial improvement following fat ingestion – a finding in agreement with other post-prandial studies (Fischer, Colombani, Langhans & Wenk, 2001; Hoyland et al., 2008).

A further factor may be the type of fat rather than total fat intake. Higher reported adherence to two different Mediterranean diets high in PUFAs and MUFAs and low in saturated fats - improved numerical WM performance relative to a control group in middle-aged adults after 6.5 years (Martínez-Lapiscina et al., 2013b). However, others have found impairments in numerical WM performance following Mediterranean diet adherence in females after 10 days (Lee et al., 2015; McMillan, Owen, Kras, & Scholey, 2011). The reasons for these discrepancies are unknown, but may be related to the duration of each diet intervention (i.e. 10 days versus 6.5 years). Additionally, the effects of various types of fat remains hard to gauge since studies investigating the effects of various fat types on WM have thus far failed to report any pertinent nutritional information, despite reporting successful adherence to the Mediterranean diet (Lee et al., 2015; Martínez-Lapiscina et al. 2013b; McMillan et al., 2011). Another study by Witte et al. (2009) failed to find changes in WM performance in elderly adults after a 3 month diet where the ratio of unsaturated fats to saturated fats was doubled, making the picture a little less clear.

In sum, there are mixed findings around WM. Significant changes in WM were reported in 3/7 with changes in energy intake, 0/2 studies with changes in protein, 5/10 studies from changes in total fat, and1/7 studies from changes in carbohydrates. Thus, few consistent changes in WM performance were evident, except some evidence that fat (and fat type) may be important here. Additionally, some tests may be more sensitive to dietary change than others, since numerical WM tests appeared to be more sensitive to dietary change than their non-numerical equivalents.

4.2.1.2 Visual-spatial memory

Only one diet intervention study has investigated the effects of energy restriction on visual-spatial memory. Martin et al. (2007) found no changes in performance on the Benton Visual Retention Test (BVRT) after a 30% energy reduction over 3 or 6 months. Thus, in agreement with human correlational data (Redman et al., 2008), visual-spatial memory function appears unaffected by changes in dietary energy intake.

Performance on tests of visual-spatial memory did not change following a brief four-day diet high in total fat (E: not reported; P: 22%; F: 56%; C: 22%), protein (E: not reported; P: 56%; F: 22%; C: 22%), or carbohydrates (E: not reported; P: 22%; F: 22%; C: 56%; Lindseth et al., 2011). Likewise, Lieberman et al. (2008) found that fat did not impact performance on the delayed spatial matching-to-sample task. Nonetheless, four other studies have found significant changes in visual-spatial memory following changes in dietary fat intake. Bayer-Carter et al. (2011) compared the effects of a four week high-fat (> 25% saturated fat), high GI (>70) diet or a low-fat (<7% saturated fat), low GI (<55) diet on the Brief Visuospatial Memory Test (BVMT) in elderly adults with and without mild cognitive impairment. In three learning trials, the participant views the stimulus page for 10 seconds and is asked to draw as many of the figures as possible in their correct location both immediately and following a 25-minute delay. Bayer-Carter et al. (2011) reported that delayed visual memory improved in participants with and without amnestic mild cognitive

impairment following the low-fat, low GI diet (E: 9088kJ; P: 15%; F: 25%; C: 60% (GI = 55)) relative to the high-fat diet (E: 8581kJ; P: 15%; F: 45%; C: 40% (GI = 70)). That is, decreases in saturated fat and GI load were associated with improved delayed visual recall in both cognitively impaired adults and healthy controls, while improvements in memory were not evident at immediate recall or in the group given the high-fat, high GI diet. Importantly, this dietary intervention was designed as a weight maintenance macronutrient manipulation and changes in memory performance were therefore due to changes in diet and unrelated to energy intake. It is unclear if the improvements in memory were driven by decreases in total fat intake, saturated fat intake, the glycaemic load of the diet or some combination of these changes. Nonetheless, these findings did reveal that improvements in visual-spatial memory associated with the low-fat diet were prevented by increases in saturated fats and GI load, implying that diet was a significant environmental factor modulating memory. In agreement with this, 6.5 years adherence to a Mediterranean diet high in PUFAs and MUFAs from extra virgin olive oil consumption led to improvements in visual-spatial performance on the both immediate and delayed memory recall of the visual-spatial Rey-Osterith Complex Figure task (ROCF) in 285 elderly individuals (Martínez-Lapiscina et al., 2013b). Likewise, McMillan et al. (2011) found that higher reported adherence to this diet improved reaction time on the spatial Corsi Block task in young females after 10 days (McMillan et al., 2011), while Lee et al. (2015) found a trend towards significance on the same task in young females after 10 days when tested in a cross-over design.

For carbohydrate intake, the findings have been mixed. Lieberman et al. (2008) reported no effect of carbohydrate content (E: 9566kJ; P: 1%; F: 0%; C: 99%) or carbohydrates and total fat (E: 11796kJ; P: 1%; F: 26%; C: 73%), on delayed spatial matching-to-sample performance over 2.5 days, while D'Anci et al (2009) found that the complete removal of dietary carbohydrates impaired visuospatial memory after 1 week, and these impairments were ameliorated with the reintroduction of dietary carbohydrate in

subsequent weeks. That is, on the visual-map task, low-carbohydrate dieters correctly placed fewer items during immediate recall and made more incorrect placements during delayed recall. Interestingly, it suggests that complete removal of dietary carbohydrates, but not other macronutrients, significantly impairs memory, suggesting a unique role of dietary carbohydrate intake. However, as no nutritional information about the diet was reported, these findings must be interpreted with caution.

Except for diets that altered fat content, there was no consistent pattern in visual-spatial memory performance across the diet intervention studies, since significant effects were reported in 0/1 studies from changes in energy intake, 0/1 studies from changes in protein, and 1/3 studies from carbohydrates. Four out of six studies found changes in visual-spatial memory after changes in fat. The evidence suggests a possible beneficial effect of *fat*, noting that the type of fat may be critical here – for example, a Mediterranean diet. In summary, visual-spatial memory performance was improved by decreases in total fat content, as well as increases in PUFAs and MUFAs, but not by changes in intake of energy or other macronutrients.

4.2.1.3 Long-term verbal memory

Restrictions in energy intake have been reported to have either no effect on verbal memory (Makris et al., 2013; Martin et al., 2007; Wardle et al., 2000) or to improve performance (Bryan & Tiggemann, 2001; Kretsch, Green, Fong, Elliman & Johnson, 1997; Witte et al., 2009). Notably, none of the diet intervention studies has reported impairments in verbal memory following energy restrictions.

Martin et al. (2007) found no significant changes in performance on a word recall task [Rey Auditory Verbal Learning Test (RAVLT)] at 3 months or 6 months following an intervention with either a 25% energy-restricted diet based on American Heart Association recommendations (≤30% total fat) or a low-energy diet derived from a liquid formula (E: 3565kJ; P: 36%; F: 12%; C: 52%). The RAVLT evaluates rate of learning, learning

strategies, interference, differences between encoding and retrieval, and retention of information. In the RAVLT, participants are given a list of 15 unrelated words repeated over five different trials and are asked to repeat immediately. Another list of 15 unrelated words is given and the participant must again repeat the original list of 15 words immediately and again after a 30 minute delay. Overall, mixed linear models found no consistent pattern of verbal memory change emerged during the trial and the degree of energy restriction was not associated with change in cognitive performance (*Cohen's d < 0.08*). Similarly, Makris et al. (2013) reported no changes in word recall performance following reductions of up to 25% in energy intake after 24 weeks. Verbal memory performance was also unaffected by reductions in energy by 20% in adults with elevated serum cholesterol over 12 weeks (Wardle et al., 2000).

In contrast, other researchers have found improvements in verbal memory following energy restriction. First, Kretsch et al. (1997) found that immediate word recall memory improved significantly by 24.4% relative to baseline in overweight women (no nutritional information was reported in this study). Second, participants were less vulnerable to interference effects and more accurate in their recall following restrictions in energy intake by 20% for twelve weeks (Bryan & Tiggemann, 2001). Specifically, free recall intrusions on the RAVLT were greater in the control group than in the diet group, indicating some positive effect of energy restriction on verbal memory recall. Lastly, Witte et al. (2009) found that, after reducing energy by 30% for twelve weeks, elderly adults remembered more words and made fewer mistakes on the RAVLT compared to baseline performance and this effect was moderate to large (*Cohen's d* = 0.66).

Increases in dietary protein intake have no effect on long-term verbal memory in frail elderly adults after 24 weeks (E: 7500kJ; P: 16%; F: 35%; C: 44%; Van Der Zwaluw et al., 2014). Increases in total fat did not affect verbal memory in males (Edwards et al., 2011; Holloway et al., 2011) or elderly adults (Bayer-Carter et al., 2011), while reductions in total

(25%) and saturated fat (7%) intake had no effect on verbal memory in elderly adults (Bayer-Carter et al., 2011). Nevertheless, Nilsson, Tovar, Johansson, Radeborg and Björck (2013) found some preliminary evidence that a diet low in saturated fat (<6%) (E: 9866kJ; P: 19%; F: 31%; C: 50%) designed to reduce markers of inflammation associated with metabolic syndrome enhances verbal memory. Overweight middle-aged adults given a diet low in saturated fat (<6%), but high in polyunsaturated (8%) and monounsaturated fats (13%) improved verbal recognition memory performance on the RAVLT relative to a control diet (E: 9657kJ; P: 15%; F: 30%; C: 55%; Nilsson et al., 2013). Despite overall increases in performance scores associated with repeated test administration, greater improvements in memory were significantly associated with reported diet adherence. These findings hint at the potential to reverse or alter the trajectory of verbal memory impairments in middle-aged adults using dietary intervention. Importantly, it also suggests that the type of fat may be important since there were no differences in total fat intake between the diet and control groups.

Other studies designed to increase PUFA and MUFA intake yielded improvements in verbal memory, with better performance on Verbal Paired Associates (Martínez-Lapiscina et al., 2013b) and fewer errors in immediate and delayed word recall (McMillan et al., 2011). By comparison, Lee et al. (2015) observed better word recognition in the control group, while the remaining studies manipulating fat type have found no discernible change in verbal memory (Wardle et al., 2000; Witte et al., 2009). Interestingly, the studies reporting significant changes in verbal memory (Lee et al., 2015; Martínez-Lapiscina et al., 2013b; & McMillan et al., 2011) also failed to report the nutritional content at the end of their respective interventions, making any conclusions about the relationship between diet and verbal memory performance problematic.

Limiting carbohydrate intake was found to affect verbal memory in one study. Krikorian et al. (2012) reported that, in older adults with mild cognitive impairment,

moderate reductions in dietary carbohydrates (E: 4339kJ; P: 27%; F: 60%; C: 13%), improved performance on the Verbal Paired Associates task (*Cohen's f = 0.26*) after six weeks relative to a high-carbohydrate diet (E: 6653kJ; P: 15%; F: 35%; C: 50%). Given that the low-carbohydrate group also consumed significantly less energy over the intervention period, it is unclear whether changes were due to reductions in carbohydrate intake, energy intake, or some combination of both. Meanwhile, other intervention studies have failed to find any change in verbal memory performance following restrictions in dietary carbohydrates from three weeks (D'Anci et al., 2009) up to twenty-four weeks (Makris et al., 2013). Makris et al. (2013) reported no changes in word recall following a high-carbohydrate (E: 6276kJ; P: 15%; F: 30%; C: 55%), or low-carbohydrate diet following the guidelines of *Dr. Atkins' New Revolution* (Atkins, 1998) (nutritional information not provided) for 2 years, showing that carbohydrate content did not affect memory. Training sessions at baseline to familiarise participants with the memory tasks may have plateaued scores preventing any further improvement in memory performance (ceiling effect). Similarly, Smith et al. (2010) found no changes in verbal paired associate learning following 4 month adherence to a high-carbohydrate DASH diet (E: 8209kJ; P: 19%; F: 28%; C: 55%) and Ngandu et al. (2015) found no differences between diet and control groups in verbal memory after a 2 year high-carbohydrate diet (E: NR; P: 15%; F: 30%; C: 50%).

Diet intervention studies reveal no consistent effect of diet on long-term verbal memory since significant effects were found in 3/6 studies from changes in energy intake, 0/1 studies from changes in protein, 4/9 studies from changes in total fat, and 1/5 studies from changes in carbohydrates. Verbal memory was improved to varying degrees by reductions in energy intake and changes to fat type (but not necessarily fat content). While the fat-related findings look disappointing, several studies hinted at potential benefits associated with varying intake of fat type in healthy adults. In agreement with this, a review found that

verbal memory performance, more than any other cognitive domain, is acutely affected at the post-prandial level (Hoyland et al., 2008).

4.2.1.4 Concluding remarks on memory

The research from diet intervention studies suggests three conclusions: (1) there is notable variation in outcomes across all cognitive domains and diets; (2) reductions in energy intake and dietary fat appear beneficial to long-term memory function especially among overweight and obese adults, although this effect was not always clear (see Table 4.1); and (3) changes in dietary fat, especially towards a more healthful Mediterranean pattern may benefit multiple types of memory.

Table 4.1. *Summary of effects of diet interventions on working and long-term memory*

Intervention		Study	Sample Population	Duration (days)	Change in energy (%)	Effect on Memory		
						Working Memory	Visual-spatial	Verbal LTM
Energy Intake	Decrease	Wardle et al. (2000)*	n = 105 middle-aged adults	84	-17	-	-	No change
		Bryan & Tiggemann (2001)	n = 42 overweight women	84	-20	No change	-	↑
		Makris et al. (2013)*	n = 47 obese adults	168	-25	-	-	No change
		Martin et al. (2007)†	n = 24 overweight	168	-25	↑	No change	No change
		Witte et al. (2009)	n = 19 overweight elderly	84	-30	No change	-	↑
		Halyburton et al. (2007)*†	n = 93 obese adults	56	-30	↑	-	-
		Pearce et al. (2012)	n = 44 obese with type 2 diabetes	56	-30	No change	-	-
		Cheatham et al. (2009)*	n = 28 overweight	180	-30	No change	-	-
		Brinkworth et al. (2009)*†	n = 64 obese adults	365	-30	↑	-	-
		Kretsch et al. (1997)	n = 14 women	105	-50	-	-	↑
Protein	Increase	Lindseth et al. (2011)	n = 45 young men	4	0	No change	No change	-
		Van Der Zwaluw (2014)	n = 65 frail elderly	168	NR	No change	-	No change
Fat	Decrease	Bayer-Carter et al. (2011)	n =11 healthy elderly	28	0	-	↑	No change
			n = 14 elderly with mild cognitive impairment	28	0	-	↑	No change
		Nilsson et al. (2013)	n = 44 healthy adults	28	0	-	-	↑
		Wardle et al. (2000)*	n = 52 middle-aged adults	84	-17	-	-	No change
	Increase	McMillan et al. (2011)	n = 12 young women	10	NR	↓	↑	↑
		Lee et al. (2015)	n = 23 young women	10	NR	↓	↑	↓
		Martínez-Lapiscina et al. (2013b)	n = 190 elderly adults	2373	NR	↑	↑	↑
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	No change	No change	-
		Lindseth et al. (2011)	n = 45 young men	4	0	↑	No change	-
		Holloway et al. (2011)	n = 16 healthy men	5	0	↓	-	No change
		Edwards et al. (2011)	n = 20 healthy men	7	0	No change	-	No change

		Bayer-Carter et al. (2011)	n =9 healthy elderly	28	0	-	No change	No change
			n = 15 elderly with mild cognitive impairment	28	0	-	No change	No change
		Witte et al. (2009)	n = 20 overweight elderly	84	0	No change	-	No change
		Wardle et al. (2000)*	n = 53 middle-aged adults	84	-17	-	-	No change
		Halyburton et al. (2007)*†	n = 48 obese adults	56	-30	↑	-	-
		Brinkworth et al. (2009)*†	n = 32 obese adults	365	-30	↑	-	-
Carbohydrate	Decrease	D'Anci et al. (2009)*	n = 9 women	21	NR	↓	↓	No change
		Makris et al. (2013)*	n = 22 obese	730	-25	-	-	No change
		Cheatham et al. (2009)*	n = 16 overweight	180	-30	No change	-	-
		Krikorian et al. (2012)*	n = 12 older adults	42	-41	-	-	↑
	Increase	D'Anci et al. (2009)*	n = 10 women	21	NR	No change	No change	No change
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	No change	No change	-
		Lindseth et al. (2011)	n = 45 young men	4	0	No change	No change	-
		Smith et al. (2010)	n = 38 obese adults	120	0	No change	-	No change
		Krikorian et al. (2012)*	n = 11 older adults	42	-6	-	-	No change
		Makris et al. (2013)*	n = 25 obese adults	168	-25	-	-	No change
		Halyburton et al. (2007)*†	n = 45 obese adults	56	-30	↑	-	-
		Cheatham et al. (2009)*	n = 12 overweight	180	-30	No change	-	-
		Brinkworth et al. (2009)*†	n = 32 obese adults	365	-30	↑	-	-
		Ngandu et al. (2015)	n = 591 elderly adults	730	NR	-	-	No change

Table 4.1. Summary of the effects of dietary change on various domains of memory. Findings have been sub-categorised according diet manipulation, degree of energy restriction (if any), and duration of diet, respectively. Significant improvements are represented by an upwards arrow (↑). Significant impairments are represented by a downwards arrow (↓). Studies that do not measure the relevant cognitive domain are represented with a dash (-).† indicates that changes in these studies may be due to methodological shortcomings, such as a practice effect. * denotes diet study manipulated both energy and macronutrient content. NR = Not reported.

4.2.2 Other Cognitive Domains

In the following part of the review, we examine diet intervention studies that have measured performance on non-memory based tasks. These have been broadly categorised into four cognitive domains: global cognitive function, executive function, attention, and information processing speed. First, we discuss tests of global cognitive function (e.g. MMSE), which are typically used to estimate the severity and progression of cognitive impairment, thus making it an effective tool to track an individual's cognitive function over time. Second, we examine executive function – a multifaceted construct consisting of a set of higher-order processes that allow individuals to make choices and to engage in purposeful, goal-directed and future-oriented behaviour. Long-term energy regulation may require planning and self-regulation to balance food consumption behaviours with the ability to suppress or inhibit those behaviours. Moreover, optimal cognitive function depends not only on the ability to retrieve information when it is needed, but also on the ability to inhibit retrieval of information when it is not needed. Third, we investigate the effects of diet on attention, including sub-tests of sustained attention and divided attention. Finally, information processing refers to ability to direct mental focus to relevant information in order to process it rapidly and efficiently, as well as make accurate and appropriate decisions based on current information and/or pre-existing knowledge. We have made an effort to classify the various tests according to the major functional areas of responses and for most, this was possible. Many others, however, involve several functions while few tests measure a single cognitive construct. For instance, the Trail Making Test (TMT) parts A and B – complex tests of attention involving a response speed component may also tap into executive function. In this way, their assignment to a particular domain was somewhat arbitrary but was based heavily on the recommendations of Lezak, Howieson, Bigler and Tranel (2012).

4.2.2.1 Global cognitive function

Global cognitive function refers to overall or general cognitive performance tapping

into various neural networks and brain regions. It includes multiple domains such as attention, memory, language, orientation and motor skills. Because of this, measures of global cognitive function are typically used as screening tools to detect general cognitive status of individuals. Nonetheless, a total of seven studies have examined the effects of changes in energy or macronutrients on global cognitive function, and are detailed below.

The effects of energy intake on global cognitive function have been explored by only two studies. Aquilani et al. (2008) showed that a protein-energy supplementation program that boosted energy intake by 22% (E: 6477kJ; P: 17%; F: 36%; C: 47%) improved global cognitive function (MMSE) in cognitively impaired sub-acute stroke patients relative to baseline performance but not relative to the control group (E: 4640kJ; P: 14%; F: 35%; C: 58%). Nevertheless, this finding should be interpreted with caution since significant changes were found in a $\log_{10}$ transformed MMSE score within the supplemented group only and not between groups, while there were no significant differences in the raw MMSE score in either group. By comparison, only one study has found that restricting energy resulted in improvements in global cognitive function in cognitively unimpaired adults. Siervo et al. (2012) found improvements on MMSE scores and the Short-Portable Mental Status Questionnaire following 40% energy restriction over 4 months in middle-aged adults (E: 6761kJ; P: 27%; F: 25%; C: 53%), and in healthy older adults (E: 5845kJ; P: 27%; F: 25%; C: 53%). Taken together, these limited findings suggest that changes in energy may be important for global cognitive function, but research is lacking.

Increases in protein did not change MMSE scores in young-old (65-74 years) type-2 diabetes subjects (Ciarambino, Ferrara, Castellino, Paolisso & Giordano, 2011) and frail elderly subjects (Van Der Zwaluw et al., 2014), while two other studies (Aquilani et al., 2008; Jakobsen, Kondrup, Zellner, Tetens & Roth, 2011) found improvements in global cognitive function following increases in protein. As mentioned previously, the $\log_{10}$ transformed improvements in MMSE scores from Aquilani et al. (2008) should be viewed

with caution. Moreover, since Aquilani et al. (2008) altered both macronutrient and energy content in one group while the control group received neither treatment, it is difficult to attribute any improvements in cognition to one dietary factor. Jakobsen et al. (2011) found significant improvements on the orientation score of the Addenbrooke Cognitive Examination – a test typically used to detect gross cognitive impairments. It is, however, likely inappropriate to use this test to detect improvements in cognitive performance in a sample population of healthy young males without any pre-existing cognitive impairments.

One key long-term prevention trial found improvements in global cognitive function following a Mediterranean diet with no change in total energy intake (Martínez-Lapiscina et al., 2013a). They compared two Mediterranean diets – one supplemented with 1L/week Extra Virgin Olive Oil [MedDiet + EVOO] or supplemented with 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts [MedDiet + Nuts] – to a control low-fat diet. Although there were no differences in energy intake within and between diet and control groups, MedDiet groups did show strong adherence to the MedDiet guidelines, which have been described in detail elsewhere (Zazpe et al., 2008). Despite a lack of nutritional information at the end of the trial, reported adherence to both MedDiets improved cognitive status (MMSE) relative to the control diet in a 6.5-year follow-up in 522 elderly adults (Martínez-Lapiscina et al., 2013a) and a random subsample (n = 285) within the same time period suggesting a robust finding (Martínez-Lapiscina et al., 2013b). Another study using a 'brain preservation' diet with the target of two fruit portions daily, three leafy green vegetable portions daily, five fish portions weekly, and avoidance of salty foods did not improve MMSE scores in elderly adults over 33 months (Kwok, Lam, Sea, Goggins, & Woo, 2012). Again, without detailed nutritional information, the relationship between diet and global cognitive function cannot be properly established.

Another comprehensive 2 year high-carbohydrate (50%) multidomain intervention program (diet, exercise, cognitive training, and vascular risk monitoring) reported

improvements in performance on the Neuropsychological Test Battery in adults 60-77 years (Ngandu et al., 2015). In this program, 591 participants were advised to consume a diet with 10–20% of daily energy from proteins, 25–35% daily energy from fat (<10% from saturated plus trans-fatty acids, 10–20% from monounsaturated fatty acids, and 5–10% from polyunsaturated fatty acids [including 2·5–3 g/day of omega-3 fatty acids]), 45–55% daily energy from carbohydrates (<10% from refined sugar), 25–35 g/day of dietary fibre, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Although dietary adherence was not recorded at the time of this review, at the end of the 2 year intervention period, a modified intention to treat analysis found that improvement in the NTB total score was 25% higher for the intervention group than in the control group (Ngandu et al., 2015). Unfortunately, since the diet intervention group also increased physical exercise, cognitive training, social activity, and intensive monitoring and management of metabolic and vascular risk factors, it is difficult to know which intervention type was most beneficial to cognitive function. One may speculate that it is likely some combination of the above, but future research should aim to isolate them to better understand the most important and useful interventions for cognitive and clinical outcomes.

Overall, global cognitive function remained relatively unaffected across the diet intervention studies, since significant changes were evident in only 2/2 studies that altered energy intake, and 4/7 studies altering macronutrient content. The findings of two macronutrient studies (Aquilani et al., 2008; Jakobsen et al., 2011) are somewhat questionable. Few diet studies have found significant changes in global cognitive function, suggesting that either 1) these tasks are insensitive to changes in diet, or 2) the neuropsychological constructs underlying these tasks are not affected by changes in diet. Given the gross nature of the multidomain cognitive test batteries, it is likely that these tests are insensitive to dietary interventions. For instance, the MMSE is typically used as a screening tool of cognitive impairment and is not intended to test treatment success. It may

be that tasks of greater difficulty, which create a higher cognitive load, may be required to detect changes following dietary manipulations. Importantly, changes in test performance lack the specificity to determine which cognitive domain may be affected.

4.2.2.2 Executive function

Generally speaking, executive function is the ability to respond in an adaptive manner to novel situations. It is the most complex of cognitive domains that includes complex higher-order thinking processes related to planning, problem solving, verbal reasoning, inhibition, mental flexibility, or set-shifting. It has been proposed that the type of diet one consumes may augment total energy intake or interfere with inhibitory processes resulting in excess energy intake and weight gain (Davidson, Kanoski, Walls & Jarrard, 2005). To date, there is little human experimental evidence to substantiate this claim. Only three studies have investigated the long-term effects of energy intake on inhibition using either the Stroop task, or a modified food-Stroop task using food-related cues. The Stroop task is a measure of inhibition – the ability to suppress automatic and habitual responses or behaviours. Bryan and Tiggemann (2001) reported significant improvements in Stroop reaction time in both the 20% energy-restricted and control groups, likely reflecting a practice effect. Two other studies reported promising changes in Stroop performance. Specifically, percentage of correct responses on the Stroop task improved over time following 25% energy restriction for 24 weeks (Makris et al., 2013), while more severe energy restrictions up to 80% for 4 weeks led to improvements in number of words read on the Stroop task (Wing, Vazquez & Ryan, 1995). Despite also manipulating carbohydrate content, both studies showed improvements in the Stroop task over time regardless of carbohydrate content, suggesting energy restrictions likely contributed to these improvements. However, in the absence of an appropriate control group (i.e., one that did not alter their diet but completed the task at the same time points), it is difficult to determine if improvements in Makris et al. (2013) and Wing et al. (1995) were due to repeated administration or a genuine consequence of energy restriction. Additionally,

it may be that the impact of energy restriction on tasks of inhibition is greater with increasing duration or magnitude of energy restriction, but this remains unexplored. As it stands, it appears that tasks of inhibition are susceptible to changes in energy intake.

Other tasks of executive function have shown no changes as a result of energy restriction. Reductions in energy intake ranging from 10% to 75% did not impact performance on executive function measures such as: (1) Self-Ordered Pointing Task or verbal fluency in women after 20% restriction over 12 weeks (Bryan & Tiggemann, 2001); (2) the Wisconsin Card Sorting Task in middle-aged adults after 25% restriction over 24 weeks (Makris et al., 2013); (3) or tasks of grammatical reasoning in healthy overweight adults after 30% restriction over 6 months (Cheatham et al., 2009). Thus, except for measures of inhibition, there is little evidence to suggest that energy intake affects executive function across various populations. Additionally, there appears to be no dosage effect based on the pattern of findings, with changes in executive function performance no more likely to occur with greater energy restriction (see Table 4.2).

Much like energy intake, measures of inhibition have presented some changes associated with diet manipulation. Jakobsen et al. (2011) found improved reaction time and fewer errors on the Go/No Go task after a three week high protein diet (E: 7485kJ; P: 35%; F: 15%; C: 50%) relative to a control diet (E: 7085kJ; P: 17%; F: 16%; C: 67%). The Go/No Go task is a reaction time task of behavioural inhibition and typically involves choosing one of two outcomes across multiple trials: one in which participants are required to make a motor response (Go), and another requires participants to withhold a response (No Go). Importantly, the significant differences in reaction time persisted even after accounting for baseline differences. On another task of inhibition, Stroop performance improved significantly following the high-carbohydrate ADA diet (E: 8368kJ; P: 18%; F: 29%; C: 55%) relative to a low-carbohydrate diet (nutritional information unavailable; D'Anci et al. (2009)). Specifically, participants on the ADA diet responded faster to non-food words over

test sessions – an effect not evident in the low-carbohydrate group. This difference may reflect a reduction in food pre-occupation. Despite this, D'Anci et al. (2009) concluded that, due to the inconsistent nature of responses in the low-carbohydrate group, it is unclear why or how diet improved Stroop performance. Likewise, the reasons for the discrepancy in findings between the Stroop task and Go/No Go task are currently unknown, but may be related to task sensitivity or difficulty associated with the different tasks of inhibition. Other studies found no changes in Stroop performance following increases or decreases in fat intake (Bayer-Carter et al., 2011), protein intake (Van Der Zwaluw et al., 2014), or carbohydrate intake (Makris et al., 2013; Smith et al., 2010).

Improved performance on other executive function tasks has been reported in a small number of studies following shifts in dietary macronutrient content. For instance, a 6.5 year diet trial (n = 522) found improvements in executive function (Clock Drawing Task) after adherence to a Mediterranean diet supplemented with extra virgin olive oil (Martínez-Lapiscina et al., 2013a). A subsequent article using a random subsample (n = 285) detected improvements in verbal fluency in the Mediterranean diet group relative to the control group, using a logistic regression model adjusting for multiple confounders (Martínez-Lapiscina et al., 2013b). Meanwhile, Ngandu et al. (2015) reported an 83% improvement in executive function performance relative to a control group following a 2 year high-carbohydrate diet (E: NR; P: 15%; F: 30%; C: 50%) in adults 60-77 years. One study that varied fat and carbohydrate content failed to find improvements in grammatical reasoning scores over a 2.5 day intervention period (Lieberman et al., 2008), but given the relatively short intervention period this finding is not surprising. The results of varying macronutrient content on executive function have yielded inconsistent findings. One problem is that some studies have altered only macronutrient content, while others have also altered energy intake to varying degrees. Despite this, there was no clear pattern of results across studies when this was taken into consideration.

Executive function tasks not involving inhibition remained relatively unaffected across the diet intervention studies, since significant effects were found in 0/3 studies from changes in energy intake, 0/1 studies from changes in protein, 2/4 studies from changes in total fat, and 1/6 studies from changes in carbohydrates. Tasks of greater difficulty, which create a higher cognitive load, may be required to detect changes following dietary manipulations. Indeed, tasks of inhibition appeared to show some sensitivity to changes in energy intake in 2/3 studies, while only 2/6 studies with macronutrient manipulations showed improvements in inhibition. A summary of the various diets and their effects on executive function can be found in Table 4.2. Another important point of consideration is that significant improvements in performance were mostly evident in reaction time measures within these tasks of inhibition. The effect of dietary intervention on reaction time will be discussed in detail in the next section.

4.2.2.3 Attention

Most everyday activities depend on intact mechanisms for directing attention, dividing attention when necessary, and sustaining attention until an activity is complete. Likewise, successful performance of many cognitive tests requires sustained and focused attention. Here, we have divided tasks according to the classifications by Lezak, Howieson, Bigler & Tranel (2012), including general measures of attention, and more specific measures including divided attention and sustained attention tasks. Divided attention occurs when we are required to perform multiple tasks at the same time and attention is required for successful performance on all tasks at hand (e.g. Trail making task part B (TMT-B)), while measures of sustained attention typically involve sequential presentation of stimuli over a period of time with instructions to indicate when target stimuli is perceived (e.g. digit vigilance task).

The majority of energy restriction studies (Cheatham et al., 2009; Kretsch et al., 1997; Makris et al., 2013; Martin et al., 2007; Pearce et al., 2012; Witte et al., 2009) have failed to

show any changes in performance on the tasks of attention (see Table 4.2 for a detailed breakdown of findings). Three studies report improvements in attention (Bryan & Tiggemann, 2001; Siervo et al., 2012; Wing et al., 1995), while only one study found impairments in attention following energy restriction (Wardle et al., 2000). For instance, adults with elevated serum cholesterol given either a 20% energy-restricted low-fat or isoenergetic Mediterranean diet over 12 weeks performed significantly worse on the Bakan vigilance task of sustained attention than the waitlist control group (Wardle et al., 2000). The reasons for this difference in performance remain unknown.

Attention, as measured by the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) improved after twelve weeks in both the 20% energy-restricted diet group and the usual diet control group, while performance on the Trail Making Task part A (TMT-A) and part B (TMT-B) remained unchanged (Bryan & Tiggemann, 2001). Since improvements in Digit Symbol Coding occurred in both groups, the effect likely resulted from repeated administrations of the test and not a consequence of the energy restriction. Siervo et al. (2012) reported that a 40% energy restriction over 4 months improved performance on the TMT-A and TMT-B in middle-aged adults (E: 6761kJ; P: 27%; F: 25%; C: 53%), and on the TMT-B only in healthy older adults (E: 5845kJ; P: 27%; F: 25%; C: 53%). The Trail Making Task involves connecting 25 consecutive targets that are all numbers in sequential order (1, 2, 3, etc.) (TMT-A), and that alternate between numbers and letters (1, A, 2, B, etc.) (TMT-B). Improvements in cognition may be a potential consequence of energy restriction and its associated weight loss. Indeed, a meta-analysis by Siervo et al. (2011) found that weight loss was associated with better performance on TMT-B, especially in older adults, suggesting that excess weight may be a risk factor for cognitive decline. Importantly, there may be sample populations who are particularly vulnerable to excess weight, and correspondingly, restrictions in energy intake.

The influence of macronutrients on attentional performance is not yet fully understood. Increased protein content has no effect on sustained attention (Jakobsen et al., 2011) or TMT-A and TMT-B performance (Van der Zwaluw et al., 2014). By comparison, Wing et al. (1995) reported greater improvement in TMT-B performance in an energy-restricted high-carbohydrate group (E: 2486kJ; P: 33%; F: 14%; C: 53%) relative to an isoenergetic low-carbohydrate group (E: 2469kJ; P: 35%; F: 58%; C: 7%). Subsequent analyses showed that this was due to baseline differences in performance on this task and not a result of the diet intervention, since performance in subsequent weeks was equivalent. Thus, it is likely that energy restriction (or even repeated administrations), and not differences in carbohydrate content, drove improvements in TMT-B performance. Three other studies also report no effect of carbohydrate content on measures of attention (Krikorian et al., 2012; Lieberman et al., 2008; Makris et al., 2013). Meanwhile, D'Anci et al. (2009) showed that, for women who self-selected two weight loss diet regimens – a low-carbohydrate diet (nutritional information not available) or a <30% fat, weight maintenance ADA diet for 3 weeks – the low-carbohydrate group showed reduced response time on the Continuous Performance Task, while it increased for the ADA dieters. That is, a diet with reduced carbohydrates improved response times in the last 10 minutes of a 15 minute task, indicating better sustained attention. Likewise, Smith et al. (2010) found that participants on the high-carbohydrate DASH diet (E: 8209kJ; P: 19%; F: 28%; C: 54%), relative to usual diet controls (E: 8765kJ; P: 17%; F: 37%; C: 46%), exhibited better performance (*Cohen's d = 0.44*) on the Ruff 2 and 7s Selective Attention Test – a test of the difference between automatic and controlled detection that provides information on attentional capacity. Improvements in the DASH diet group were comparable to an 8.3-year improvement in automatic detection speed and a 9.6-year improvement in controlled detection speed, while the control group exhibited relatively smaller improvements, with a 0.6-year improvement in automatic detection speed and a 3.6-year improvement in controlled detection speed.

Certainly, this test of attentional capacity has been shown to differentiate between right and left-side brain lesions (Ruff, Niemann, Allen, Farrow & Wylie, 1992).

Some studies have revealed adverse effects of increased total fat intake on measures of attention. Males performed significantly worse on tasks measuring focused and sustained attention following a five day high-fat (70%) diet compared to an isoenergetic low-fat (24%) diet (Holloway et al., 2011). Likewise, sedentary males given a high-fat, low-carbohydrate diet for seven days exhibited impairments in the Rapid Visual Processing Speed (RVIP) task of sustained attention compared to performance on a low-fat control diet (Edwards et al., 2011). Wardle et al. (2000) also found impairments in sustained attention following either a low-fat or a Mediterranean diet, but since these diets were also energy-restricted, the exact role of fat content is difficult to determine. In the same way, changes in other tasks of attention were not significant and the reasons for the absence of improvement following reductions in fat may be related to the lack of dietary target adherence. Wardle et al. (2000) reported that, despite different dietary fat targets in the low-fat and Mediterranean diet groups, MUFA and PUFA intakes were equivalent, while total fat intake had decreased relative to the control group (statistics not reported).

Nilsson et al. (2013) reported that reducing the intake of saturated fat by 7% and increasing PUFA and MUFA intakes by 8% and 13%, respectively, significantly increased correct responses and decreased reaction time on a test of selective attention after four weeks (Nilsson et al., 2013). Importantly, they reported no significant no changes in total fat intake. It is unclear if improvements in attention were related to the reduction of saturated fats or the commensurate increase in PUFAs and MUFAs. One study found that neither increases nor decreases in total and saturated fat intake had any effect on attention (TMT-A) in elderly adults with or without MCI (Bayer-Carter et al., 2011), while other studies involving increases in PUFA and MUFA intake found no changes in attention (Lee et al., 2015; McMillan et al., 2011; Martínez-Lapiscina et al., 2013b), leaving this question unanswered.

Hence, as it stands, there is some evidence that attention is influenced by energy intake and fat content, but this remains to be seen given the paucity of research. Overall, significant changes in attention were found in 4/10 studies from changes in energy intake, 0/2 studies from changes in protein, 4/9 studies from changes in fat, and 3/6 studies from changes in carbohydrates. Indeed, there was no clear direction in the pattern of findings and, given the substantial variability in findings and the lack of reported statistics, this is not surprising.

4.2.2.4 Information processing speed

Many cognitive tasks require sufficient information processing speed for relevant operations to be executed within the time allowed. Speed of information processing constitute the basic dimensions of attention since how much the attentional system can process at once depends on how fast it operates. The speed at which information is processed, typically measured by reaction time tests, is a relatively direct means of measuring processing speed and understanding the nature of attentional deficits.

Information processing speed, typically measured by reaction time tasks, was unchanged in four energy restriction studies (Brinkworth et al., 2009; Cheatham et al., 2009; Pearce et al., 2012; Wardle et al., 2000), while the remaining three reported some interesting changes across various processing speed tasks. Buffenstein, Karklin and Driver (2000) found that that a four week energy-restricted diet (3347 kJ/day) was associated with improvements in a complex reaction time, while simple reaction time was unaffected relative to baseline performance. However, there was no control group and the researchers did suggest that the improvement might have been a ‘practice effect’ (Buffenstein et al., 2000). Another study revealed that the minimum amount time to identify a target stimulus over progressively shorter time intervals (i.e. inspection time task) improved following a 30% energy restriction over 8 weeks (Halyburton et al., 2007). However, performance on this task returned to baseline levels when tested at 1 year (Brinkworth et al., 2009). Only one study reported impairments in processing speed following energy restriction. A 50% energy-restricted

weight reducing diet for obese pre-menopausal women impaired simple reaction time after 15 weeks (Kretsch et al., 1997). Compared to baseline, simple reaction time on the finger tapping task was significantly slower at the end of energy restriction (-5.2%) and continued to slow further during the 3-week weight stabilisation period (up to -10.9% slower). Of particular importance was the finding that reaction time performance did not readily improve following the restoration of energy intake to maintain weight. The reasons for this lack of reversibility remain unclear.

One study indicated that dietary protein might provide some benefit for processing speed in the elderly. Specifically, reaction time improved more (68ms) in frail elderly adults supplemented with protein and energy relative to a non-isoenergetic placebo group (18ms) given a supplement containing no protein (Van Der Zwaluw et al., 2014). Since participants did not compensate for the additional protein supplementation, the authors concluded that increasing protein intake (from 1.0kg/b-w to 1.4kg/b-w) was responsible for the improvements in processing speed. It should be noted that, despite reduced energy intake in both groups (excluding the supplement), the additional energy intake from the supplement program was not reported, making it difficult to determine the degree of energy restriction. In contrast, Jakobsen et al. (2011) found no improvements in reaction time in young men following increases in dietary protein over 3 weeks. It may be that additional dietary protein may benefit elderly adults, who likely have age-related cognitive impairments relative to their younger counterparts.

There are mixed findings with respect to the relationship between processing speed and fat and carbohydrate content. Edwards et al. (2011) reported that sedentary males given a high-fat, low-carbohydrate diet for seven days exhibited impairments in simple reaction time compared to performance on a low-fat control diet. Ngandu et al. (2015) found that improved processing speed in adults 60-77 years after a 2 year high-carbohydrate diet (E: NR; P: 15%; F: 30%; C: 50%) was 150% higher than the control group. It may be processing

speed has a positive and inverse relationship with carbohydrate and fat content, respectively. In a test of this, Halyburton et al. (2007) reported improved performance on a speed of processing task following an energy-restricted diet either high in fat or carbohydrate diet over eight weeks, but showed greater improvement over time in the high-carbohydrate, low-fat diet (E: 6319kJ/day; P: 23%; F: 26% (5.6% SFA); C: 45%) relative to a low-carbohydrate/high-fat diet (E: 6636 kJ/day; P: 33%; F: 61% (21% SFA); C: 4%) . Adding to the mixed pattern of findings and despite greater improvements in inspection time in the former over the latter ($\eta^2 = 0.04$), change in performance scores were positively correlated with percentage of energy from fat (r = 0.23), saturated fat (r = 0.21) and MUFA (r = 0.23) and negatively associated with carbohydrate intake (r = -0.21), suggesting a favourable role of fat on processing speed (Halyburton et al., 2007). Interestingly, at 1-year follow-up, speed of processing decreased to baseline levels in both diet groups (Brinkworth et al., 2009). The reasons for these discrepancies are unclear, but may be related to the restriction in energy rather than the macronutrient content of either test diet.

Other studies involving changes in total fat content or relative ratios of fat types (e.g. Mediterranean diet) failed to find differences in information processing speed after dietary change (Lee et al., 2015; Lieberman et al., 2008; McMillan et al., 2011; Wardle et al., 2000). Likewise, most studies have failed to find any long-term benefit of changing dietary carbohydrate intake on performance on measures of reaction time or other measures of processing speed (Cheatham et al., 2009; Lieberman et al., 2008).

Overall, there have been mixed findings across the diet intervention studies, since significant changes were found in 3/7 studies from changes in energy intake, 1/2 studies from changes in protein, 2/7 studies from changes in fat, and 2/5 studies from changes in carbohydrates. Despite these inconsistent findings, there is some evidence of an inverse relationship between processing speed and energy intake, while carbohydrate may have a positive relationship with processing speed. However, given the inconsistencies in findings

across studies, as well as the inter-dependency of processing speed measures with other measures of cognitive functions, it is unclear whether measures of processing speed are sensitive to changes in diet.

4.2.2.5 Concluding remarks on other cognitive domains

Based on the experimental findings, tasks of global cognitive function appeared insensitive to dietary alteration. Executive function – particularly tasks involving inhibition – showed promising changes in the presence of energy restriction. Measures of attention and processing speed presented quite varied findings, occasionally in opposite directions. Across the various domains, changes to energy intake and fat content appeared most impactful, but once again, the pattern is not entirely clear.

Table 4.2. *Summary of effects of diet interventions on other cognitive domains*

Intervention		Study	Sample Population	Duration (days)	Change in energy (%)	Effect on other cognitive domains			
						Global Cognitive Function	Executive Function	Attention	Information Processing Speed
Energy Intake	Decrease	Wardle et al. (2000)*	n = 105 middle-aged adults	84	-17	-	-	↓	No change
		Bryan & Tiggemann (2001)†	n = 42 overweight women	84	-20	-	↑	↑	-
		Martin et al. (2007)	n = 24 overweight	168	-25	-	-	No change	-
		Makris et al. (2013)*	n = 47 obese	168	-25	-	↑	No change	-
		Halyburton et al. (2007)*†	n = 93 obese	56	-30	-	-	-	↑
		Pearce et al. (2012)	n = 44 obese with type 2 diabetes	56	-30	-	-	No change	No change
		Witte et al. (2009)	n = 19 overweight elderly	84	-30	-	-	No change	-
		Cheatham et al. (2009)*	n = 28 overweight	180	-30	-	No change	No change	No change
		Brinkworth et al. (2009)*	n = 64 obese	365	-30	-	-	-	No change
		Siervo et al. (2012)	n = 21 middle and old aged	116	-40	↑	-	↑	-
		Kretsch et al. (1997)	n = 14 women	105	-50	-	-	No change	↓
		Buffenstein (2000)†	n = 9 overweight women	28	-66	-	-	-	↑
		Wing, Vazquez & Ryan (1995)*	n = 21 overweight women	28	-80	-	↑	↑	-
	Increase	Aquilani et al. (2008)	n = 24 elderly	21	+22	↑	-	-	-
Protein	Decrease	Ciarambino et al. (2011)	n = 52 overweight with T2DM	28	0	No change	-	-	-
	Increase	Van Der Zwaluw et al. (2014)*	n = 65 frail elderly	168	NR	No change	No change	No change	↑
		Jakobsen et al. (2011)	n = 11 healthy men	21	0	↑	↑	No change	No change
		Aquilani et al. (2008)	n = 24 elderly	21	+22	↑	-	-	-
Fat	Decrease	Bayer-Carter et al. (2011)	n =11 healthy elderly	28	0	-	No change	No change	No change
			n = 14 elderly with mild cognitive impairment	28	0	-	No change	No change	No change
		Nilsson et al. (2013)	n = 44 healthy adults	28	0	-	-	↑	-

		Wardle et al. (2000)*	n = 52 middle-aged adults	84	-17	-	-	↓	No change
	Increase	McMillan et al. (2011)	n = 12 young females	10	NR	-	-	No change	No change
		Lee et al. (2015)	n = 23 young females	10	NR	-	-	No change	No change
		Martínez-Lapiscina et al. (2013a)	n = 390 elderly subjects	2373	NR	↑	↑	-	-
		Martínez-Lapiscina et al. (2013b)^	n = 190 elderly subjects	2373	NR	↑	↑	No change	-
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	-	No change	No change	No change
		Holloway et al. (2011)	n = 16 healthy men	5	0	-	-	↓	-
		Edwards et al. (2011)	n = 20 healthy men	7	0	-	-	↓	↓
		Bayer-Carter et al. (2011)	n =9 healthy elderly	28	0	-	No change	No change	No change
			n = 15 elderly with mild cognitive impairment	28	0	-	No change	No change	No change
		Kwok et al. (2012)	n = 149 elderly care subjects	990	0	No change	-	-	-
		Wardle et al. (2000)*	n = 53 middle-aged adults	84	-17	-	-	↓	No change
		Halyburton et al. (2007)*†	n = 48 obese	56	-30	-	-	-	↑
		Brinkworth et al. (2009)*	n = 32 obese	365	-30	-	-	-	No change
Carbohydrate	Decrease	D'Anci et al. (2009)*	n = 9 overweight women	21	NR	-	No change	↑	-
		Makris et al. (2013)*	n = 22 obese	168	-25	-	No change	No change	-
		Cheatham et al. (2009)*	n = 16 overweight	180	-30	-	No change	-	No change
		Krikorian et al. (2012)*	n = 12 older adults	42	-41	-	-	No change	-
		Wing, Vazquez & Ryan (1995)*†	n = 11 overweight women	28	-80	-	-	↑	-
	Increase	D'Anci et al. (2009)*	n = 10 overweight women	21	NR	-	↑	↓	-
		Ngandu et al. (2015)	n = 591 elderly adults	730	NR	↑	↑	-	↑
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	-	No change	No change	No change
		Smith et al. (2010)	n = 38 obese	120	0	-	No change	↑	-
		Krikorian et al. (2012)*	n = 11 older adults	42	-6	-	-	No change	-

Makris et al. (2013)*	n = 25 obese	168	-25	-	No change	No change	-
Halyburton et al. (2007)*†	n = 45 obese	56	-30	-	-	-	↑
Cheatham et al. (2009)*	n = 12 overweight	180	-30	-	No change	-	No change
Brinkworth et al. (2009)*	n = 32 obese	365	-30	-	-	-	No change
Wing, Vazquez & Ryan (1995)*†	n = 21 overweight women	28	-80	-	-	↑	-

Note: Sample populations derived from diet groups only. Significant improvements are represented by an upwards arrow (↑). Significant impairments are represented by a downwards arrow (↓). Studies that do not measure the relevant cognitive domain are represented with a dash (-).† indicates that changes in these studies may be due to methodological shortcomings, such as a practice effect. Studies that manipulate both energy and macronutrient content are marked with an asterisk (*). (^) Martínez-Lapiscina et al. (2013b) used a random subsample of 285 subjects from the total pool of 522 subjects used in Martínez-Lapiscina et al. (2013a). NR = Not Reported.

4.3 Summary of findings

Of the 32 published articles relevant to 30 different diet interventions, 27 studies found significant changes in cognition following dietary manipulation. Briefly, despite notable variation in outcomes across all cognitive domains and diets, the literature indicates that reductions in energy intake and dietary fat appear beneficial to all types of memory function and measures of attention, while changes in dietary fat, especially towards a more healthful Mediterranean pattern may benefit multiple types of memory. Interestingly, although verbal memory did not show consistent changes following diet interventions, medium to strong effects were found following changes in energy intake (Witte et al., 2009) or fat intake (Nilsson et al., 2013). Based on the findings, information processing speed appeared insensitive to dietary alteration, while executive function showed some changes, noting that these were mostly apparent in tasks of inhibition. Meanwhile, working, visual-spatial, verbal memory and measures of attention evidenced some changes after diet manipulations (see Figure 4.3). Across the various domains, changes to energy intake and fat content appeared most impactful (see Figure 4.4), but given the variability in findings, this effect is not robust.

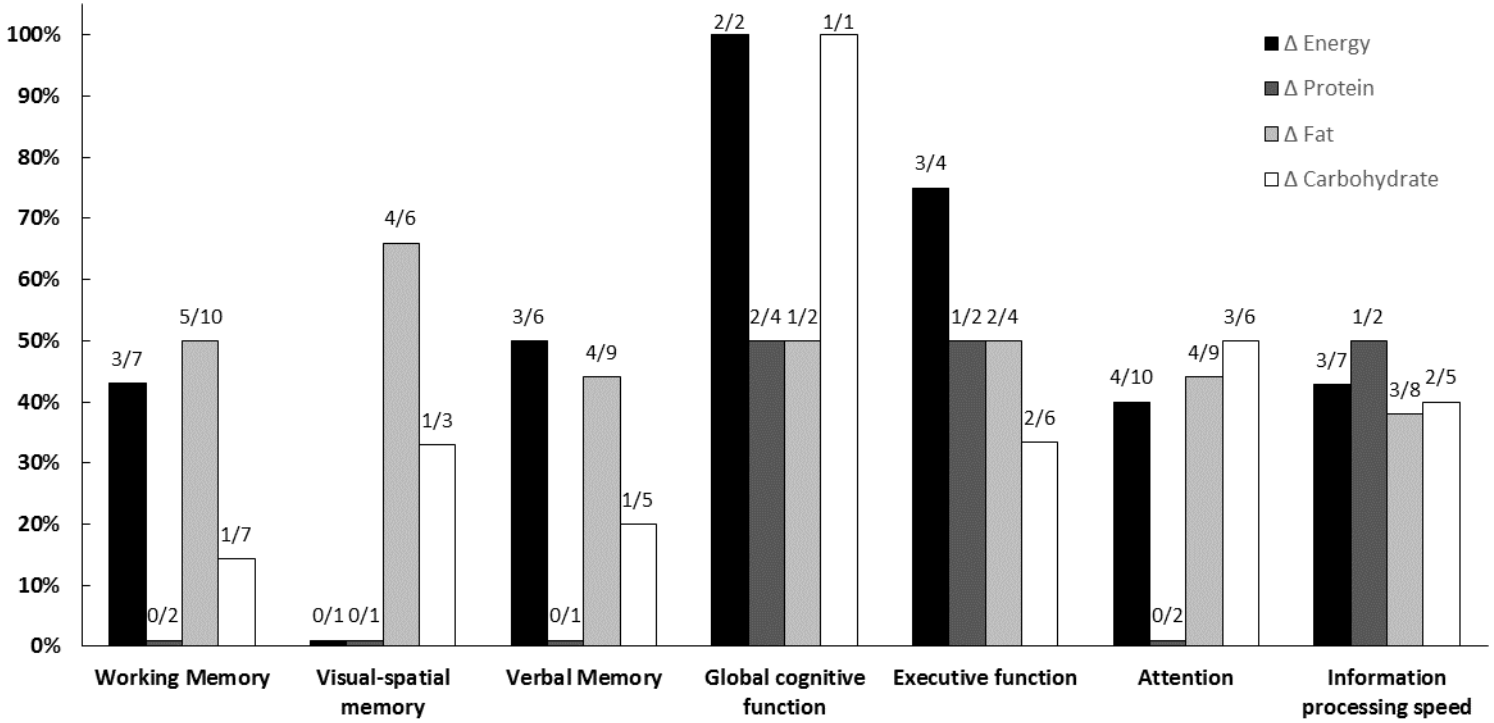

Figure 4.3. A summary of the pattern of results showing the number of studies with significant changes in each cognitive domain with respect to the total number of studies within each domain, sub-categorised by diet type. All tasks of memory appear to show some changes after diet manipulation, while non-memory tasks present mixed findings.

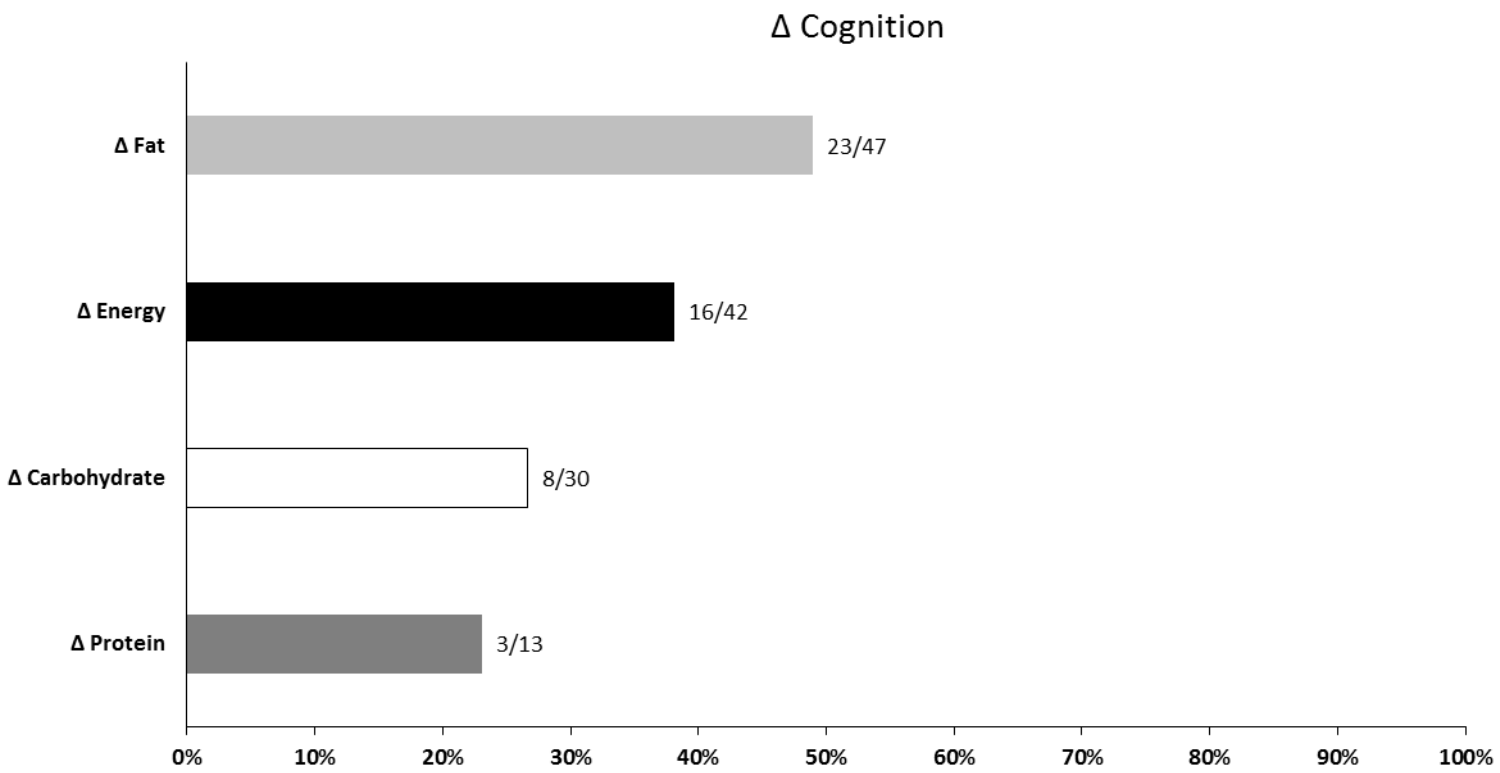

Figure 4.4. A summary of the pattern of results showing that, across the various cognitive domains, fat and energy intake appear to be most impactful on cognitive change (regardless of direction), while carbohydrate and protein appear to have minimal impact. Here, it appears that changes in fat and energy intake affect various areas of cognition (memory and non-memory) more so than changes in protein and carbohydrates.

4.4 Discussion

The focus of this manuscript was to review the experimental evidence of the relationship between diet and cognition. Overall, there was some evidence that both memory performance and attention were affected by changes in dietary energy intake and fat intake. Measures of attention, working, visual-spatial and long-term memory appeared most sensitive to changes in macronutrient content, with large but inconsistent effects found in verbal memory. Most notably, performance on tasks of longer-term memory appeared to be influenced by changes in energy and fat intake – an idea is consistent with animal data, which have found impairments in hippocampal-dependent learning and memory following an energy-rich HFS diet (Beilharz, Maniam & Morris, 2014; Davidson et al., 2013; Jurdak & Kanarek, 2009; Molteni et al., 2002). One potential explanation of this pattern of results might be that diet might affect specific brain regions associated with performance on these various measures (Kallus, Schmitt & Benton 2005; Monti, Baym & Cohen, 2014; Vuoksimaa et al., 2013), but this has yet to be tested experimentally.

Any causal inference about the relationship between diet and cognition would be supported substantially by related physiological changes. Research on the potential physiological mechanisms involved in diet-induced cognitive changes may provide some insight into which dietary components are important. Moreover, the criteria for establishing causality (e.g. the Bradford-Hill criteria) include a biological gradient – greater exposure should generally lead to greater incidence of the effect. A small number of studies have explored various mechanisms including insulin (Witte et al., 2009), ketones (Makris et al., 2013), and inflammation (Nilsson et al., 2014; Witte et al., 2009). These potential mechanisms mediating the relationship between diet and cognition have been discussed in detail elsewhere (see; Francis & Stevenson, 2013; Parletta, Milte, & Meyer, 2013). Briefly, the experimental evidence has demonstrated a negative relationship between verbal memory performance and insulin following decreases in energy (Witte et al., 2009), carbohydrates

(Krikorian et al., 2012) and fat, (Nilsson et al., 2013) indicating a significant role of glucoregulatory processes in mediating the relationship between diet and memory function. Additionally, improvements in memory performance were significantly associated with reductions in inflammatory markers following decreases in energy (Witte et al., 2009) and fat intake (Nilsson et al., 2013). Levels of ketones – a metabolite from fat in the absence of dietary carbohydrate and upon depletion of glycogen stores –were positively correlated with verbal memory performance ($r = 0.45$) in response to a relatively brief period of carbohydrate restriction (Krikorian et al., 2012). WM and executive function were not affected by the level of dietary carbohydrate – supporting the notion that carbohydrate restriction affects long-term memory via ketone metabolism.

4.4.1 Recommendations for Future Studies

The findings from experimental studies to date have been inconclusive. A reasonable argument can be made that this is in part due to substantial variability in the designs of diet interventions. In the studies reviewed here multiple designs were employed, including between-subjects (23 studies), within-subjects (2 studies), or mixed designs such as randomised cross-over trials (5 studies). Within-subjects and mixed designs offer a practical approach to diet manipulation, since fewer subjects are required with subjects serving as their own controls. However, if diet has a long-lasting or persistent effect on cognition, then a within-subjects or mixed design would be inappropriate and may confound identification of causality. Thus, from an experimental standpoint, a between-subjects design is recommended to better isolate the effects of diet on cognition and to avoid carry-over or interference between diet conditions.

The reviewed studies varied dramatically in their dietary interventions making it difficult to compare their findings. Some experimental studies administered stringent and clear diet guidelines (Bayer-Carter et al., 2011; Nilsson et al., 2013), while others did not (Bryan & Tiggemann, 2001; Ciarambino et al., 2011). Ideally, well-defined dietary

guidelines on what participants are allowed to consume during the intervention period should be provided to standardise test conditions. Alternatively, individually tailored dietary plans that ensure macronutrient proportions, while also giving each person their required daily energy intake will likely improve overall dietary compliance and is also recommended for future studies. It may also be worthy of consideration to increase the variety of foods available within a dietary intervention as a means of increasing diet compliance. Few diet intervention studies accounted for major confounds including physical activity, stress levels or sleep patterns. Indeed, accounting for these sources of variance can influence diet effects. For instance, Smith et al. (2010) found that improvements in cognition associated with diet compliance were attenuated when variables of physical activity were accounted for statistically. Given that the majority of diet interventions considered in this review were weight-loss diets, accounting for physical activity levels would allow researchers to explore the individual and combined contributions of the diet intervention and physical activity to changes in cognitive function. Additionally, it would be interesting to investigate whether participants compensate for substantial changes in diet (e.g., increasing fat intake: Holloway et al., 2011). Consequently, researchers should be aware of and account for major confounds including stress, alcohol and caffeine intake, and sleep and physical activity habits.

Long-term benefits of diet should, presumably, be easier to observe after longer periods of time (e.g. Martínez-Lapiscina et al., 2013a, 2013b). Importantly, the amount of time it takes for dietary intake to affect cognition depends on various factors including, but not limited to the area of cognition being tested, the absolute and relative macronutrient intake in the diet, adherence to the diet, and sample population. Although some researchers have taken these factors into consideration to varying degrees, one important caveat of diet research that remains unclear relates to the earliest occurrence of cognitive changes. Indeed, it may be worthy of consideration to determine the minimum amount of time to observe significant changes in cognitive function, which will likely reduce the amount of time and

resources required from both researchers and participants. A fortunate consequence of this may be increased diet adherence and reduced attrition. Most studies found significant changes in various cognitive domains even at short time periods (Edwards et al., 2011; Holloway et al., 2011; Lee et al., 2015; Lindseth et al., 2011; McMillan et al., 2011), while no changes were reported after a 2 day diet intervention (Lieberman et al., 2008), suggesting that cognitive changes occur after 5 or more days (e.g. Holloway et al., 2011). However, the experimental studies revealed no clear pattern of results in relation to duration of diet. The reason for this inconsistency is unclear, and the minimum duration for a diet to affect cognition remains unknown.

The abundance of potential validated cognitive tasks available to researchers means that cognitive tasks can be combined and tailored to the specific requirements or hypotheses of the study. It has been previously recognised that there is no definitive guide for the selection of cognitive tests within the field of diet research (Wesnes, 2010). A failure to detect an effect of a diet on cognition may due to a true absence of cognitive change, or it may reflect poor sensitivity in the chosen cognitive tasks. Cognitive tasks that measure an appropriate function with low sensitivity will not likely demonstrate the expected effect of a diet intervention. Moreover, the difficulty of the cognitive task may determine its sensitivity to changes in diet (Hoyland et al., 2008). Thus, cognitive tasks of increasing difficulty should be used to detect the subtle effects of diet interventions, while alternate (or parallel) forms of the same task will also serve to reduce practice effects, and minimise variability in task performance. The absence of alternate forms of a cognitive task greatly limits its utility in diet research in which the principal goal is to detect change.

Studies should aim to assess multiple cognitive domains to correctly interpret findings (Schmitt, Benton & Kallus, 2005). The assessment of various cognitive domains may provide insight into the specificity of a diet-induced effect, as well as potentially determining the primary source and sequence of cognitive changes. In addition, the optimal functioning

of one domain may depend on the quality of another related domain. For instance, Tam & Schmitter-Edgecombe (2013) found that performance on a visual-spatial task (BVMT) was dependent on the quality of processing speed in healthy older adults. Changes in processing speed could influence performance on this task, but this can only be established if tests of processing speed are performed concurrently. Consensus about which cognitive tests to use has not been reached, but in order to satisfactorily compare studies, measures should be consistent and only changed with sufficient justification. Caution should be taken in developing series of cognitive tasks, since a lengthy battery can lead to fatigue and diminished motivation. An extensive battery has the potential to determine a wide range of effects and to determine if some domains are more sensitive to dietary change than others. Based on the findings in this review, we recommend a cognitive battery including a measure of numerical WM (e.g. digit span), a free word recall task of verbal memory (e.g. RAVLT), visual-spatial memory (e.g. ROCF), attention (e.g. RVIP), and inhibition (e.g. Go/ No Go task). The items on this battery have been derived from thorough examination of the most sensitive cognitive tasks used in diet intervention studies (see Figure 4.1. for a summary).

An interesting point to take into consideration is that particular subsets of macronutrients may differentially affect cognition, but this has not been well explored. Without an appropriate breakdown of the types of macronutrients, it is difficult to conclude how specific components of a diet impact cognition. For instance, knowing the total carbohydrate intake does not inform us of the relative or absolute intake of simple or complex carbohydrates, which may prove vital since simple and complex carbohydrates differentially influence short-term cognitive performance (Benton et al., 2003) and may have long-term consequences. Based on the findings of the experimental studies, we speculate that decreases in energy intake by at least 20% may be sufficient to observe changes in cognitive performance, especially in memory tasks. Increases in fat greater than 30% may affect cognition, noting that fat type might be important here. The findings around protein and

carbohydrates are mixed, but the degree of dietary manipulation will likely be dependent of the goals of the study.

It is worth noting that there may be populations more vulnerable to the effects of diet change. The cognitive impairments associated with increased weight have been well documented (e.g. Smith et al., 2011), and while the arrow of causality has yet to be determined, obese subjects may benefit most from dietary intervention that improves both weight loss and cognitive outcomes. A meta-analysis by Siervo et al. (2011) found that weight loss was associated with better performance on TMT-B, especially in older adults, supporting the notion that excess weight may be a risk factor for cognitive decline. Likewise, populations with existing impairments might see improvements in cognition, but the most sensitive cognitive domains have yet to be established. Recent research has sought to use dietary interventions to enhance the cognitively impaired (e.g. Aquilani et al., 2008) or as a means of primary prevention of pathological cognitive aging (e.g. Martínez-Lapiscina et al., 2013a). These diets typically move away from one pattern of diet intake (e.g. the Western diet), to one associated with better health outcomes (e.g. the Mediterranean diet). To date, the majority of studies have improved cognitive performance following adherence a Mediterranean-like diet (Lee et al., 2015; McMillan et al., 2011; Martínez-Lapiscina et al., 2013a; 2013b). On the other hand, there is very little experimental evidence that shifting away from the Mediterranean diet towards the Western diet leads to impaired cognitive function, with only a few studies testing the effects of a high-fat diet (Bayer-Carter et al., 2011; Edwards et al., 2011; Holloway et al., 2011; Lindseth et al., 2011). It would be interesting to investigate the effects of long-term consumption of a Western-like diet on cognitive function, but such long-term RCTs may be harmful and potentially unethical. One way around this complication is to group participants retrospectively, but no human studies exist to date. It may be that a Western diet high in fat and sugar has little effect on cognition in humans, but these effects remain relatively unexplored. Notably, no human studies have

as yet examined if the effects of diet on cognitive function are reversible, which could be crucial in determining the role of diet in cognitive function.

4.4.2 Potential for Remediation

Diet interventions may provide a practical approach to enhancing cognition, although such an approach would be well advised to wait until diet-cognition relationships are considerably better understood. There is accumulating evidence that the ratio of various fats may be important. The ratio of omega-6 to omega-3 polyunsaturated fats, which may be up to 15 times higher in a typical Western diet (Simopoulos, 2008), is linked to cognitive decline later in life (Loef & Walach, 2013). To date, only one experimental study measured this ratio and found memory improvements associated with its decrease (Nilsson et al., 2011). Meanwhile, the Mediterranean diet – one high in PUFAs and MUFAs may be effective for both weight loss maintenance (Panagiotakos et al., 2006) and improvements in cognition, especially in older individuals. For instance, adherence to the Mediterranean diet for 6.5 years improved global cognitive performance (scores on MMSE and Clock Drawing Task) compared to a low-fat control diet (Martínez-Lapiscina et al., 2013a). Indeed, determining the absolute changes in saturated, monounsaturated and polyunsaturated fats (as well as their relative ratios) associated with improved memory is essential since the relative intake of omega-6 to omega-3 fatty acids is positively associated with cognitive decline and incidence of dementia (Loef & Walach, 2013).

4.4.3 Conclusions

This is the first review of the experimental evidence of diet-induced changes in cognitive function. In summary, there was a trend showing that memory and attention were most sensitive to changes in energy and fat intake, but no consistently clear dietary effect was found since many studies yielded results in the opposing direction. Unfortunately, there is a paucity of high-quality long-term RCTs testing diet-induced changes in cognitive function. In order to strengthen the knowledge base, there is a clear need for better quality RCTs in the

diet intervention literature to determine the causative role of diet in cognitive function. Future experimental research should aim to account for important confounds (e.g. physical activity levels), administer distinct and well-controlled dietary interventions and determine optimal diet duration. Diet intervention studies should also aim to report all pertinent nutritional information as well as the relevant statistical data. We will have a much clearer understanding of our current position and where the diet-cognition literature is headed once the findings have been compiled and analysed quantitatively (i.e., a meta-analysis).

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Chapter 5: Methodological considerations for longitudinal diet interventions

The aim of the current chapter is to discuss the methodological considerations associated with experimental diet studies in humans, and in particular, in the context of determining the effect of a Western-style diet on hippocampal-dependent learning and memory (HDLM) – the focus of Chapter 6. Within each section of this chapter, the methodological issues are systematically discussed in the following manner. First, common approaches within the field of nutrition and psychology are outlined, along with common challenges associated with these approaches. Second, potential ways for dealing with such challenges are discussed, with specific reference to the experimental study presented in Chapter 6 of this thesis (i.e., examining whether switching to a Western-style diet impairs HDLM). Third, the most suitable and appropriate method for Chapter 6 is described, along with the rationale for its selection.

5.1 Methodological Considerations in Longitudinal Studies

5.1.1 Study Design

The aim of the experiment in Chapter 6 is to detect impairments in HDLM following a shift to a high-fat high-sugar (HFS) diet. The review in Chapter 4 revealed that a common study design employed by previous experiments is a between-subjects design, where the effects of diet on cognition in an experimental condition are compared to a control condition. However, between-subjects designs introduce additional inter-individual variation, making it more difficult to observe diet-related changes in cognition. Specifically, the detection of diet-induced changes in cognitive performance must compete with additional sources of variation (e.g., level of education, IQ, gender, age, and body mass index (BMI)). One potential way to deal with this is to use a cross-over design. In this design, the sample population receives both the experimental and control conditions (the order of which is randomised), separated by a wash-out period to

prevent contamination between conditions. The major advantage of this design is that participants serve as their own control, thereby minimising inter-individual variation. Cross-over designs may therefore be more sensitive to diet-related changes than other designs. The influence of confounding factors is minimised and the study requires fewer participants. However, a cross-over design would not be suitable nor appropriate for the experiment in Chapter 6. There are several reasons for this assertion. First, cross-over designs also increase the time and resource burden for both researcher and participant, and hence increase the likelihood of attrition. This may explain why the majority of diet intervention studies to date have employed a between-subjects design, while relatively few have employed a cross-over design (Attuquayefio & Stevenson, 2015). Second, one major drawback of cross-over designs relates to carry-over effects or cross-contamination between treatment groups, which has been reported in previous diet intervention studies (e.g., Krikorian et al., 2012). If diet has long-lasting or persisting effects on cognition, then this design would be inappropriate and may confound the identification of causality. Third, based on animal evidence, it is anticipated that shifting an individual to a Western-style diet will lead to impairments on hippocampal-related memory tasks, and controlling for cross-contamination or carry-over effects between conditions would be difficult. Finally, since it is unclear when changes in cognition occur or how long they persist, an appropriate wash-out period (the time allowed to elapse between conditions to prevent cross-contamination) cannot be determined.

An alternative to this may be within-subjects and mixed designs. A within-subjects design compares all subjects on the treatment conditions (i.e., an HFS diet and a control diet), and therefore would measure differences between treatment conditions within the same group of subjects. Like cross-over designs, it eliminates inter-individual variability and requires fewer

participants. Again, similar to the problems identified in cross-over designs, if diet has a long-lasting or persistent effect on cognition, then a within-subjects would be inappropriate and may confound the identification of causality. Likewise, the risk of carry-over effects is greater and change over time cannot be measured. A mixed design, using elements from both between (experimental group vs control group) and within (before treatment vs after treatment) designs, may offer a reasonable alternative since separate conditions can be compared over time, cross-contamination is unlikely, and each person serves as their own control, thereby minimising variability in responses. Furthermore, differences in test performance between the experimental and control groups would reveal the impact of the manipulation over and above the improvements associated with repeated administration. Based on these reasons, a mixed design is employed in Chapter 6 to determine the effects of an HFS diet over time on an experimental group, relative to a control group. Subjects are also be randomly allocated to either the experimental group receiving the HFS diet, or a control group who consume an appropriate control diet (discussed in further detail in Section 5.1.3.).

5.1.2 Study Participation

5.1.2.1 Participant characteristics

The target population is an important consideration in the selection of measures used to explore diet-related changes in cognition. For instance, diet interventions may be particularly beneficial in those identified as at risk of cognitive decline, with some populations more susceptible to the effects of diet on cognition. The cognitive impairments associated with increased weight have been well documented (e.g. Smith et al., 2011), and while the arrow of causality has yet to be determined, obese subjects may benefit most from dietary intervention

that improves both weight loss and cognitive outcomes. For example, a meta-analysis found that weight loss in obese adults was associated with improved performance on executive function tasks, especially in older adults (Siervo et al., 2011). Given that both overweigh and cognitively-impaired individuals present with similar impairments, recent research suggests that diet may be an underlying factor in the prevalence or maintenance of such impairments. However, the considerable variability in methodologies and, in particular, in sample population, there are several complications. These are detailed below.

The majority of diet intervention studies reviewed in the Chapter 4 recruited overweight or obese adults (e.g., Siervo et al., 2012) or elderly adults with mild cognitive impairment (e.g., Aquilani et al., 2008) to form the sample population, in an effort to determine whether changes in diet can improve cognitive function. Since the aim of Chapter 6 is to determine whether the presence of an HFS diet *impairs* hippocampal-related memory (as the animal data have consistently shown), careful consideration must be given to the sample population. For example, an HFS diet is argued to impair brain areas related to memory and energy regulation processes, and this impairment is responsible (at least in part) for an increase in body weight and ultimately obesity. Therefore, using an overweight or obese population may be problematic as such populations may have existing impairments in processes related to cognitive function (e.g., Smith, Hay, Campbell & Trollor, 2011) or sensitivity to hunger and fullness (e.g., Francis & Stevenson, 2011). Likewise, poorer HDLM is associated with increased weight (e.g., Cournot et al., 2006) and higher consumption of fat and sugars (e.g., Francis & Stevenson, 2011). Therefore, it may be more prudent to use a population without these existing problems (i.e., lean individuals) and for whom such foods are not commonplace (i.e., a generally healthy diet low in saturated fats and refined sugars).

Another important reason for using healthy lean adults is that this population parallels the animals from which the human literature is based. That is, animals are typically healthy weight and maintained on a nutritious lab chow before being shifted to a diet high in saturated fats and refined sugars (e.g., Beilharz, Maniam & Morris, 2016). Thus, by recruiting lean adults with a diet typically low in fats and sugars, more reasonable conclusions from the findings can be drawn when population characteristics are more consistent with the animal research. In addition, pre-existing problems in the sample related to weight or diet are minimised and the chances of observing changes following an HFS are improved.

5.1.2.2 Recruitment and attrition

Recruitment of eligible participants and attrition are two common challenges associated with dietary interventions. While some have previously recruited from a clinical population (e.g., Aquilani et al., 2008), it is also common to use university students available on campus to form the sample population (e.g., Holloway et al., 2011). There are several distinct advantages of using a university population. First, students typically attend research for course credit, reducing the financial costs associated with research. Second, recruitment from this population may be easier than recruiting from the general population as students are in plentiful supply and immediately available to researchers on campus. Third, in the context of the experiment in Chapter 6, the pool of students from which to choose is likely sufficient in size to find potential participants with a diet low in saturated fats and sugars. Finally, it may be easier to recruit lean adults from a university population than the general population, thereby allowing recruitment of the sample population with the desired attributes (described earlier).

Another issue related to recruitment is attrition – the loss of participants to follow-up during the study. Attrition is problematic as it can result in a study being statistically

underpowered and can threaten external validity if it results in a more homogenous sample relative to the original group. The treatment effect can also be impacted as attrition may lead to non-random missing data from incompletion of the full intervention (i.e., systematic differences between participants that dropout in the treatment group compared to the control group). One way to minimise attrition is to reduce the burden associated with participation, but this must also be balanced with a sufficient diet manipulation and adequate cognitive testing. For example, lean individuals may find it difficult to consume foods with much higher levels of fat and sugar. The experiment in Chapter 6 addresses this issue by requiring participants to attend the laboratory once-daily over four consecutive days to consume a prescribed breakfast varying in fat and sugar content, with cognitive tests administered on the first and last days of the experimental period. By reducing the time associated with participation (i.e., consumption of the HFS diet and the relevant cognitive tests), the burden is reduced and a common source of attrition is eliminated.

5.1.2.3 Power analysis

It has been argued that researchers should use effect sizes based on previous research to improve confidence that null findings are due to a lack of effect, rather than a lack of power (Adolphus, Lawton, Champ & Dye, 2016). However, the review in Chapter 4 reveals that this is not possible, since effect sizes within the field of diet studies are seldom reported or cannot be easily extrapolated from the statistics provided. Thus, calculations based on a previous literature are not possible and conventional effect sizes were used to perform power analyses (using G*Power version 3.1) for the experiment in Chapter 6. Previous work has found a small-to-medium relationship between HFS intake and HDLM (e.g., Attuquayefio et al., 2016; Francis & Stevenson, 2011), similar effects were expected in the subsequent study. Specifically, since a

moderate effect size (d = 0.5) was anticipated for the main outcome variables of HDLM (outlined in Section 5.1.4.), a power analysis indicated that 128 individuals (64 per group) were required in order to have an 80% chance of rejecting the null hypothesis at $\alpha = 0.05$. Additionally, anticipating that some would have missing data or would be lost to attrition, every effort was made to recruit approximately 60 participants per group.

5.1.3 Dietary Manipulation

5.1.3.1 Nutritional profile of the diet

There is extensive animal research showing hippocampal-dependent tasks are impaired following diets high in saturated fats (e.g., Morrison et al., 2010), sucrose (e.g., Jurdak & Kanarek, 2009) and saturated fats and sugars (e.g., Beilharz, Maniam & Morris, 2014). Based on this, it is believed that similar diet-induced changes in cognition could also occur in humans, with some evidence from correlational studies supporting this claim (Attuquayefio et al., 2016; Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011). What remains to be tested experimentally in humans is whether shifting towards a Western-style diet leads to impairments in HDLM.

Findings from the review in the Chapter 4 suggest that cognitive tasks are sensitive to dietary manipulations. The findings indicated that decreases in energy intake by at least 20% and that increases in fat by at least 30% may be sufficient to observe improvements (although this was not always the case) in cognitive performance, especially in memory tasks. There are, however, two central issues in these experimental studies that make it difficult to accurately predict the effects of a Western-style diet on hippocampal function. First, the absence of a detailed breakdown of the nutrient profile of each diet has limited conclusions relating to how

specific components of a diet (e.g., saturated fats) impact cognition. For instance, while increases in fat by at least 30% typically improve cognition, the type of fat may be important in determining the direction of change in cognitive performance in experiments. Greater self-reported adherence to a prescribed Mediterranean-style diet – one high in polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) improves cognition (Lee et al., 2015; McMillan, Owen, Kras & Scholey, 2011), while other have found that increases in total fat impair cognition (Edwards et al., 2011; Holloway et al., 2011). Likewise, the breakdown of carbohydrates into starches and refined sugars is seldom reported (e.g., Halyburton et al., 2007) and changes in carbohydrates are often conflated with changes in energy intake (e.g., Krikorian et al., 2012). As a result, reasonable conclusions regarding the effects of macronutrients on cognition are limited.

The second major challenge is the lack of human experimental evidence with the specific aim of observing *impairments* in cognition following a diet. The majority of experimental studies have investigated how diet can improve cognitive performance. However, the aim of the experiment in Chapter 6 is to detect impairments in one particular aspect of cognition following an experimental diet high in saturated fats and refined sugars. A handful of experimental studies have tested the effects of a high-fat diet on cognition, with mixed results. Impairments in cognition were evident following a brief high-fat diet (Edwards et al., 2011; Holloway et al., 2011; Lindseth et al., 2011). Meanwhile, another study failed to find changes in verbal memory following a high-fat (50% (saturated fats >25%)), high glycaemic index (>70) diet maintained over 4 weeks in adults with and without mild cognitive impairment, but a low-fat diet did improve memory recall (Bayer-Carter et al., 2011). However, the authors concede that the small sample size (~25 per group) may have affected the power to detect diet-related impairments (see

Section 5.1.2.3. on a discussion of power calculations). An alternative source of information into the effects of an HFS diet comes from single meal studies, which typically provide participants a single meal varying in macronutrient content in a lab setting. While a review of single meal studies found that consumption of soluble glucose enhances verbal memory (although not consistently), the amount of glucose is typically low (~25g) (Hoyland, Lawton & Dye, 2008). Indeed, it may be that larger doses of glucose (i.e., a refined sugar) are required to observe impairments in HDLM, as seen in animals. For instance, a more recent study found that a single meal high in fat (50% total fat and 25% saturated fat) and high in sugar (with a glycaemic index >70) leads to deficits in delayed verbal memory in older adults without cognitive impairment (Hanson et al., 2015). This single meal study provides some evidence that changes in cognition are detectable in humans after a short period. It also provides some insight into appropriate parameters for an experimental diet in a younger lean population.

Based on the evidence, a high-fat (~50g total fat with 30g from saturated fats) and high-sugar (~50g) diet has been formulated for Chapter 6 to determine its effects on HDLM tasks. One challenge in formulating an HFS diet is formulating an appropriate matched control diet. That is, while the saturated fat and refined sugar intake varies between groups, the control diet must also be matched (as much as possible) on energy intake, volume, satiating value, and palatability. Pilot testing confirmed equivalency on these attributes between diets (more on this in Chapter 6). The control diet is therefore low in saturated fats and refined sugars, and high in protein – a macronutrient that does not seem to greatly affect cognition (Attuquayefio & Stevenson, 2015). Additionally, the control diet is likely to reflect the typical low-fat low sugar diet of the lean individuals that form the pool from which groups are randomly formed.

5.1.3.2 Diet instruction and adherence

The studies reviewed in Chapter 4 varied dramatically in the type of dietary intervention, making it difficult to compare findings. Some experimental studies provide general instructions only (e.g., Bryan & Tiggemann, 2001), while others provide all foods and beverages of the prescribed diet (e.g., Bayer-Carter et al., 2011). Ensuring participants adhere to the prescribed diet is a challenge, and each of these methods has its advantages and disadvantages. The provision of instructions to participants has more flexibility, allowing participants to consume foods based on individual preferences, which may improve adherence and retention. This type of intervention also reduces the logistic and financial resources required to implement the diet. However, there are important disadvantages to this method, including: (1) less control over what and how much is consumed, typically relying on self-report measures to check for adherence, and (2) such instructions cannot guarantee the desired manipulation in diet. For instance, despite imposing restrictions on carbohydrate intake only, Krikorian et al. (2012) reported significant differences in total energy intake between groups over the intervention period.

The alternative to instructions is the provision of all foods for the diet manipulation. While this increases the financial and time commitment for both participant and researcher, it boosts diet adherence and allows greater control over the nutritional profile of the diet. If a researcher is to argue that a specific dietary profile (e.g., saturated fats and refined sugars) impacts HDLM, then providing the diet in its entirety ensures the intended macronutrient manipulation, as well as potentially avoiding problems associated with concurrent variation in energy intake, as previously noted (e.g., Krikorian et al., 2012). Based on this, participants are provided with certain foods in the experiment in Chapter 6, thereby maximising adherence in the both diet groups and safeguarding the diet manipulation. Specifically, participants are required

to attend the laboratory to consume the test meals, allowing greater control over the components of the diet. Moreover, only a breakfast meal is provided to participants over the diet period. This is done to ensure diet adherence, but not increase participant burden (see Section 5.1.2.2.).

The rationale for requiring participants to attend the laboratory in the experiment in Chapter 6 is to ensure diet adherence. However, in an effort to decrease the burden to participants in this experiment, only one meal daily is consumed in the laboratory. While the ideal situation would involve controlling and manipulating all foods over the diet period, this is financially and logistically untenable in the current study. Therefore, to determine the effects of the daily prescribed breakfast meal on subsequent food intake (and hence overall dietary change), it is also important to measure the dietary habits outside of the laboratory during the diet period. There may be two possible outcomes from the experimental diet. First, lean individuals may compensate for the HFS breakfast by changing their subsequent intake throughout the day, thereby maintaining a daily energy balance. Alternatively, the consumption of an HFS diet may impact their subsequent nutritional quality, possibly shifting it towards more palatable but unhealthy foods – a phenomenon predicted by others previously (Davidson, Kanoski, Walls & Jarrard, 2005; Hargrave, Jones & Davidson, 2016). Thus, to determine the effects of the HFS diet on subsequent eating behaviour, participants are required to complete a comprehensive food diary. Moreover, given the mixed design of the experiment (see Section 5.1.1.), food diary measurements are collected at two time points prior to the experiment to obtain a more realistic, typical indication of dietary habits, and twice during the experiment (at the start and at the end), to track changes over the diet period.

5.1.3.3 Duration of diet manipulation

It is currently unclear when changes in cognition are initially detectable, and if such changes occur immediately, or occur steadily or worsen over time. The amount of time to observe changes in cognition depends on various factors, which are discussed throughout this chapter, including: (1) the sensitivity of cognitive tests (Section 5.1.4.2.); (2) the magnitude of dietary shift (Section 5.1.3.1.); (3) how well participants adhere to the prescribed diet (Section 5.1.3.2.); and (4) the sample population used (Section 5.1.2.1.). In animals, impairments on hippocampal-dependent tasks are evident after 3-7 days (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Kanoski & Davidson, 2010; Tran & Westbrook, 2015). In humans, diets as brief as 4-10 days have resulted in impairments (Edwards et al., 2011; Holloway et al., 2011; Lindseth et al., 2011) or improvements in cognition (Lee et al., 2015; McMillan et al., 2011), implying that diet-induced changes in cognition, regardless of direction, are possible after a short period of time.

As noted previously, the parameters of an experiment to induce cognitive changes from an HFS diet have not been previously explored. However, the fact that impairments can be seen after a relatively brief period in in humans (e.g., four days) suggests that a shift to an HFS diet may also impact cognition within a similar time period. Additionally, an HFS diet may have a greater impact on cognition than other types of diet shifts previously employed (e.g., Lindseth et al., 2011). As such, Chapter 6 sought to detect changes in HDLM and interoception following a shift to an HFS diet over a four-day period. Additionally, a shorter duration is likely to improve recruitment prospects, decrease attrition and resources required, as well as reducing the risk to participants since a shift to Western-style diet is believed to have adverse impacts on memory and eating behaviour.

5.1.4 Neuropsychological Tests

5.1.4.1 Domains of interest

The animal data indicate that tests that are hippocampally-dependent are impaired following an HFS diet, while tests that are independent of hippocampal function remain unchanged (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Tran & Westbrook, 2015). In humans, tests of verbal memory – known to be hippocampally-based – appear to be most sensitive to experimental manipulations of macronutrient content (Attuquayefio & Stevenson, 2015; Hoyland et al., 2008). Likewise, correlational studies have found that habitual consumers of a Western-style diet are impaired on tasks of verbal memory, including long-term memory recall (e.g., Francis & Stevenson, 2011) and word-list learning (Attuquayefio et al., 2016). Importantly, as in animals, performance on non-hippocampal-related measures is not predicted to be related to HFS diet consumption. Therefore, the experiment in Chapter 6 used cognitive tests known to be hippocampally-dependent. Furthermore, a non-hippocampal test was also included to reveal the suggested specificity of diet-related changes in cognition to hippocampal function. The criteria for the selecting which tests to use are described in detail in the next section.

5.1.4.2 Criteria for the selection of neuropsychological tests

The animal data indicate that hippocampal-dependent tests are sensitive to shifts towards a Western-style diet, while non-hippocampal tests remain stable. Correlational evidence in humans indicates that this might also be true in humans, but no experimental test of this exists to date. There is a plethora of hippocampal-dependent and hippocampal-independent tests available. While the criteria for selection of cognitive tests used in nutritional studies has been

comprehensively reviewed elsewhere (de Jager et al., 2014; Schmitt, 2010; Wesnes, 2010), the following are considered the most relevant psychometric properties for the selection of cognitive tests. That is, neuropsychological tests should: (1) measure what they purport to measure (i.e., hippocampal or non-hippocampal function); (2) have established sensitivity to variation in diet either from correlational or experimental findings; (3) have good reliability over multiple administrations (i.e., test-retest reliability); (4) have alternate forms available to minimise practice effects; and (5) have good utility (i.e., ease and time of administration) as this is likely to decrease participant burden and minimise cognitive fatigue. Based on the above criteria, the following tests have been selected for the experiment in Chapter 6: Logical memory (LM) test of the Wechsler Memory Scale Fourth Edition (Wechsler, 2009), the Hopkins Verbal Learning Test Revised edition (HVLT-R; Brandt, 1991), and the Digit span (DS) test of the Wechsler Memory Scale Third Edition (Wechsler, 1997). The rationale for selecting these neuropsychological tests is detailed below.

Logical memory (LM) was selected because performance on LM is sensitive to hippocampal damage (Sass et al., 1992) and varies as a function of fat and sugar intake (Francis & Stevenson, 2011). The LM test also shows good test-retest reliability (r = 0.71-0.74), and eight validated alternate forms are available (Schnabel, 2012; Sullivan, 2005), making it ostensibly suitable for repeat testing. The test takes 10 minutes to administer and detailed scoring guidelines are available.

Another hippocampally-dependent test was also selected – Hopkins Verbal Learning Test (HVLT-R). Similar to LM, the HVLT-R is significantly associated with hippocampal volume and neuronal activity in healthy and cognitive impaired aged adults (Sexton et al., 2010). While this particular test has not been used in experimental diet studies, other similar word-list tasks

have previously shown sensitivity to shifts in diet (Bryan & Tiggemann, 2011; Kretsch et al., 1997; Krikorian et al., 2012; Lee et al., 2015; McMillan et al., 2011; Nilsson, Tovar, Johansson, Radeborg & Björck, 2013; Witte, Fobker, Gellner, Knecht & Flöel, 2009), as well as impaired paired associate learning in individuals with a higher intake of saturated fats and refined sugars (Attuquayefio et al., 2016). The HVLT-R was selected over other tests (e.g., California Verbal Learning Test) because it is shorter and therefore easier to administer and unlikely to lead to cognitive fatigue. The three immediate recall trials and the delayed recall and recognition trials take up to 10 minutes to administer compared to the 20 minutes for the California Verbal Learning Test. Importantly, the HVLT-R shows good consistency with the longer California Verbal Learning Test (Lacritz & Cullum, 1998). The test-retest reliabilities are modest (r = 0.50) for HVLT-R (Woods et al., 2005), and six alternate forms are available for multiple testing (Brandt, 1991).

The non-hippocampal measure (i.e., digit span) selected was based on its association with non-hippocampal brain areas such as the frontal cortex (Leskelä et al., 1999) and the dorsolateral prefrontal cortex (D'Espossito & Postle, 1999), as well as its established sensitivity to changes in diet (Brinkworth et al., 2009; D'Anci, Watts, Kanarek & Taylor, 2009; Halyburton et al., 2007; Martínez-Lapiscina et al., 2013). It is commonly used as a test of working memory because rehearsal processes are minimised as subjects repeated the remembered information immediately following presentation. The Digit span test, which has two components – the forwards and backwards span – also has good test-retest reliability (r = 0.83-0.89), and is easy to administer taking approximately five minutes.

In sum, human research suggest that hippocampal-dependent measures (i.e., verbal memory tests) may be sensitive to shifts in fats and sugar intake, while non-hippocampal

measures are likely to be spared. Thus, based on the selection criteria outlined above, the experiment in Chapter 6 uses hippocampal-related memory tests (i.e., Logical memory and HVLT-R) to determine the effect of an HFS diet on cognition. Furthermore, to demonstrate the specificity of this effect to hippocampal function, a non-hippocampal measure (i.e., digit span) is also used.

5.1.5 Physiological Tests

The findings presented in the preceding chapters of this thesis have established a framework of evidence demonstrating the impact of diet on specific types of cognitive (i.e., verbal memory) and behavioural tasks (i.e., eating behaviour) related to specific brain areas (i.e., the hippocampus). The majority of support has come from animal research, with emerging evidence in humans through correlational studies. As mentioned previously, the animal literature suggests that an HFS diet causes impairments in cognitive and appetitive behaviours related to hippocampal function. One requirement for establishing causality is a plausible physiological mechanism underlying the effects of dietary manipulations on cognition. Any causal inference about the relationship between diet and cognition would be supported substantially by changes in physiological markers. Accordingly, numerous physiological markers associated with hippocampal-related impairments have been explored as potential pathways by which an HFS cause impairments in this brain area (e.g., Beilharz, Maniam & Morris, 2016; Dandona, Ghanim, Chaudhuri, Dhindsa, & Soo Kim, 2010; Kanoski, Meisel, Mullins & Davidson, 2007; Pistell et al., 2010; Stranahan et al., 2008). However, research has yet to determine if such a causal pathway exists in humans.

Extensive research on the impact of HFS diets on HDLM, along with evidence of mechanisms underlying these effects, has come mainly from animal studies. Animals shifted to

a HFS diet impair hippocampal-dependent memory and the degree of this impairment was related to the magnitude of insulin sensitivity (e.g., Stranahan et al., 2008), levels of brain-derived neurotrophic factor (e.g., Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002), oxidative stress (e.g., Wu, Ying & Gomez-Pinilla, 2004), and inflammation (e.g., Beilharz, Maniam & Morris, 2016). However, as noted previously, no experimental evidence to date has determined if a Western-style diet impacts cognition. Furthermore, the mechanisms underlying diet-induced changes in cognition remain relatively unexplored in humans, especially in the context of diet-related impairments in cognition. A small number of experimental diet studies have measured various mechanisms including insulin (Witte et al., 2009), ketones (Makris et al., 2013), and inflammation (Nilsson et al., 2013; Witte et al., 2009). The potential physiological mechanisms to explore are numerous and have been discussed elsewhere (Francis & Stevenson, 2013; Parletta, Milte, & Meyer, 2013). In the context of an HFS diet experiment, two physiological markers are of special interest – blood glucose and blood triglycerides. Briefly, these were selected based on the ease of testing and the likely importance they have in the diet-cognition relationship.

5.1.5.1 Glucoregulatory processes

Glucoregulation is the maintenance of steady levels of glucose in the body, with the hormone insulin acting as the primary regulator. Blood glucose levels are the most important signal to the insulin producing cells, and as they are largely due to dietary carbohydrate intake, diet controls major aspects of metabolism via insulin. There is a strong indication from both animal and human research that changes in glucoregulatory processes (blood glucose and insulin) are important mechanisms involved in diet-related changes to brain function. For instance, the hippocampus receives inputs from neurochemicals including insulin, and changes in

glucoregulatory processes may be one way by which a Western-style diet impacts hippocampal functions. In animals, HFS diets known to impair hippocampal function also increase blood glucose levels (Cao, Lu, Lewis & Li., 2007; Jurdak & Kanarek, 2009; Jurdak, Lichtenstein & Kanarek., 2008; McNeilly, Williamson, Sutherland, Balfour, & Stewart, 2011; Souza et al., 2007; Stranahan et al., 2008). In humans, poorer glucoregulation has consistently been associated with impairments in hippocampal-related memory tests, such as tests of delayed verbal memory (Gold et al. 2007; Convit, Wolf, Tarshish & Leon, 2003). Likewise, impaired cognitive performance is related to hippocampal insulin resistance (Biessels & Reagan, 2015) and impaired glucose tolerance (Lamport, Lawton, Mansfield & Dye, 2009). Experimental studies also show a negative relationship between verbal memory performance and glucoregulation, with some showing improvements following restrictions in energy (Witte et al., 2009), fat (Nilsson et al., 2013) or carbohydrate intake (Krikorian et al., 2012) while increases in fat impair cognition (Edwards et al., 2011). Specifically, Witte et al. (2009) found that improvements in hippocampal-related verbal memory performance in elderly adults following a 20% energy-restricted diet were significantly correlated with decreases in fasting plasma levels of insulin (r = -0.48). That is, individuals with reduced insulin function showed a small improvement in verbal memory following an energy-restricted diet. Likewise, the strongest predictor of verbal memory performance after a low-fat diet was glucose concentration (R^2 = -0.44) (Nilsson et al., 2013). Moderate reductions in dietary carbohydrates improve verbal memory after six weeks and reduced fasting glucose and insulin (r = -0.43) (Krikorian et al., 2012). On the other hand, others have found an opposite pattern of results, showing a 29% decrease in plasma insulin levels following a high-fat diet that also impaired episodic memory (Edwards et al. 2011). Thus, there is strong evidence in animals and humans that impairments in

insulin function are associated with impairments in cognition and diets that impact insulin function also affect cognition.

Another important consideration is the dietary glycaemic load – the extent to which particular food raises a person's blood glucose concentration and is based on the quality and quantity of dietary carbohydrate. The glycaemic load is typically much higher in a Western-style diet than earlier pre-industrialised diets (Cordain et al., 2005) and dietary glycaemic load has been linked to poorer cognitive performance (Power et al., 2015). The HFS diet provided in Chapter 6 has a high glycaemic load, and therefore the increases in blood glucose concentration associated with its consumption may be one way by which the HFS diets impacts hippocampal function. Taken together, these studies suggest that the deficits in hippocampal-related memory are associated with poorer glucoregulation are related to irregularly high blood glucose levels. Similarly, evoked glucose measures (i.e., blood glucose concentrations following meal consumption) were most often correlated with cognitive performance (Messier, Tsiakas, Gagnon, & Desrochers, 2010). Thus, measures of blood glucose concentration may be more sensitive to shifts in diet, noting the additional advantage of its ease of administration and immediacy of results. Another reason for using this over other measures of glucoregulation (e.g., plasma insulin or HOMA-IR) is that blood glucose concentrations may vary more as a function of diet and therefore be more sensitive to changes in diet, especially within the brief time period. Based on this, blood glucose concentration is measured at various time points in the experiment in Chapter 6 to track changes in glucoregulation over the brief diet period.

5.1.5.2 Triglycerides

Another related mechanism that may play a role in changes in cognition is blood lipids, namely triglycerides. The rationale for selecting this marker is based on three important

findings. First, it has been well established that glucoregulation is associated with lipid regulation (Farquhar, Frank, Gross, & Reaven, 1966). In the same way as blood glucose concentration, blood triglycerides may be able to detect subtle variations as a result of the brief HFS diet, relative to the control group. The second reason for including this measure is based on the fact that there is evidence in humans that a Western-style diet impacts this physiological marker. For instance, consumption of an HFS meal leads to marked increases in both blood glucose and triglyceride levels (Hanson et al., 2015; Koopman et al., 2014). Third, chronically high triglyceride levels (hypertriglyceridemia) is strongly linked with cognitive impairment (Farr et al., 2008; Morley, 2013; Morley & Banks, 2010) and have been argued to be one mechanism mediating the neurological consequences of impaired hippocampal synaptic plasticity in obesity (Grillo et al., 2011).

5.1.5.3 Measurement of blood markers

The biomarkers argued to have a causal role in diet-induced changes in cognitive function are typically analysed from blood, urine, or tissue. One common method in diet research is to collect a blood sample using an intravenous catheter and analyse the various markers using relevant assay kits (e.g. ELISA kits). While this is considered the gold standard approach, it is labour and resource intensive and increases participant burden substantially. Recent advances in technology have allowed researchers to use portable devices that allow biomarkers to be tested immediately and results returned within minutes using a fingerstick method. Fingerstick measurement is accurate and has good clinical utility to identify individuals with abnormal blood lipids or inflammation levels. Importantly, fingerstick measurements provide the distinct advantages of reduced cost, reduced logistical concerns such as sample

storage, reduced participant burden that likely improves recruitment prospects and reduce dropouts, and give immediate results with equivalent accuracy to more expensive blood sample assay kits. Additionally, the ease with which blood samples can be collected at various times without the need for storage substantially increases its utility. As a result, fingerstick measurements are used in Chapter 6 to explore whether changes in blood glucose concentrations and triglycerides are associated with changes in HDLM following a shift to an HFS diet.

5.1.5.4 Anthropometric measures

Two anthropometric measures are of interest – BMI and waist circumference. Although used as a rough guide, BMI provides the least-invasive and most useful population level measure of overweight and obesity (WHO, 2008). Waist circumference – made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest – is used as a measure of central adiposity and is combined with BMI to better estimate obesity (WHO, 2008). The rationale for including weight, BMI and waist circumference in the experiment in Chapter 6 is based on two reasons. First, as described in Section 5.1.2.1., lean adults form the sample population from which groups are randomly formed, and taking these anthropometric measures is used as a verification of this criterion. Second, as an HFS diet results in rapid weight gain in animals (e.g., Beilharz, Maniam & Morris, 2016), it is also of interest to determine if variability in weight, BMI and waist circumference can be explained by group allocation (i.e., whether or not participants received the HFS diet).

5.1.6 Summary

The aim of this chapter was to highlight the methodological challenges associated with experimental diet studies, with the primary aim of determining the design and parameters of the

experiment in Chapter 6. There is a wealth of evidence in animals that an HFS diet impacts HDLM. The systematic review in Chapter 4 provided some evidence-based clarification around the magnitude of cognitive change following alterations in protein, fats and carbohydrate content, with evidence that memory tests were sensitive to shifts in diet. The parallel between animal and human evidence suggests similar pathways underlying diet-related effects on cognition, and several putative physiological mediators have been discussed. Based on the information reviewed in this chapter, the first experimental test of this is provided in Chapter 6, with the following parameters: (1) a mixed design is employed, testing differences between an experimental and control group over time; (2) lean individuals with a typical diet low in saturated fats and refined sugars form the sample population; (3) a minimum of 50 participants per group is required to detect changes in cognition; (4) the HFS breakfast contains 50g total fat (30g from saturated fats) and 50g sugar, while the control diet is low in fat (13g total fat [4g from saturated fats]) and low in sugar (18g); (5) participants are required to attend the laboratory to consume the HFS breakfasts; (6) participants are required to complete a food diary to track eating behaviours during and prior to the experiment; (7) the duration of the diet is four days; (8) cognitive tests are hippocampally-dependent (Logical memory and Hopkins Verbal Learning Test) and not hippocampally-dependent (Digit span); (9) blood glucose and triglyceride measures are taken to determine how these relate to diet-induced changes in HDLM; and (10) weight, BMI and waist circumference are measured to determine if these vary with diet.

5.2 References

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Chapter 6: A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity

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A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity

The hippocampus is a brain structure long considered important for learning and memory (Squire, 1992). An extensive body of animal data now suggests that a Western-style diet, characterised by high intakes of saturated fats and added sugars (an HFS diet) causes rapid impairments to hippocampal-dependent learning and memory (Beilharz, Maniam & Morris, 2014; Davidson, Kanoski, Walls & Jarrard, 2005; Hargrave, Jones & Davidson, 2016; Kanoski & Davidson, 2011; Parent, Darling, & Henderson, 2014). Consistent with these findings, are the observations in humans that poorer hippocampal-dependent learning and memory is associated with greater consumption of a Western-style diet (Attuquayefio et al., 2016; Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011; Gibson, Barr & Jeanes, 2013). In this study, we test whether HFS diets *cause* similar impairments in hippocampal-dependent learning and memory in healthy lean young people.

Animals show quite clear impairments in hippocampal-dependent learning and memory (HDLM) when they are fed a diet high in saturated fat (Greenwood & Winocur, 1990; Greenwood & Winocur, 1996; Granholm et al., 2008; Morrison et al., 2010), high in sucrose (Greenwood & Winocur, 2001; Jurdak, Lichtenstein, & Kanarek, 2008; Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney & Corbit, 2013), or high in both saturated fat and sucrose (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Darling, Ross, Bartness, & Parent, 2013; Francis, Mirzaei, Pardey, Haynes & Cornish, 2013; Goldbart et al., 2006; Hoane, Swan & Heck, 2011; Kanoski & Davidson, 2010; Kanoski, Zhang, Zheng, & Davidson, 2010; Messier, Whately, Liang & Puissant, 2007; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Tran & Westbrook, 2015). Importantly, such diet-induced impairments appear to be specific to

hippocampally-based tasks, since non-hippocampal measures remain unaffected. For example, an HFS diet impairs hippocampal-dependent place-recognition memory while object recognition memory (non-hippocampal) remains stable (Beilharz, Maniam & Morris, 2014). Another important consideration is how quickly a shift in diet from healthy rat chow to an HFS diet can impact HDLM. Impairments in a HDLM task can be found after 3 to 5 days exposure (Beilharz, Maniam & Morris, 2014; Kanoski & Davidson, 2010).

An important question based upon these animal findings is whether something similar happens to the human hippocampus when it is exposed to an HFS diet. Correlational evidence in humans has provided some support for these animal data. Greater consumption of an HFS diet is associated with impairments in HDLM in children (Baym et al., 2014; Burrows, Goldman, Pursey & Lim, 2016), adults (Attuquayefio et al., 2016; Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011; Gibson, Barr & Jeanes, 2013) and the elderly (Gardener et al., 2014; Granic et al., 2016), suggesting that an HFS diet impacts HDLM across the lifespan. The claim that such a diet impacts HDLM rests upon the ability of certain neuropsychological tests, such as the delayed recall of stories or word lists, to selectively measure hippocampal function. This is supported by the following findings: (1) hippocampal damage severely impairs performance on such tasks (e.g., Sass et al., 1992); (2) reduced hippocampal activation during fMRI is associated with poorer verbal memory recall (Bonner-Jackson, Mahmoud, Miller & Banks, 2015; Maki et al., 2009); and (3) hippocampal volume best predicts performance on such tests (Kramer et al., 2004; Travis et al., 2014). In addition, as in animals, diet-related cognitive effects appear to be specific to tests sensitive to hippocampal function, as cognitive tests not related to hippocampal function (attention and working memory) are unimpaired by HFS consumption (Francis &

Stevenson, 2011). In sum, there is clear evidence for a relationship between HFS diet and poorer HDLM in humans.

While findings from animal studies indicate that HDLM worsens as a consequence of consuming an HFS diet, this directional causal link has not been tested in humans. However, current human data suggests *improvements* in memory and executive function can occur, although not consistently, following reductions in energy intake and fat (Attuquayefio & Stevenson, 2015). Briefly, performance on HDLM improves following a shift to a Mediterranean diet (Lee et al., 2015; Martínez-Lapiscina et al., 2013; McMillan, Owen, Kras & Scholey, 2011) or to a diet low in saturated fats and refined sugars (Bayer-Carter et al., 2011; Nilsson, Tovar, Johansson, Radeborg, & Björck, 2013). If we consider experiments that have *increased* components of a Western-style diet over days or weeks, very few studies are available. Increasing *total* fat leads to deficits in working memory, attention and processing speed in healthy men after 5 days (Holloway et al., 2011) and in reaction time and attention in male athletes after 7 days (Edwards et al., 2011). However, these studies are problematic for the following reasons. First, these studies used a cognitive battery (Simpson, Surmon, Wesnes & Wilcock, 1991) using tests not dependent on hippocampal function, so it is unclear if HDLM performance would have changed from these diets. Second, changes in cognition were only evident on reaction time tasks, which improve following fat ingestion (e.g., Hoyland, Lawton & Dye). Third, since only changes in total fat were reported, conclusions regarding the effect of fat type on cognition are not possible. Thus, there is currently no human experimental evidence that components of a Western-style diet impair HDLM.

Though the hippocampus is traditionally associated with learning and memory, it also appears to be important for ingestive control (Kanoski & Davidson, 2011; Parent, Darling, &

Henderson, 2014). One such ingestive control concerns the ability to perceive internal states such as hunger and satiety (i.e., interoception). Hippocampal lesions can produce impairments in accurately sensing signals of hunger and satiety (interoception) in animals (Clifton, Vickers, Somerville, 1998) and humans (Hebben, Corkin, Eichenbaum, & Shedlack, 1985, Rozin, Dow, Moscovitch & Rajaram, 1998). Given the human and animal data suggest that exposure to a Western-style diet impairs hippocampal function, this should in turn result in downstream effects on the control of ingestive behaviour. This has been demonstrated in animal research showing that an HFS diet impairs the ability to use interoceptive cues of hunger and fullness (Davidson et al., 2009; Davidson et al., 2010; Sample, Martin, Jones, Hargrave & Davidson, 2015) Likewise, in humans, habitual consumers of a Western-style diet show reduced sensitivity to signals of hunger and satiety (Francis & Stevenson, 2011) and thirst (Brannigan, Stevenson & Francis, 2015), and an impaired ability to use such interoceptive cues to modulate appetitive behaviour (Attuquayefio et al., 2016). Whether an HFS diet causes reductions in sensitivity to signals of hunger and satiety has not as yet been established in human studies.

Various neurobiological mechanisms may mediate the effects of an HFS diet on the hippocampus. Animal data show that HFS diets lead to marked deficits in glucoregulation, insulin sensitivity and relatedly elevated blood triglycerides (Davidson et al., 2010; Stranahan et al., 2008), persistent increases in inflammation (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Hsu et al., 2015; Pistell et al., 2010; White et al., 2009) and reductions in brain-derived neurotrophic factor (Kanoski, Meisel, Mullins & Davidson, 2007; Molteni et al., 2002; Pistell et al., 2010; Wu, Molteni, Ying & Gomez-Pinilla, 2003; Wu, Ying & Gomez-Pinilla, 2004). In humans, there are similar links between impairments in memory and the aforementioned neurobiological mechanisms (for a review, see Francis & Stevenson, 2013;

Kanoski & Davidson, 2011). In particular, poorer insulin sensitivity is associated with impaired cognitive performance (Kaplan, Greenwood, Winocur & Wolever., 2000; Kalmijn, Feskens, Launer, Stijnen & Kromhout, 1995; Vanhanen et al., 1998) and adults with type 2 diabetes are also impaired on tests of delayed verbal memory (Gold et al., 2007; Greenwood, Kaplan, Hebblethwaite, & Jenkins, 2003; Stewart & Liolista, 1999). This suggests that one likely and plausible mechanism by which diet may affect the hippocampus in humans may involve glucoregulation.

The present study sought to investigate the impacts of briefly consuming an HFS diet over four days relative to one lower in saturated fat and added sugar, on hippocampal-related functioning. More specifically, we wanted to determine if, in a sample of lean healthy young adults who generally consumed a diet of adequate nutritional quality (i.e., one not characterised by high levels of saturated fat and added sugar), a four-day shift to an HFS diet would lead to: (1) poorer HDLM performance but with no change in control non-hippocampal measures; (2) reduced sensitivity to hunger and fullness; (3) differences in biological markers (i.e., blood glucose and lipids) and; (4) changes to diet outside of the laboratory manipulation (i.e., compensation) – all relative to controls.

6.1 Method

6.1.1 Participants

Participants were students of Macquarie University recruited between February 2014 and May 2016. Power analysis indicated that approximately 100 individuals (50 per group) were required in order to have an 80% chance of rejecting the null hypothesis if changes in the

primary outcome variable (HDLM) were of a moderate effect size (d = 0.5-0.6) with an $\alpha = 0.05$. Inclusion criteria involved participants reporting in a pre-study screen: (1) a BMI less than 25kg/m^2; (2) a diet-screener score ≤60, indicative of a diet relatively low in saturated fat and added sugar for this student population (more below); (3) fluency in English; (4) no food allergies and omnivorous; and (5) not currently dieting. A total of 885 individuals started the screening process (detailed below) of which 244 were deemed eligible, and of whom 145 consented to participate. From this, 127 participants commenced the experiment, 25 failed to complete it, leaving 102 cases for analysis (see Table 6.2 for participant details).

6.1.2 Design

This study was a between-subjects experimental design with randomised allocation to one of two groups - one exposed to four days of breakfasts high in saturated fat and added sugar (Experimental group) and the other given a breakfast of similar palatability and food types (i.e., toasted sandwich, etc.), but significantly lower in saturated fat and added sugar (Control group). Participants were randomised to a group by order of arrival to the experiment. The primary outcome variable was change in HDLM measured at the start and at the end of the experiment (alongside other behavioural and physiological variables). All participants were tested at Macquarie University between February 2014 and May 2016.

6.1.3 Breakfast Meals

The breakfasts presented to each group comprised a toasted sandwich and a chocolate milkshake and these had markedly different nutrient profiles (see Table 6.1). Each of these breakfasts was pilot tested to ensure equivalent palatability and flavour profile. Twelve healthy lean participants consumed a half-portion sample (~250g) of each breakfast in counterbalanced

order. Participants completed a set of ratings of how much they liked the sample, as well as ratings of how sweet, sour, bitter, salty, fatty and healthy they thought each sample was on a 7-point category rating scale (anchors 1 = *Not at all* and 7 = *Very*). This testing revealed no significant differences between the two breakfasts in terms of palatability, flavour profile, or ratings of healthiness (*p*s > .10).

Table 6.1. *Nutritional data for the two breakfasts*

	Experimental group breakfast	Control group breakfast
Total mass (g)	431	471
Energy (kJ)	3658	2941
Total fat (%)	53	17
Saturated fats (%)	30	6
Carbohydrates (%)	36	32
Sugar (%)	18	11
Protein (%)	11	51

6.1.4 Measures

Pre-study screening tests. Potential participants were screened using an online battery of questionnaires. This battery was composed of: (1) a demographic and medical history questionnaire; (2) a 26-item food frequency questionnaire (scores ranging from 26 to 130) to measure added sugar and saturated fat intake – the Dietary Fat and Sugar Questionnaire (DFS: Francis & Stevenson, 2013); (3) the 18-item Three-Factor Eating Questionnaire (TFEQ-R18; Karlsson, Persson, Sjöström & Sullivan, 2000) to assess eating attitudes (cognitive restraint,

uncontrolled eating, and emotional eating); (4) the International Physical Activity Questionnaire-short form (IPAQ-SQ; Papathanasiou et al., 2010) to assess physical activity; and (5) the 10-item Kessler Psychological Distress Scale (K-10; Kessler et al., 2002) to determine current mental well-being. Participants were excluded from the study if they reported a BMI > 25 kg/m^2, a DFS score > 60, were currently dieting or reported any food allergies.

Hopkins Verbal Learning Task-Revised (HVLT). The HVLT (Brandt, 1991) is a 12-item word list that is read to the participant three times, requiring recall after each presentation. Following a 20-25 minute delay, participants are asked to recall all the words they remember from that list (delayed recall). This is followed by recognition test, which was not used here due to lack of variance. The HVLT-R has six alternate forms that make it ideal for repeat testing, and these were counterbalanced across participants.

Logical Memory (LM). The LM test (Wechsler, 2009) involves listening to two short stories. Participants are then asked to repeat back as many details as possible immediately after hearing the story and then again after a 20-30 minute delay. The standard Wechsler Memory Scale (WMS) IV stories were used in combination with six alternate stories (counterbalanced across participants), whose structural and statistical properties were compatible with the standard WMS-III (Sullivan, 2005) and WMS-IV stories (Schnabel, 2012).

National Adult Reading Test (NART). The NART (Nelson & Willison, 1991) is 50-item single word reading test of graded difficulty, where all words are irregular and violate grapheme-phoneme correspondence rules (e.g., ache, thyme, topiary) and was used here as a measure of intelligence (Crawford, Deary, Starr & Whalley, 2001) to check for any group differences in this variable.

Digit Span (DS) test of the Wechsler Memory Scale-III (WMS-III). Participants were read a sequence of numbers of increasing length (two trials per sequence), which they then had to repeat back either in the same order as delivered or in reverse order. This test, drawn from the WMS-III (Wechsler, 1997) was administered as per the manual, to determine any general decline in cognitive functioning or motivation across the experiment.

Biological measures. Height and weight for each participant were used to calculate body mass index (BMI). Waist circumference was also measured. Blood glucose and triglycerides measurements were taken using the CardioChek PA® Analyzer. Measurements ranges in each test were 20-600mg/dL for blood glucose and 50-500mg/dL for triglycerides. One 50µL whole blood sample was taken for all three measurements using a fingerstick method (UniStick®3 21 Gauge 2.0mm depth).

Food Diary. Participants were required to fill in an online food diary to track their daily eating behaviours (i.e., energy and macronutrient intake) prior to and during the experiment. Participants were asked to record, in as detailed a manner as possible, every item that they had eaten and drunk, the time they consumed it, the amount consumed and how it was prepared. Participants could estimate portion size using household measures, weight on packaging or from 15 sets of colour photographs depicting small, medium and large portions of frequently consumed foods (Medical Research Council, 2008). The food diary was adapted from that developed by the Medical Research Council collaborative centre for Human Nutrition Research (Cambridge, UK). The food diary data were analysed using FoodWorks 8 Premium software, which uses food composition data from several sources including 5740 Australian foods and beverages (AUSNUT, 2011-13) and 7906 food items from the United States (USDA SR27).

Interoception and current Mood ratings. Participants completed a set of ratings for how hungry, full, thirsty, alert and happy they were plus how strong their appetite for something sweet was, and how strong their appetite for something savoury was – in that order – each on a separate 7-point category rating scale (anchors *1 = Not at all* and *7 = Very*).

6.1.5 Procedure

The study protocol was approved by the Macquarie University Human Research Ethics Committee and written consent (including notification of their right to withdraw without penalty at any time) was provided by each participant, with debriefing of the detailed study aims at the end of the experiment. In the week preceding the study, participants were asked to complete the food diary on two occasions to determine their pre-study dietary habits, from which a daily average was computed (noting that there were no significant differences in daily intakes on the two occasions). On the first experimental day (Day 1), and following an overnight fast (with no restrictions on fluid intake), participants arrived for testing between 6am and 12pm. They then attended the laboratory at the same time for the remaining three consecutive days of testing.

On Day 1, participants completed the immediate recall measures of the LM and HVLT tests, followed by the Digit Span and NART, and had their height, weight and waist circumference measured. A whole blood sample was then taken to measure blood glucose and triglycerides. Participants were then asked to recall the stories and words from the LM and HVLT tasks, respectively. The first set of interoception and mood ratings were then completed, and this was followed by the breakfast meal, with each participant asked to consume as much of it as possible. Participants were left alone for twenty minutes to eat and were given the option to watch TV or read a magazine. Following this, the experimenter removed all uneaten food for later weighing. Participants then completed a second set of interoception and mood ratings, post-

prandial neuropsychological (LM, HVLT and DS) and blood tests (blood glucose and triglycerides) in the same manner and order as above (excluding the NART). Participants were requested to fill in the food diary for the remainder of Day 1.

Participants attended the lab on Days 2 and 3 to consume breakfast, completing the interoception and mood ratings prior to and following the breakfast. Again, each breakfast was weighed before and after consumption to assess food intake. While the breakfasts and interoception ratings were given across the four consecutive test days, neuropsychological and blood tests were only administered on Day 1 and 4 of the study. The procedure on Day 4 was identical to Day 1 (except the NART was not repeated). Participants were then requested to fill out the food diary for the remainder of Day 4 (noting that Day 1 and 4 diary entries did not differ and these were collapsed for analysis).

6.1.6 Analysis

All neuropsychological measures were scored as per their respective manuals. For the memory measures, percent retention scores were computed for both the HVLT (delayed recall trial/ highest score taken from immediate recall trial 2 or 3) x 100) and for LM (delayed recall/ immediate recall) x 100). For Digit Span two scores were computed; forwards recall of numbers (Digit Span forwards; score range 0-16) and the reverse recall of numbers (Digit Span backwards; score range 0-14). The HVLT data for Day 1, first test were non-normal, and this was driven by one outlying value. This data point was replaced by their less extreme Day 1 second test value. Coefficient alphas across the 4 testing occasions were adequate for HVLT retention ($\alpha = 0.70$), poor for LM retention ($\alpha = 0.52$), and good for Digit Span forwards ($\alpha = 0.89$) and backwards ($\alpha = 0.88$).

Three other variables were identified as being non-normal – the interoceptive data, blood triglycerides, and participants age, and these were all transformed (root for the former two, reciprocal for the latter) enabling parametric testing. For the biological measures, coefficient alphas were adequate for blood glucose ($\alpha = 0.62$) and good for triglycerides ($\alpha = 0.88$).

Multiple ratings of current mood and cravings for savoury and sweet foods were obtained during the study. Preliminary analyses revealed no significant effects of interest and so these ratings are not further reported. A two-tailed alpha of 0.05 was used for all reported tests, with all analyses being conducted using SPSS version 21.

6.2 Results

6.2.1 Participant Characteristics

A total of 102 participants completed the study and their characteristics are summarised by Group in Table 6.2. The two groups were similar in age, mental well-being (K-10), exercise habits (IPAQ), eating attitudes (TFEQ) and estimated IQ (NART). Some differences were noted in BMI and waist circumference, which were significantly higher in the Control group, alongside a trend for greater habitual consumption of saturated fat and added sugar (DFS) in this group as well. While there was no significant group difference in Gender distribution, we note that there was nearly double the number of men in the Control group, relative to the Experimental group. To control for any effect of these differences – and recalling that participants were randomly assigned to groups – these identified variables (BMI, waist circumference, DFS & gender) were included as covariates (following Z-transformation) in all of the analyses.

Table 6.2. *Baseline descriptive statistics for each group*

Variable	Descriptive statistics, Number/Mean (SD)		Difference
	Experimental group	Control group	p-value
Number	51	51	-
Gender (Female/Male)	44/7	38/13	0.14
Age	20.2 (3.9)	21.0 (6.6)	0.50
BMI	20.8 (2.3)	22.1 (2.5)	0.01*
Waist circumference (cm)	72.9 (7.3)	75.9 (6.3)	0.03*
DFS (diet) score	51.4 (6.7)	53.6 (5.7)	0.07
K-10	18.5 (6.3)	18.8 (5.2)	0.82
IPAQ	9.8 (3.2)	10.7 (3.8)	0.20
TFEQ-R18			
Cognitive restraint	13.1 (3.5)	13.6 (3.3)	0.52
Uncontrolled eating	15.5 (5.3)	16.5 (3.8)	0.25
Emotional eating	5.8 (2.4)	6.2 (2.3)	0.45
NART Full Scale IQ	108.1 (5.8)	108.7 (5.1)	0.57

* $p < .05$

6.2.2 Experimental Manipulation

Participants eating the Experimental breakfast consumed more energy, total fat, saturated fat, total carbohydrates and sugar (*p*s <.001), but less protein (p <.001) at breakfast, than those eating the Control breakfast (see Table 6.3). As our principal interest was in the effect of dietary composition (i.e., added sugar and saturated fat) rather than total energy intake on the test breakfasts, and also because individuals within each group varied in how much of each breakfast they consumed – we used total energy intake (Z-transformed) at breakfast as a further covariate

(except in analyses where energy intake was already included within the dependent variable – more below).

Table 6.3. *Nutritional breakdown of breakfasts consumed, averaged across test days*

Variable	Descriptive statistics, Mean (SD)		Difference
	Experimental group	Control group	p-value
Volume	423 (65)	435 (65)	.37
Energy (kJ)	3593 (550)	2716 (412)	.00*
Total Fat (%)	53.0 (0.7)	15.9 (2.1)	.00*
Saturated fat (%)	30.3 (0.1)	5.3 (0.6)	.00*
Total carbohydrates (%)	35.7 (1.4)	31.8 (0.6)	.00*
Sugars (%)	17.7 (2.5)	10.0 (0.6)	.00*
Protein (%)	11.5 (0.7)	51.3 (3.1)	.00*

Sig* = significance level p <.05 of independent samples t-test; kJ = kilojoules.

6.2.3 Neuropsychological Measures

6.2.3.1 Hopkins-Verbal Learning Test (HVLT)

The HVLT percent retention data were analysed with a three-way mixed design ANCOVA, with Day (Day 1[pre-exposure] vs. Day 4 [post-exposure]) and Time (pre-breakfast vs. post-breakfast) as the within factors and Group (Control vs. Experimental) as the between factor, with BMI, waist circumference, average breakfast energy intake, DFS score, and gender as covariates.

The ANCOVA revealed a main effect of Day ($F(1,94) = 24.54$, partial eta-squared = 0.21, $p < 0.001$), which was qualified by an interaction between Day and Group ($F(1,94) = 4.54$, partial eta-squared = 0.05, $p = 0.038$). Further pairwise comparisons revealed that retention was

significantly poorer in the Experimental group at the end of the study relative to the start (*M* = -15.7%, *p* < 0.001), but not in the Control group (*M* = -3.9%, *p* = 0.251; see Figure 6.1.) consistent with our hypothesis.

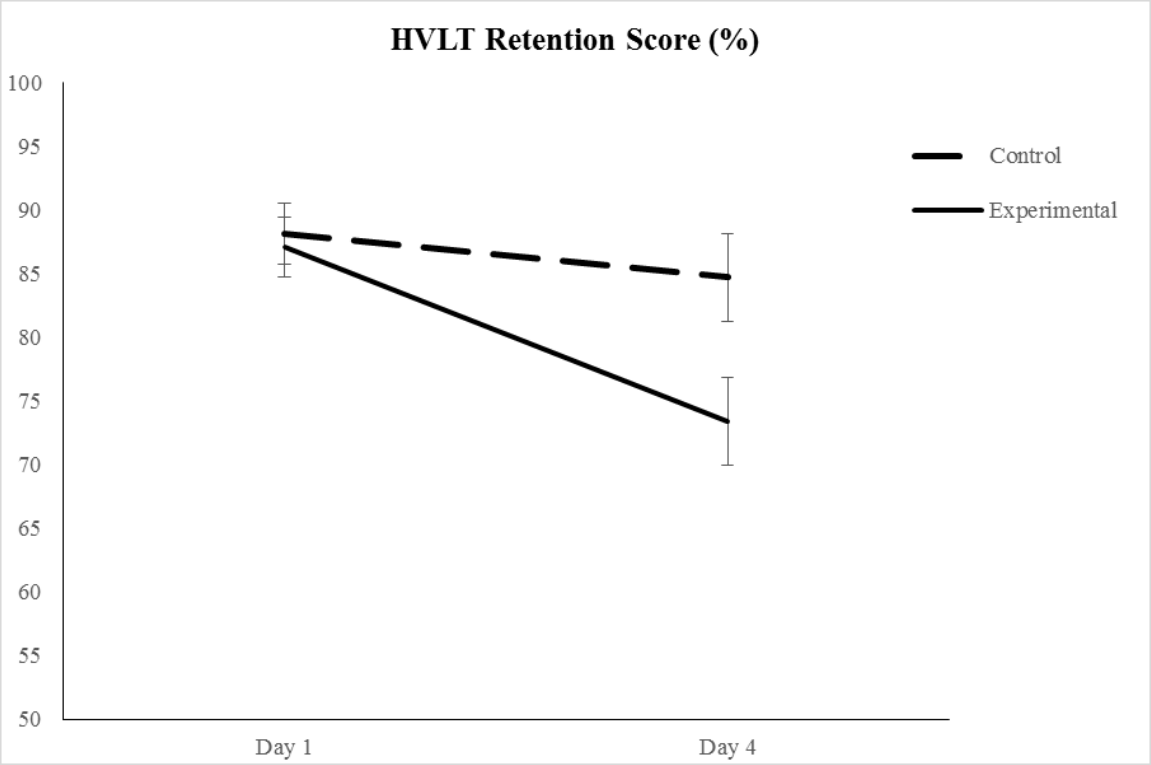

Figure 6.1. Mean (± standard error) HVLT retention score (%) on test days one and four for the Experimental and Control groups.

Prandial-related effects were also observed, with a main effect of Time ($F(1,94) = 47.46$, partial eta-squared = 0.34, $p < 0.001$), which was qualified by an interaction between Time and Day ($F(1,94) = 12.84$, partial eta-squared = 0.12, $p = 0.001$). Retention was poorer after breakfast than before, with this drop being larger on Day 4 (*M* = -19.5%) than on Day 1 (*M* = -7.9%). There were no other significant effects.

6.2.3.2 Logical Memory (LM)

The LM percent retention score data were analysed using the same three-way mixed design ANCOVA described above. The only significant outcome was a main effect of Group ($F(1,94) = 5.33$, partial eta-squared = 0.05, $p = 0.023$), with the Experimental group ($M = 85.9\%$) performing more poorly overall than the Control group ($M = 91.9\%$).

6.2.3.3 Forwards and backwards digit span

The forwards and backwards digit span data were analysed separately in two further three-way mixed design ANCOVAs. For the forwards digit span data, there were significant main effects of Day ($F(1,94) = 15.57$, partial eta-squared = 0.14, $p < 0.001$) and Time ($F(1,94) = 4.46$, partial eta-squared = 0.05, $p = 0.037$) and an interaction between these two variables ($F(1,94) = 5.75$, partial eta-squared = 0.06, $p = 0.018$). Forwards digit span increased from Day 1 ($M = 10.5$) to Day 4 ($M = 11.1$), with a larger prandial improvement evident on Day 1 (M change = 0.5) relative to Day 4 (M change = 0.1). There were no other significant effects. For the backwards digit span data, only one effect was significant, Day ($F(1,94) = 20.59$, partial eta-squared = 0.18, $p < 0.001$). Participants backwards digit span increased from Day 1 ($M = 6.9$) to Day 4 ($M = 7.5$). As no alternate forms of either forwards or backwards digit span were used, these improvements may reflect the effects of practice.

6.2.4 Interoceptive Measures

For Day 1 and Day 4 respectively, the energy consumed at Breakfast by each participant was divided by their change in hunger and fullness ratings combined (as these two variables significantly correlate, median r = -0.51), with the resulting group means displayed in Figure 6.2. This value (the interoception score) reflects the number of kilojoules (kJ) required to shift hunger

and fullness ratings by 1 point. Following transformation, as the variables were non-normal, and with Day 4 interoception score serving as the dependent variable, we conducted a univariate ANCOVA, with Group as the between factor, and Day 1 interoception score, BMI, waist circumference, DFS score, and gender as covariates.

The ANCOVA revealed a significant main effect of Group ($F(1,93) = 7.43$, partial eta-squared = 0.07, $p = 0.008$). Thus, after controlling for differences on Day 1 interoception score, the Experimental group became significantly less sensitive to the effects of the breakfast, requiring more energy to shift hunger and fullness ratings one point ($M = 719$ kJ) on Day 4, relative to the Control group ($M = 427$ kJ).

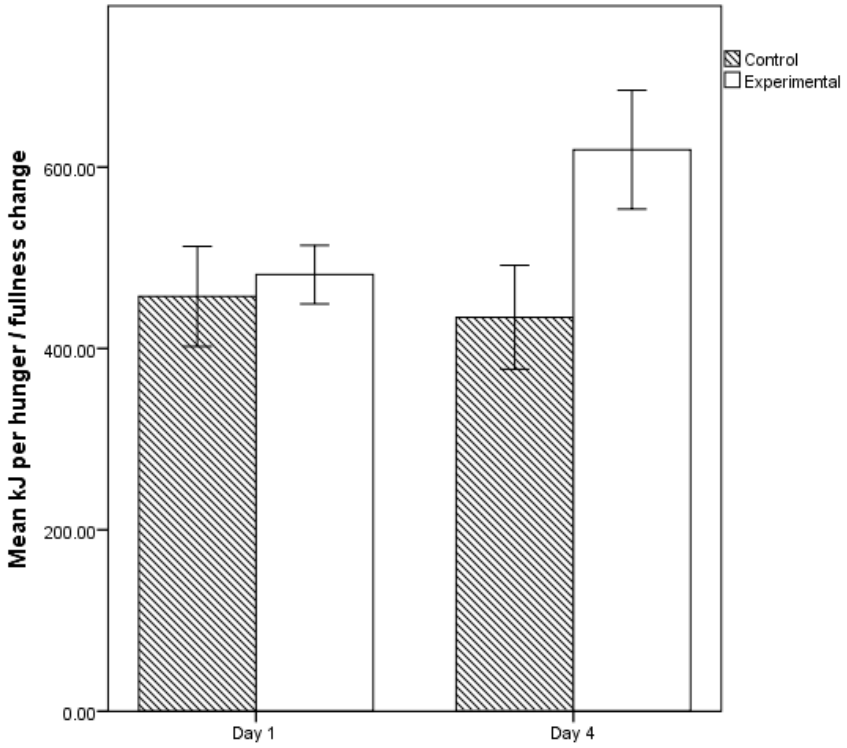

Figure 6.2. Mean (± standard error) kilojoules (kJ) required to shift hunger and fullness ratings on days one and four for each group.

6.2.5 Biological Measures and their Relationships

6.2.5.1 Blood glucose

Blood glucose data were analysed using the same three-way mixed design ANCOVA as described for the neuropsychological data. The ANCOVA revealed a main effect of Time ($F(1,83) = 135.1$, partial eta-squared = 0.62, $p < 0.001$), and an interaction of Time by Group ($F(1,83) = 15.82$, partial eta-squared = 0.16, $p < 0.001$). Figure 6.3 illustrates the Time by Group effect. It is evident that blood glucose readings increase across a meal (Time effect), and to a considerably greater extent in the Experimental group than for Controls (Time by Group).

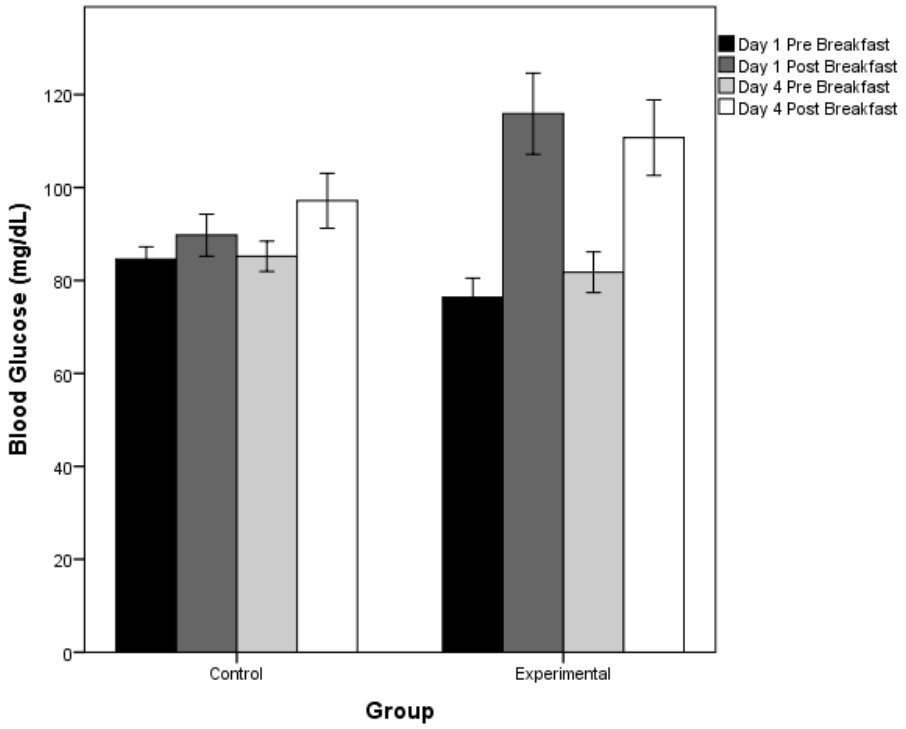

Figure 6.3. Mean (± standard error) pre- and post-prandial blood glucose levels at the start and end of the study for each group.

We then examined whether the Group-related blood glucose effect (i.e., change across Time) was associated with changes in the neuropsychological measures of memory and the

measure of interoception. To assess this, we used partial correlations, controlling for BMI, waist circumference, DFS score, gender, and either average breakfast energy intake (for the memory correlation) or Day 1 interoception score (for the interoception correlation).

A larger decline in HVLT score between Day 1 and Day 4 was significantly associated (Partial $r(83) = -0.24$, $p = 0.028$) with greater increase in blood glucose across the breakfasts (i.e., main effect of Time; see Figure 6.4). There was no significant relationship between the interoception score and change in blood glucose. To determine whether changes in HVLT performance were mediated by blood glucose alterations, we also conducted a three-way ANCOVA, as with the neuropsychological measures, and included blood glucose change across time as an additional covariate. As expected, taking into account blood glucose change between meals, the Day by Group interaction for HVLT retention was not statistically significant, ($F(1,82) = 3.11$, partial eta-squared = 0.037, $p = 0.082$).

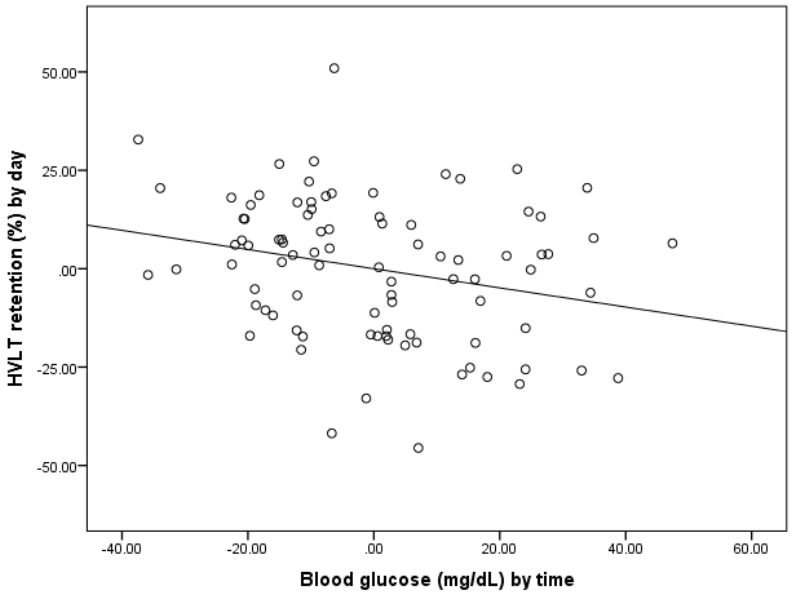

Figure 6.4. Scatterplot of the negative linear relationship between HVLT retention score (%) by day (Day 4 – Day 1) and blood glucose levels (mg/dL) by time (post-breakfast – pre-breakfast).

6.2.5.2 Triglycerides

Similar to the blood glucose findings, the ANCOVA on the triglycerides data revealed main effects of Time ($F(1,83) = 16.29$, partial eta-squared = 0.16, $p < 0.001$) and Time by Group ($F(1,83) = 7.23$, partial eta-squared = 0.08, $p = 0.009$). As can be seen in Figure 6.5, blood triglycerides tended to increase after a meal (main effect of Time) and to a significantly greater extent in the Experimental group relative to the Controls (Time by Group). There were no significant partial correlations between changes in blood triglycerides across Time and neuropsychological or interoception measures. Furthermore, including blood triglyceride changes as a covariate in an ANCOVA resulted in a non-significant Day by Group interaction for HVLT retention, ($F(1,82) = 3.67$, partial eta-squared = 0.042, $p = 0.059$), albeit to a lesser extent than blood glucose.

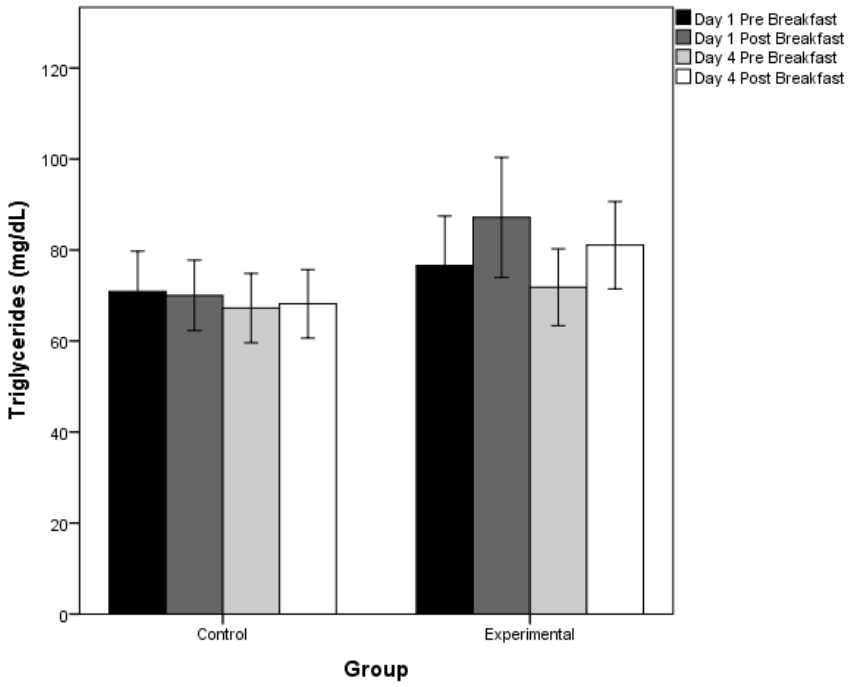

Figure 6.5. Mean (± standard error) pre- and post-prandial triglyceride levels at the start and end of the study for each group.

6.2.5.3 Anthropometric Data

There were no significant differences in BMI or waist circumference across the experiment, between groups. Changes in BMI and waist circumference were not significantly associated with the neuropsychological or interoception measures.

6.2.6 Food Diary Data

The descriptive statistics for the nutrient profile of the food diaries (averaged across the two entries for the pre and during study periods) are provided in Table 6.4. The dietary data were analysed using a three-way mixed design ANCOVA, with Week (Week 1[pre-study] vs. Week 2 [during study]) and Time (breakfast vs. post-breakfast) as the within factors and Group (Control vs. Experimental) as the between factor, with BMI, waist circumference, DFS score, and gender as covariates.

Table 6.4. *Nutritional breakdown of self-report food diaries prior to and during the study*

Variable	Descriptive statistics, Mean (SD)				Week by group
	Pre-study		During study		
	Exp. (n = 48)	Control (n = 48)	Exp. (n = 48)	Control (n = 48)	Sig*
Volume	2180.8 (1018.2)	2164.9 (927.9)	2117.5 (645.9)	2216.9 (853.9)	.04*
Energy (kJ)	7766.9 (1937.4)	7627.9 (2192.5)	8463.4 (1833.6)	8522 0 (2069.9)	.59
Total Fat (%)	35.0 (7.6)	35.0 (5.9)	42.0 (5.0)	27.7 (5.4)	.00*
Saturated fat (%)	13.1 (3.7)	13.1 (3.3)	19.5 (3.1)	9.8 (2.9)	.00*
Carbohydrates (%)	43.7 (8.5)	42.1 (6.7)	40.6 (4.9)	39.9 (5.9)	.51
Sugars (%)	16.3 (6.2)	16.6 (6.3)	15.9 (4.9)	14.0 (4.7)	.36
Protein (%)	18.5 (4.7)	20.2 (5.8)	15.6 (3.4)	30.5 (6.8)	.00*

Exp. = Experimental group; Sig* = significance level $p<.05$ of repeated measures ANCOVA for Week (Week 1[pre-study] vs Week 2 [during study]) by Group interaction; kJ = kilojoules.

For energy intake, the ANCOVA revealed a main effect of Week ($F(1,91) = 11.42$, partial eta-squared = 0.11, $p = 0.001$), a main effect of Time ($F(1,91) = 375.45$, partial eta-squared = 0.81, $p < 0.001$), and a significant three-way interaction between Time, Week and Group, ($F(1,90) = 18.08$, partial eta-squared = 0.17, $p < 0.001$). Importantly, there was a non-significant Week by Group interaction, ($F(1,90) = 0.29$, partial eta-squared = 0.003, $p = 0.59$). Despite consuming more energy at breakfast (shown earlier), the Experimental group consumed significantly less energy the rest of the day (i.e., caloric compensation) during the experimental period, relative to the Control group (see Figure 6.6).

The Experimental group appear to have achieved this by reducing carbohydrate and sugar intake post-breakfast. Thus, while carbohydrate intake was significantly greater at breakfast in the Experimental group relative to the Control group, as with added sugar, overall intake did not differ between groups either before or during the experiment (see Table 6.4).

The Experimental group did not show compensation over the course of the day for total fat, saturated fat, or protein intake (see Table 6.4**)**. That is, relative to intake prior to the study, there were significant increases in the Experimental group in total fat, ($F(1,90) = 21.04$, partial eta-squared = 0.19, $p < 0.001$), saturated fat, ($F(1,90) = 60.27$, partial eta-squared = 0.40, $p < 0.001$), and in protein, ($F(1,90) = 73.59$, partial eta-squared = 0.45, $p < 0.001$) relative to the Control group.

In sum, while energy, fat and sugar intakes were significantly higher at breakfast in the Experimental group providing a discrete 'burst' of these nutrients, group differences in energy and sugar intake were not evident when the whole experimental days intake was computed. Across the whole of the experimental days, only differences in fat and saturated fat and protein were evident.

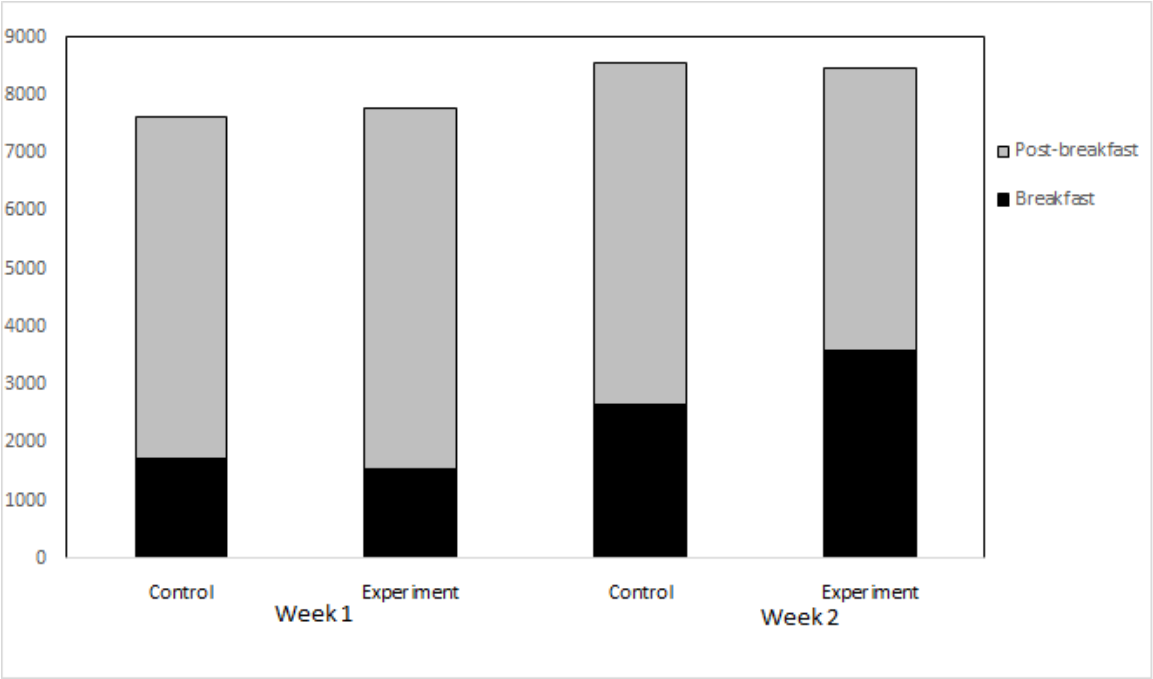

Figure 6.6. An illustration of the compensation of energy intake across weeks and between groups, following the breakfast manipulation. Overall energy intake is greater in Week 2 relative to Week 1, with no differences between groups (i.e., caloric compensation).

6.3 Discussion

The primary aim of this study was to determine if an HFS diet causes poorer performance on tests of HDLM. Additionally, we examined for changes in interoceptive sensitivity for hunger and fullness, as well as testing whether any observed changes in behavioural measures were associated with biological markers (i.e., blood glucose and lipid measures). Our key findings were: (1) a brief four-day HFS intervention led to significantly poorer memory retention, relative to the Control group, on the HVLT test, but not on the LM test; (2) the magnitude of this change in HVLT performance was significantly associated with the change in blood glucose across the experimental meals; (3) the Experimental group became significantly less sensitive to the effects of the breakfast, requiring more energy to shift hunger and fullness

ratings an equivalent amount on Day 4 relative to Day 1; and (4) the Experimental group did not consume more energy than the Controls overall, despite consuming significantly more energy at breakfast. Most of this compensation was for carbohydrate intake, as the Experimental group still consumed more saturated fat.

The principal finding from this study was the decline in performance on the HVLT retention score in the Experimental group, relative to the Control group. This is the first experimental evidence in humans that a brief dietary manipulation of saturated fat and added sugar intake leads to poorer performance on tests known to be hippocampally-related. To the best of our knowledge, this is the first experimental study in humans to parallel the findings in the animal literature. Moreover, the reduction in HDLM performance (as in the animal data) was evident after a relatively brief period of exposure to the diet. Another important element of this finding is that HDLM impairments were independent of energy intake, and thus were a consequence of the macronutrient profile of the diet. While there were postprandial changes in performance, the fact that there was a decline in HDLM performance across days supports the argument that cognitive changes were related to the dietary manipulation. Again, similar to animals, impairments in HDLM occurred in a healthy and lean population. Importantly, performance on non-hippocampal control measures did not deteriorate as a function of diet (noting that this is based on a limited set of such measures – forwards and backwards digit span), suggesting that HFS diets impact hippocampal measures specifically. Indeed, this diet-related specificity would likely be supported further by the use of multiple non-hippocampal measures in future studies.

The food diary data indicate the Experimental group, despite consuming more energy at breakfast than the Control group, did not consume more energy overall relative to the Control

group. While daily energy intake was comparable, macronutrient intake differed between groups. Specifically, there were no difference in *daily* carbohydrate and sugar intake (i.e., evidence of compensation), while *daily* total and saturated fat intake remained elevated. An interesting question raised by the food diary data is what particular aspect of the dietary manipulation led to the change in HVLT performance. There are at least three possibilities. The first is that the breakfast 'burst' of saturated fat and added sugar in the Experimental group was the causative factor. Indeed, tests of verbal memory – known to be hippocampally-based – appear to be most sensitive to experimental manipulations of macronutrient content (Attuquayefio & Stevenson, 2015; Hoyland, Lawton & Dye, 2008). Likewise, the design of this study (i.e., a brief exposure to an HFS diet giving a 'burst' of saturated fats and refined sugars) is consistent with rodent studies showing that animals given restricted access to HFS foods show similar deficits in learning and memory performance (e.g., Baker & Reichelt, 2016; Furlong, Jayaweera, Balleine & Corbit, 2014). The second possibility is that the greater net intake of saturated fat and total fat inside and outside of the laboratory in the Experimental group– across all four experimental days – represents the causative factor. The third possibility is that overall saturated fat and added sugar intakes (and perhaps overall energy intake) were *actually* higher in the Experimental group, but this was disguised deliberately or otherwise by dietary underreporting. We would suggest that the first alternative may be the most plausible, simply because we observed a relationship between changes in blood glucose across breakfast and change in HVLT performance across Days, with additional evidence that changes in blood glucose mediated alterations in HVLT performance. This would suggest that it was something about the breakfasts that led to changes in HDLM. The second possibility cannot, however, be discounted. Diets rich in just saturated fat can lead to impairments in HDLM in animals (e.g.,

Greenwood & Winocur, 1990; Greenwood & Winocur, 1996; Granholm et al., 2008; Morrison et al., 2010) and are associated with poorer memory recall in young women (e.g., Gibson, Barr & Jeanes, 2013), and so this could represent either an alternative or additional route to changes in HVLT performance in the Experimental group. However, given that few human studies have effectively manipulated saturated fat intake (Attuquayefio & Stevenson, 2015), it is unclear whether saturated fat or sugar intake alone evoked such changed in HDLM performance. While the third account is plausible, it may be the least likely. Dietary underreporting seems to be a more persistent phenomenon for the obese (e.g., Tooze et al., 2004), with healthy weight participants generally being more accurate reporters. Finally, while we note that protein intake also differed between the groups, we are not aware of any mechanism by which this macronutrient could generate the observed outcomes.

An unexpected finding was that while the HVLT was sensitive to changes in dietary fat and sugar intake, the LM measure showed no such change. One possible reason for this difference may arise in the appropriateness of using alternate forms of each test. The HVLT has six alternate forms that make it ideal for repeat testing, and these have been cross-validated and are indeed recommended and considered appropriate to be used in such a manner. On the other hand, the alternate forms of the LM test were taken from Schnabel (2012) and Sullivan (2005), which have been validated against the LM test from the Wechsler Memory Scale 4th edition and the Wechsler Memory Scale 3rd edition, respectively. Importantly, while multiple forms of the LM test were required for this study, these alternate forms have not been validated against each other, making the assumption of equivalency across these alternate forms *potentially* problematic. That alternate forms may be a problem for the LM test comes from consideration of coefficient alpha. For the HVLT this was adequate ($\alpha = 0.70$), but it was poor for LM

retention ($\alpha = 0.52$). It may ultimately be this poorer reliability that accounts for the failure to detect any diet-related changes with LM.

The Experimental group breakfasts led to far greater increases in blood glucose and triglycerides than the breakfasts consumed by the Control group. Furthermore, controlling for meal-related changes in these markers removed the difference between groups in HVLT performance across days, suggesting that significant alterations in these markers may contribute to changes in cognitive performance. That blood glucose and triglycerides show a similar pattern of change is not surprising. Glucoregulation is associated with lipid regulation (Farquhar, Frank, Gross, & Reaven, 1966), and consumption of HFS foods leads to marked increases in both blood glucose and triglyceride levels (Hanson et al., 2015; Koopman et al., 2014). As we noted in the Introduction, impaired glucoregulation may represent one putative causal pathway by which an HFS diet may adversely affect the hippocampus. Consistent with this possibility, we observed a significant association between blood glucose changes across the test breakfasts and changes in HDLM on the HVLT across the course of the study. Whether this effect is mediated directly by changes in blood glucose or indirectly via some other mechanism (e.g., inflammation) remains to be established. Support for an inflammatory mediation account comes from the well-established relationship between inflammation and impaired HDLM (Marin & Kipnis, 2013; Yirmiya & Goshen, 2011). In addition, animal studies show that diet-induced impairments in HLDM are linked to increased levels of inflammation (Beilharz, Maniam & Morris, 2014; Beilharz, Maniam & Morris, 2016; Boitard et al., 2014; Pistell et al., 2010; White et al., 2009) and changes in blood glucose concentration are correlated with elevated markers of inflammation in the hippocampus, but not the perirhinal cortex or hypothalamus (Beilharz, Maniam & Morris, 2016). Likewise, a diet high in processed meat, refined grains and sugar-sweetened beverages is strongly related to

inflammatory markers in women with type-2 diabetes (Schulze et al., 2005), and increasing sucrose intake in overweight individuals increases inflammation (Sørensen, Raben, Stender & Astrup, 2005). Recent evidence suggests that poor diet may also contribute to neuroinflammation and neurodegeneration (Cai, 2013). The potential link between glucoregulation and inflammation may be a causative factor in diet-induced impairments in HDLM, but remains to be experimentally verified for the paradigm used here.

Another consequence of shifting healthy subjects to an HFS diet was that the Experimental group showed evidence of reduced sensitivity over days to changes in hunger and fullness following breakfast consumption. The Experimental group required more energy on Day 4 than on Day 1 to shift hunger and fullness ratings an equivalent amount relative to the Control group. Our findings parallel correlational research in humans linking HFS diet and an impaired sensitivity to hunger and fullness (Attuquayefio et al., 2016; Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011). It is possible that differences in the satiating value of the test meals may contribute to this pattern of results. However, given the limited research regarding the interactions between the satiating value of foods and its energy density, this remains speculative but warrants further investigation. Another important consideration here is that the groups were not matched for BMI and waist circumference. While this was controlled for statistically, it would be worthwhile for future studies to methodologically account for these potentially important variables by, for example, stratifying groups by BMI, as biological interactions with these factors cannot be ruled out.

The findings here suggest that an HFS diet not only impairs performance on hippocampal-related memory tasks, but also the ability to accurately sense changes in hunger and fullness. Davidson et al. (2005) have previously argued that the regulation of appetitive

behaviour is based on the ability of satiety to inhibit food-related associations and this ability depends on the functional integrity of the hippocampus. A Western-style diet impacts hippocampal function and therefore the ability of satiety cues to inhibit this association, ultimately leading to excess weight gain (Davidson et al., 2005). Here, we provide evidence of impaired sensitivity to hunger and fullness following experimental manipulation of HFS intake in healthy lean humans. In conclusion, we show that brief consumption of a Western-style diet leads to impairments in HDLM and interoception in healthy lean young adults. Further, these changes in HDLM were linked to shifts in blood glucose across breakfast, suggesting one potential mechanism by which a Western-style diet can affect hippocampal function.

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Chapter 7: Discussion

7.1 Thesis Summary

The studies in this thesis were designed to address three aims: (1) to provide correlational evidence that a Western-style diet is associated with poorer inhibitory regulation of eating behaviour; (2) to review human causal evidence of diet on cognitive function; and (3) to provide experimental evidence that hippocampal-dependent learning and memory and interoceptive sensitivity is impaired following a Western-style diet. It was hypothesised in Study 1 that individuals who frequently consumed foods rich in saturated fats and refined sugars would present with poorer memory recall performance on hippocampal-dependent learning and memory tasks, poorer inhibition and with reduced sensitivity to changes in hunger and fullness, relative to individuals who infrequently consumed these foods. It was hypothesised in Study 3 that changes in performance on these measures would be detectable in lean weight subjects shifted to a diet high in saturated fats and refined sugars. The findings from this thesis are consistent with animal research by providing correlational and experimental evidence in humans that a Western-style diet impacts functions related to the hippocampus, and these findings are summarised below.

7.2 Study 1 (Chapter 3)

The aim of Study 1 was to provide evidence that inhibitory processes arguably mediated by the hippocampus would be impaired in individuals with a diet rich in saturated fats and refined sugars. It also aimed to replicate previous findings showing that a high-fat high-sugar (HFS) diet was associated with poorer hippocampal-dependent learning and memory (HDLM) and poorer interoceptive sensitivity. As predicted, stepwise regression analyses showed that self-

reported frequency of HFS intake was a significant predictor of learning rate on an HDLM task, noting that a slower learning rate was associated with greater reported HFS intake. Additionally, HFS intake was also associated with reduced interoceptive sensitivity (i.e., smaller changes in hunger and fullness), and greater intake of a palatable test lunch. Reduced skin yellowness readings from the spectrophotometer, used as a proxy measure of fruit and vegetable intake, was also associated with greater HFS intake. Indeed, this is not surprising given that reduced fruit and vegetable intake and increased intake of saturated fats and refined sugars are features characteristic of a Western-style diet (Cordain et al., 2005).

The findings from Study 1 show that greater intake of an HFS diet was associated with smaller reductions in wanting relative to liking of palatable food snacks between hungry and sated states, which was also linked to greater energy intake. That is, individuals with an HFS diet are poorer at inhibiting wanting ratings (relative to liking) based on hunger state. Importantly, this impaired ability to modulate ratings of wanting based on hunger state was strongly related to HDLM performance, *suggesting* mediation by the hippocampus. Further, spectrophotometer readings indicate that skin yellowness (i.e., fruit and vegetable intake) was not a significant predictor of either of these hippocampal-related effects. What this suggests is that the presence of an HFS diet (rather than the absence of fruit and vegetables) may be a contributing factor to changes in hippocampal function.

It should be noted that another inhibition task argued to be related to the hippocampus (Anderson & Green, 2001) was found not to be related to HFS intake. This may be due to the contribution of more frontal brain regions in task performance on the task. Alternatively, it may be that not all inhibition tasks related to the hippocampus are equally sensitive to diet, or that diet

may only impact hippocampally-dependent measures directly related to the regulation of eating behaviour.

The findings from this study not only replicate the relationship between HFS intake and HDLM in humans (Baym et al., 2014; Brannigan, Stevenson & Francis, 2015; Devore et al., 2009; Francis & Stevenson, 2011; Gardener et al., 2014; Granic et al., 2016), but also extend on previous research, by showing that inhibitory processes related to ingestive behaviour (i.e., modulation of wanting based on hunger state) are linked to dietary intake of fats and sugars. Study 1 lends credence to the notion that HFS intake impairs the ability of the hippocampus to regulate ingestive behaviour based on hunger state.

7.3 Study 2 (Chapter 4)

The premise that diet impacts cognitive function is based largely on animal evidence. While experimental evidence exists in humans, no systematic examination of such evidence has been performed. In this way, Study 2 aimed to systematically review the long-term impacts of dietary changes in macronutrients or energy on cognitive function. Overall, there was a trend showing that tests of working memory, long-term memory and attention were most sensitive to changes in energy and fat intake. However, the findings were more notable for their variability, likely related to multiple inconsistencies between studies, which included: variability in study design (cross-over vs. between-subjects), not accounting for potential confounds (e.g., physical activity levels), varying levels of dietary guidance (strict guidelines vs. general advice), and diet duration. Importantly, many studies often confounded changes in macronutrients and energy intake, without attempting to control this issue, making it problematic to determine which dietary factor contributed to observed changes in cognitive function. The review also identified that

there was a paucity of high-quality long-term experiments. Only ten studies articulated specific a priori research hypotheses, while the cognitive-related data appears to have been auxiliary in nature in the remaining 22 studies. Importantly, the review also identified that changes in energy intake and dietary fat more consistently resulted in changed cognitive performance, although the specific nature of such changes varied considerably.

7.4 Study 3 (Chapter 6)

Animal research showing that an HFS diet impacts HDLM and eating behaviour is robust (e.g., Beilharz, Maniam & Morris, 2016; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). However, there has been no experimental test as to whether an HFS diet causes these impairments in humans. Therefore, the aim of Study 3 was to provide experimental evidence that an HFS diet intervention for 4 days leads to impairments in HDLM and reduced interoceptive sensitivity to satiety. Study 3 also aimed to determine if there were corresponding changes in potential physiological markers argued to be related to hippocampal dysfunction.

Using an experimental design, lean individuals on a generally healthy diet were randomly allocated to receive either over 4 days a once-daily meal rich in saturated fats and refined sugars, or one low in these nutrients. This experimental study showed that consumption of the HFS meals impaired HDLM (i.e., memory retention on the Hopkins Verbal Learning Test) relative to the control group. It should be noted that another HDLM test (the Logical Memory subtest of the Wechsler Memory Scale) did not show significant changes as a function of diet over the four days, possibly due to insensitivity of alternate forms used across the diet period (i.e., its low reliability as measured by the coefficient α). Meanwhile, non-hippocampal-related measures did not significantly change over the diet intervention. Given that the non-hippocampal measures

(i.e., digit span forwards and backwards tests) were administered multiple times, it is possible that repeated administration may have masked deterioration in task performance from the HFS diet. However, this is unlikely as these tests have not been linked with hippocampal function (Leskelä et al., 1999), and show little change following dietary change (Attuquayefio & Stevenson, 2015). Therefore, HFS-diet induced changes in HDLM performance (while non-hippocampal measures remain unaffected) supports the assertion that HFS diets impact hippocampal function specifically. Further, the diet-induced HDLM impairment was also independent of total energy intake, suggesting that HFS intake was a major contributor to diet-related impairments to hippocampal function. Importantly, a larger increase in blood glucose levels from before to after the HFS meal was significantly associated with a greater decline in HDLM performance, suggesting that changes in blood glucose from HFS intake may be contributing to hippocampal dysfunction.

In addition to diet-induced impairments in HDLM, individuals given the HFS meals also became significantly less sensitive to the effects of the meals, requiring more energy to shift hunger and fullness ratings an equivalent amount on the final day of testing relative to the first day of testing. Interestingly, those given the HFS meals did not consume more energy than the control group, despite consuming significantly more energy at breakfast. There was some evidence of energy compensation later in the day, mostly from total carbohydrate intake, while saturated fat intake remained elevated. Thus, it was conjectured that the breakfast 'burst' of HFS intake likely led to impairments in HDLM and interoceptive sensitivity.

There are several important parallels between the findings from Study 3 and those from animals. First, lean weight subjects on a relatively healthy low-fat low sugar diet were shifted to an HFS diet, as in animals (e.g., Molteni et al., 2002). Second, consumption of an HFS diet

impaired HDLM, while non-hippocampal control measures were not affected (e.g., Beilharz, Maniam & Morris, 2016), and Study 3 provides the first experimental evidence of this specificity in humans. Third, impairments in HDLM were observed after a relatively brief period, again as in animals (e.g., Kansoski & Davidson, 2010). Lastly, diet-induced changes in hippocampal memory were also linked to changes in physiological markers known to be associated with hippocampal integrity (e.g., Gold et al., 2007). While potential mechanisms are well explored in animals, Study 3 suggests that abrupt alterations in blood glucose levels from HFS intake (especially repeatedly over an extended period of time) may adversely impact hippocampal functioning, suggesting one way diet impacts the brain. Overall, this experimental study provides the first causal evidence that shifting a lean individual from a healthy diet to an HFS diet causes impairments in HDLM and leads to reduced sensitivity to interoceptive signals, implying that HFS intake adversely impacts the hippocampus. In this way, the experimental findings of this thesis make a significant contribution to the current understanding of the impact of an HFS diet on HDLM and ingestive behaviour.

7.5 Implications of Current Thesis Findings

The following sections outline the implications of the current thesis findings for appetite regulation and ingestive behaviour, cognitive functioning and for the general population. First, the implications of this thesis for appetite regulation are considered in the context of a model of obesity (i.e., Davidson, Kanoski, Walls & Jarrard, 2005), drawing parallels between current findings and animal research. In addition, potential ways by which an HFS diet impacts ingestive behaviour are discussed. Second, the longer-term implications of an HFS diet for

cognitive function, and in particular for neurodegenerative disease, are discussed. Third, the wider implications of an HFS diet are outlined, including strategies to reduce HFS intake.

7.5.1 Implications for Appetite Regulation and Ingestive Behaviour

This thesis demonstrates in humans that an HFS diet impacts sensitivity to hunger and fullness (Study 3), increases food intake irrespective of hunger state (Study 1), and impairs the ability to regulate wanting of food based on hunger state (Study 1). Moreover, the findings from this thesis may have important implications in the regulation of eating behaviour, especially for habitual consumers of a Western-style diet. For example, the ability to use satiety to inhibit ingestive behaviour, which arguably depends on the functional integrity of the hippocampus, is impacted by greater consumption of a Western-style diet (Davidson et al., 2005). Consequently, habitual consumption of a Western-style diet gradually weakens the ability of satiety signals to control eating behaviours, thereby increasing the susceptibility to consuming those same foods that leads to further impairment – the so-called 'vicious cycle' model (Davidson et al., 2005). In this way, a Western-style diet may affect eating behaviour and lead to excess weight gain.

Another plausible way a Western-style diet may influence hippocampal function may be related to its variability in satiating value. A distinguishing feature of a Western-style diet is the availability of many different highly palatable foods, which may increase eating behaviour. One review showed that humans consume 22% more energy when a variety of foods is available (relative to one food), with each additional food contributing an extra 50–60 kcal per day (McCrory, Burke & Roberts, 1999). Since different types of the same foods may have varying energy densities, dietary variability may compromise the predictive satiating value of foods (Martin, 2016). For example, consuming the same brand of pepperoni pizza multiple times arguably allows an individual to associate the orosensory properties (i.e., taste, odour, texture)

with its energy density, and hence predict its satiating value. However, with increased dietary variability where many pizza brands are available (e.g., 71 different brands in the UK) with varying energy densities (e.g., between 501 and 1909 kcals), inconsistent associations between food cues and energy density may make satiety unpredictable (Hardman, Ferriday, Kyle, Rogers & Brunstrom, 2015). A consequence of this may be poorer energy compensation when consuming a more energy dense food, leading to excess energy intake. Indeed, individuals exposed to the greatest variability in energy density of pizza rated a standardised slice of pizza in the lab as less satiating and were poorer at compensating for the additional energy in a later test (Hardman et al., 2015). Thus, an individual's experience with dietary variability influenced the satiating value of a food and subsequent ingestive behaviour. Likewise, frequent consumption of artificially sweetened beverages may similarly interfere with learned responses between energy from sugars and homeostasis, increasing the risk of excessive weight gain by inducing metabolic derangements (Swithers, 2013). Indeed, habitual consumers of artificially sweetened beverages show weaker brain reward activation (Green & Murphy, 2012; Rudenga & Small, 2012), suggesting dietary variability may disrupt learned 'sweet-calorie' associations. Despite this, evidence for this 'flavour-nutrient learning' has been elusive (Yeomans, 2012), and it is not known if disruption to hippocampal function is a cause or consequence of the variable 'flavour-nutrient' associations of foods in a Western-style diet (whose learning may be state-dependent).

It is interesting to note that memory and interoceptive impairments were observed only after four once-daily exposures to the test meals in Study 3, since it represents quite a modest change in diet. What remains unclear is what happens when lean individuals are exposed to this diet for a longer period of time, where the effects of an HFS diet are likely to be exacerbated. One animal study appears to suggest that, following HFS-induced cognitive impairments, weight

gain, and glucodysregulation, upon return to a standard chow animals continue to exhibit impaired HDLM, although weight and glucoregulation recovers to control-equivalent levels (Wang et al., 2015). A related point to consider is the eating behaviour following exposure to an HFS diet. In contrast to Wang et al. (2015), animals fed an HFS diet show increases in body weight and adiposity when shifted to an HFS diet, but fail to return to a healthy body weight when shifted back to the standard lab chow (e.g., Beilharz, Maniam & Morris, 2014). While these findings seem at odds, the latter finding is supported both conceptually and empirically. That is, HFS-diet induced changes in hippocampal functioning may have adverse consequences for eating behaviour (even when that food is nutritious lab chow), and increase the likelihood of excess energy consumption and therefore weight gain. This also has important consequences for obesity treatment and prevention, since it suggests that diet-induced weight gain (particularly in central adipose tissue) may not be easily reversible. This line of argument is consistent with the 'vicious cycle' model (Davidson et al., 2005), where HFS diets generally (in contrast to specifically for certain food types) impact the ability of the hippocampus to regulate eating behaviour. Moreover, adverse changes to hippocampal function, and not just a Western-style diet, may be a persisting contributory factor in excess weight gain. That is, diet-induced hippocampal dysfunction may be permanent, and may explain, at least in part, the high incidence of dietary relapse and weight regain in humans.

7.5.2 Implications for HDLM and Cognitive Decline

The findings for Study 1 parallel those from animals showing that an HFS diet impairs HDLM (e.g., Beilharz, Maniam & Morris, 2016), while Study 3 provided the first experimental evidence that shifting lean weight adults to an HFS diet leads to detectable changes in performance on HDLM tasks. That an HFS diet impairs HDLM is important as hippocampal

damage and impaired HDLM are key features of neurodegenerative diseases, and this diet may contribute to such progressive declines in neurological function. Indeed, several human studies show that greater intake of a Western-style diet increases risk of cognitive impairment from Alzheimer's disease (Berrino, 2002; Gardener et al., 2014; Granic et al., 2016; Grant, 1997; Grant, 2014; Gu, Nieves, Stern, Luchsinger & Scarmeas, 2010; Morris et al., 2003; Torres et al., 2012).

Recent research suggests that sugar intake may increase the risk of cognitive impairment or neurodegeneration, so much so that Alzheimer's disease has been termed 'Type-3 diabetes' (de la Monte & Wands, 2008). This is based on that findings that: (1) poorer cognitive performance is associated with habitual intake of added sugars (Ye, Gao, Scott & Tucker, 2011) and sugar-sweetened beverage intake (Crichton, Elias & Torres, 2016); (2) lower simple carbohydrate intake is associated with slower cognitive decline over two years (Morris et al., 2015); (3) higher glycaemic diets are associated with poorer cognitive ability (Simeon et al., 2015); (4) high blood glucose levels are associated with poorer cognitive performance, and with greater decline in general cognitive ability, perceptual speed, verbal ability and spatial ability over 16 years (Seetharaman et al., 2014); (5) the risk of mild cognitive impairment or dementia almost doubles with increasing % carbohydrate intake, especially from sugars (Roberts et al., 2012); (6) diagnosis of diabetes mellitus almost doubles the risk of dementia (Ott et al., 1999); and (7) experimentally impairing brain insulin signalling via intracerebral administration of streptozotocin impairs molecular and cognitive function in much the same way as Alzheimer's disease (de la Monte & Wands, 2008). Based on such evidence, global trends towards a Western-style diet (high in refined sugars) may have negative consequences for hippocampal

learning and memory processes, with the *potential* for cumulative risk of neurodegeneration later in life.

There is emerging evidence that dietary interventions may be a strategy to attenuate the adverse effects of a Western-style diet on cognitive function late in life. Elderly adults with higher adherence to a 'prudent diet' (i.e., one high in vegetables, fruit, cooking/dressing oil, cereals and legumes, whole grains, rice/pasta, fish, low-fat dairy, poultry, and water) showed a smaller decline in cognitive performance over a 6 year period, relative to individuals with higher adherence to a Western-style diet (Shakersain et al., 2016). Similarly, the findings from the systematic review in Study 2 also suggest an amelioration of cognitive decline by dietary intervention is possible (e.g., Aquilani et al., 2008). Evidence-based diet interventions have the potential to delay dementia onset at a population level, and high public demand for dietary guidance to aid in prevention or treatment will likely drive such change. While the evidence is not yet at a point where sound dietary recommendations can be made, findings from this thesis such as the systematic review (i.e., Study 2) contribute to the current understanding of dietary interventions on subsequent cognitive function, at least in the short term.

7.5.3 Implications for General Population

The findings from this thesis provide evidence of causal data that: (1) may raise concerns both about the implications of a Western-style diet on cognitive and health-related outcomes, but also invoke considerable public interest in reducing exposure to them; (2) may increase awareness of the adverse consequences of diet that is little known to the general public; and (3) may provide the impetus for shifting dietary habits away from processed foods to one with a higher intake of vegetables, fruits and fibre. Importantly, this thesis now provides correlational and experimental evidence that greater HFS intake, a key characteristic of a Western-style diet,

may be a major contributing factor to adverse changes in hippocampal function. That is, while a Western-style diet is characterised by reduced complex carbohydrate, fruit, vegetable and fibre intake, the adverse consequences of this diet on cognitive function (e.g., Berrino, 2002) and body weight (e.g., Newby et al., 2003) may be driven by excessive consumption of saturated fats and refined sugars. Findings from Study 1 support this idea, with the spectrophotometer readings (a proxy measure of fruit and vegetable intake) contributing non-significant variance to hippocampal-related task performance. That is, HFS intake appears to be driving these impairments, and fruit and vegetable intake may not be a protective factor against such changes. One way to provide additional evidence for this assertion would be to compare varying levels of fruit and vegetable intake in individuals with similar HFS intake. It would be important for individuals and for targeted interventions to know if reducing fat and sugar intake is more impactful to cognitive and health outcomes than simply incorporating more fruits and vegetables into a diet already rich in saturated fats and refined sugars.

The issue of reducing the health impacts of highly processed sugar and saturated fat-laden energy dense foods prevalent in Western diets is one of concern for researchers and public health policy. Dietary guidelines or interventions aimed at modifying food choice and increasing physical activity would likely aid in reducing the prevalence of overweight and obesity by helping individuals better manage their dietary intake and physical activity (Popkin, Adair & Ng, 2012). One potential strategy that may be beneficial is the implementation of cognitively based interventions aimed at improving cognitive control over ingestive behaviour. For example, inhibitory control training over eating behaviour, where individuals learn to associate appetitive cues with the inhibition of behaviours, may facilitate better eating practices. A meta-analysis of laboratory studies revealed that inhibitory control training reduces food consumption, with the

level of successful inhibitions moderating this effect (Jones et al., 2016). Another cognitively based intervention may involve recalling memories of previous meals or eating bouts, as this reduces subsequent food intake (e.g., Higgs, Williamson & Attwood, 2008). Yet another strategy may involve 'mindful eating', where the goal is to help individuals to reduce automatic and binge-like eating by cultivating awareness of hunger and satiety cues, the foods they crave, eating behaviours and the emotional and cognitive states associated with eating. Research shows that 'mindful eating' practices reduce hunger (Dalen et al., 2010), reduce food intake (Jordan, Wang, Donatoni & Meier, 2014), and improve eating behaviour (O'Reilly, Cook, Spruijt-Metz & Black, 2014). Alternatively, if a Western-style style impairs cognitive control processes involved in ingestive behaviour, then treatment and prevention strategies that are not cognitively based may be more effective. Such strategies include: (1) heavier taxes on highly processed, sugar and saturated fat-laden foods to act as a disincentive to consume these foods (e.g., Sarlio-Lähteenkorva & Winkler, 2015); (2) pharmacological interventions to influence eating behaviour (Rodgers Tschöp & Wilding, 2012); or (3) surgical interventions such as bariatric surgery, which influences subsequent food preferences and cravings (e.g., Pepino et al., 2014), or faecal matter transplants to alter gut microbiota, which are sensitive to in rats shifted to an HFS diet (e.g., Beilharz, Kaakoush, Maniam & Morris, 2016).

7.6 Strengths and Limitations

A key strength of this thesis is that it builds from correlational research into experimental evidence in a logical manner to provide a clearer picture of the impact of a Western-style diet on cognition in humans. Study 1 shows that an HFS diet is associated with HDLM deficits and increased food intake. This study also provides evidence that inhibitory processes associated

with appetitive behaviour (i.e., shift in wanting ratings based on hunger state) are also impaired in individuals with an HFS diet, with evidence that this is hippocampally-mediated. Study 1 also provides human evidence to support the animal-based model of inhibitory regulation of ingestive behaviour featured throughout this thesis (Davidson et al., 2005).

A unique feature of Study 1, presented in Chapter 3, was the use of explicit wanting and liking ratings to represent an individual's likelihood of engaging in behaviour aimed at obtaining food (wanting) relative to their evaluation of the food itself (liking). It should be noted that Berridge and Robinson (2003) have distinguished between explicit wanting and implicit wanting. Implicit wanting involves the Pavlovian system to make cue-triggered trigger motivational responses that occur without conscious experience, although this has been notoriously difficult to demonstrate in humans (Havermans, 2012).

Explicit wanting, on the other hand, is driven by conscious cognitive mechanisms, relying on the remembered pleasantness based on previous experience with the food (Berridge, 2009). Explicit wanting may therefore be driven by hippocampally-based episodic memory processes, where individuals draw upon a remembered liking to determine food intake. Support for this comes from studies showing that remembered liking: (1) differs from liking at the time of consumption and best predicts future expected enjoyment (Robinson, 2014); (2) increases the likelihood of choosing and consuming that food in the future (Robinson, Blissett & Higgs, 2012); and (3), impacts subsequent food choice (Robinson, 2014), with evidence that the most recent memory of that food influences later eating behaviour (Garbinsky, Morewedge & Shiv, 2014). That remembered liking impacts eating is consistent with previous literature demonstrating the role memory plays in eating behaviour (Higgs, 2008; Higgs, Williamson & Attwood, 2008). The fact that the explicit 'want more' ratings in Study 1 presented a larger HFS-diet related effect

suggests that it may be a purer measure of explicit wanting and therefore may better draw upon episodic memory processes.

Additionally, the results from Study 1 are consistent with incentive-sensitisation theory (Robinson & Berridge, 2003), where repeated exposure to energy dense palatable foods leads to exaggerated wanting for these foods in the absence of commensurate shifts in liking. This theory was originally aligned with implicit wanting in animals, and has been difficult to operationalise in humans (see Havermans (2012) for further discussion). However, it can also be applied to the relationship between explicit wanting and diet. In other words, as a Western-style diet weakens the ability of satiety to inhibit the association between a cue and its learned post-ingestive consequences, one may continue to explicitly 'want' food or 'want more' food even when sated, while liking would not show this pattern. Indeed, this is what was demonstrated in Study 1 of this thesis. The findings are important as they suggest that greater intake of an HFS diet may affect cognitive and motivational processes related to ingestive behaviour, whose dysfunction may play a role in excess weight gain and disordered eating (e.g., Mela, 2006).

Another key strength of this thesis is the provision of experimental evidence that an HFS diet impacts HDLM and interoceptive sensitivity. Previous studies in humans have found a relationship between HFS intake and HDLM performance and interoceptive sensitivity (e.g., Francis & Stevenson, 2011). However, such findings have been correlational in nature, which is inherently limited in its explanatory power. This issue was addressed in this thesis by undertaking an experimental approach in Study 3. One distinct advantage of experimental evidence over correlational evidence is the investigation of causality (i.e., does consumption of a Western-style diet *cause* impairments in HDLM?). Indeed, Study 3 formed the focal point of

this thesis, providing experimental evidence that a Western-style diet leads to impairments in HDLM and in interoceptive sensitivity in lean individuals.

One potential concern may arise from the sample population used in Study 3, namely lean weight individuals that rarely consume HFS foods recruited from undergraduate university students. The benefit of drawing upon this population is that they are typically healthy and lean, and of similar socio-economic background, and thus generally more homogeneous (in much the same way animals are). Furthermore, this population was believed to best parallel lean animals, who show robust HFS diet-induced hippocampal impairments when shifted from a nutritious (i.e., low-fat low sugar) lab chow diet. It was believed that this parallel would therefore increase the likelihood of diet-related impairments in hippocampal function in humans. While the use of this population is useful in the context of the experiment in Study 3, it may limit its external validity to the general population who may be more heterogeneous and who therefore may vary considerably on many factors that are also known to impact hippocampal functioning (e.g., body weight, dietary habits, physical activity, smoking etc.). For instance, in a more heterogeneous sample, factors likely to impact hippocampal function such as poor sleep quality (e.g., Reimann et al., 2007) or increased BMI (e.g., Taki et al., 2008) may act synergistically with a Western-style diet to further deteriorate hippocampal function and make it more difficult to regulate eating behaviour. It would therefore be worthwhile to investigate whether diet works synergistically with other factors (e.g., sleep quality and BMI) to affect hippocampal function.

The notion that an HFS diet impairs HDLM is based on the premise that such neuropsychological tasks (e.g., The Hopkins Verbal Learning Test) selectively measure hippocampal function. In other words, it is often inferred that HDLM measures effectively assess the structural integrity of this brain area. There are several reasons for thinking that this is

a plausible assertion. First, episodic memory refers to the system that enables conscious recollection of events within a time and place. Performance on these tasks (similar to the tasks used in this thesis) is associated with hippocampal activation (Kesler et al., 2013; Maki et al., 2009; Saling et al., 1992; Sass et al., 1992), while performance on non-episodic memory tasks such as working memory is not related to hippocampal activation (Travis et al., 2014). Second, hippocampal volume best predicts performance on episodic memory tasks (Kramer et al., 2004). Third, damage to the hippocampus selectively impairs performance on episodic memory tasks of word recall and story recall (Squire, 1992; St-Laurent, Moscovitch, Jadd & McAndrews, 2014). Based on such evidence, it is reasonable to argue that episodic memory tasks are related to hippocampal function and any factor (e.g., a Western-style diet) argued to influence the hippocampus would likely affect performance on episodic memory tasks. Indeed, this is what was empirically shown in chapters three and six of this thesis.

The findings from this thesis draw heavily upon the self-report of intake frequency of refined sugars and saturated fats over the past year, as measured by the Dietary Fat and Sugar (DFS) questionnaire. The DFS has been validated against more a comprehensive self-report food frequency questionnaire and a food diary, with evidence that the DFS is selective to dietary intake of the target nutrients (Francis & Stevenson, 2013). Additionally, the DFS was validated by the spectrophotometer findings from Study 1, showing reduced skin carotenoid levels indicative of lower fruit and vegetable intake in those with higher DFS scores – a pattern characteristic of a Western-style diet (Cordain et al., 2005). That is, the evidence from a self-report dietary questionnaire is consistent with objective spectrophotometer readings, suggesting construct validity of the DFS to measure dietary habits.

One potential criticism is that self-report dietary measures may be problematic due to underreporting. This is based on the finding that, in comparing what one would need to eat to maintain current body weight and what people self-report, individuals typically underreport the amount of food they consume (e.g., Schoeller, 1995). Underreporting is also more common in individuals with a higher BMI (e.g., Macdiarmid & Blundell, 1998; Tooze et al., 2004), where factors such as social desirability may play a role. However, it can be argued that the underreporting of dietary intake of fats and sugars (as in Study 1) would likely affect the variability in these ratings and hence the magnitude, but not the direction, of the relationship between HFS intake frequency (i.e., the DFS) and HDLM performance. Likewise, Study 3 attempted to address this potential concern by using a lean healthy-eating sample population who would likely be more accurate in their recall (e.g., Francis & Stevenson, 2011) and less likely to underreport (e.g., Braam, Ocké, Bas Bueno-de-Mesquita, & Seidell, 1998).

7.7 Future Directions in Research

A major challenge for human research in this field is the development of high-quality experiments to establish causal links between consumption of an HFS diet and impairments in hippocampal functions. Many of these considerations were discussed in Chapter 5 of this thesis. While this thesis provides initial causal evidence of the impact of a Western-style diet on the hippocampus in humans, several important factors are still unknown.

First, it is not clear whether diet-related changes to HDLM, interoception and blood glucose persist after individuals revert to their habitual diet (i.e., its reversibility). Second, it is unclear how long it would take to ameliorate such diet-related impairments. Third, since there is preliminary evidence that greater HFS intake leads to hippocampal-related impairments, it is

unclear if the reduced intake or removal of HFS foods would lead to improvements over time, or if the addition of other nutrients is required (i.e., increasing fruit and vegetable intake). Indeed, the findings from Study 1 suggest that the former may be more important here, but his has yet to be empirically tested in humans.

Finally, the simultaneous testing of various blood markers related to hippocampal function (e.g., blood glucose/insulin, inflammation, brain-derived neurotrophic factor) prior to, during and after a nutritional intervention would likely provide clearer direction as to the mechanisms involved in diet-related cognitive changes. It would also determine which markers are impacted first and in what order. Study 3 investigated whether changes in blood glucose levels co-occur, or even precede neuropsychological impairments from the experimental diet. However, there are other physiological markers known to be related to hippocampal function that may also be sensitive to changes in diet, including inflammation (e.g., tumor-necrosis factor-α, interleukin 6), glucoregulation (e.g., insulin, insulin growth factor 1) and several others (e.g., brain-derived neurotrophic factor, oxidative stress). Furthermore, alterations in glucoregulatory and inflammation markers have been linked with a Western-style diet and obesity (e.g., Manzel et al., 2014), suggesting that they may play a role in the onset or maintenance of diet-related hippocampal impairments linked to obesity. It would be of interest to explore several of these markers to observe which are most sensitive to an HFS diet.

Diet-related impairments in cognitive function appear to be linked to the alterations in particular physiological mechanisms (for a review, see Hsu & Kanoski, 2014). Animals fed a HFS diet for 3-10 days show reduced glucose uptake by the brain (Jais et al., 2016) and reduced expression of the glucose-transporter GLUT-1 at the site of the hippocampus (Hargrave, Davidson, Lee & Kinzig, 2015). Alternatively, HFS-diet-induced changes to blood brain barrier

permeability are specific to the hippocampus (Davidson et al., 2013; Kanoski, Zhang, Zheng, & Davidson, 2010). Importantly, in humans, increases in hippocampal blood brain barrier permeability have been linked memory impairments later in life (Montagne et al., 2016), with evidence that these physiological changes occur years before cognitive dysfunction (Montagne et al., 2015). While it is beyond the breadth of this dissertation to explore this further, greater consideration of diet-related changes in blood brain barrier permeability (especially at the site of the hippocampus) as a precursor of both HDLM dysfunction and impaired inhibitory control of food intake is warranted.

One question yet to be addressed adequately in the animal or human literature relates to the specificity of hippocampal impairments from a Western-style diet. That is are any particular regions of the hippocampus specifically impacted by diet more than others? For instance, the hippocampus can be functionally divided into dorsal and ventral regions (Fanselow & Dong, 2010), with the former argued to play a role in the utilisation of episodic memory in ingestive behaviour (Parent, 2016). This is, in part, based on that findings that inactivation of the dorsal hippocampus in rodents decreases time between meals (Henderson, Smith & Parent, 2013), and a high-fat diet alters neuropeptide levels in the dorsal hippocampus (Gan et al., 2015). Alternatively, episodic memory performance in humans has been linked to activation of particular subfields of the hippocampus, including the dentate gyrus (Travis et al., 2014) and CA1/CA3 subfields (Mueller, Chao, Berman & Weiner, 2011). Another study showed that a Western-style diet is associated with smaller left hippocampal volume (independent of age), while right hippocampal volume is not related to diet in elderly adults (Jacka, Cherbuin, Anstey, Sachdev & Butterworth, 2015). Although yet to be resolved which are most important, these findings suggest that performance on episodic memory tasks may be related to the integrity of

these regions, with particular regions or subfields being more susceptible than others to dietary insult. Recent research in rodents suggests that the dorsal striatum (involved in the processing of reward value of foods) and the dorsal and ventral regions of the hippocampus (interoception, memory and inhibition) are impacted by a Western diet (Hargrave, Davidson, Zheng & Kinzig. 2016), but such specificity remains to be seen in humans. While there is emerging evidence in humans of brain areas associated with relational memory, diet, interoception, or inhibition, there is little evidence linking all of these factors (as argued by the Davidson et al. (2005) model). There is great potential for neuroimaging studies to provide objective evidence of the impact of a Western diet on these arguably hippocampal-based processes. Indeed, neuroimaging data on the hippocampal function and structure associated with adiposity, dietary intake, age, cognitive functioning, inhibition and interoception would provide substantive evidence of the vulnerability of the hippocampus to dietary insult. Important, the shift to a Western diet (as in Chapter 4) combined with neuroimaging evidence of functional or structural changes following this diet would provide a strong evidence for causality.

Indeed, an important consideration in the context of this thesis is the argument for the direction of causation. This thesis takes the stance that greater intake of refined sugars and saturated fats typical of a Western-style diet leads to impairments in using hippocampal-related functions of memory, satiety and inhibition to regulate eating, thereby promoting eating in the presence of satiety and ultimately leading to weight gain and obesity. An alternative to this interpretation may be that individuals more prone to palatable food consumption may be more likely to consume a Western-style diet and subsequently eat when sated. However, there are several reasons to conclude that the former is more likely. First, animals show impairments on hippocampal-related tasks following a Western-style diet (e.g., Beilharz et al., 2016). Second,

this cause-effect evidence is found in C57BL/6 mice with a genetic predisposition to diet-induced diabetes and obesity (e.g., Messier, Whately, Liang, Du & Puissant, 2007). Taken together, these studies suggest that an HFS diet leads to hippocampal impairments, regardless of one's predisposition to weight gain. Lastly, the experimental evidence from Study 3 shows that shifting lean individuals with a generally healthy diet to an HFS diet leads to impairments on tasks argued to be mediated by the hippocampus. The fact that animal and human evidence are consistent suggests an HFS diet causes impairments in hippocampal function related to learning and memory processes, eating behaviour and the ability to accurately sense hunger and fullness.

7.8 Conclusions

The findings from this thesis reveal that a Western-style diet is associated with deficits in hippocampal-related learning and memory, and inhibition, and these changes may influence eating behaviour. Importantly, this thesis also provided the first causal evidence in humans that an HFS diet impairs hippocampal functioning including HDLM and sensitivity to internal states. The parallel between previous animal research and the human findings in this thesis suggest that a Western-style diet may have long-term implications for appetite regulation and cognitive functioning, leading to excess weight gain and ultimately obesity.

7.9 References

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Appendix 1: Human Ethics Approval for Study 1

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24 March 2015

Professor Richard Stevenson
Department of Psychology
Faculty of Human Sciences
Macquarie University
NSW 2109

Dear Professor Stevenson

Reference No: 5201500019

Title: *Eating, diet and behaviour study*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Human Sciences & Humanities)) at its meeting on 27 February 2015 at which further information was requested to be reviewed by the Ethics Secretariat.

The requested information was received with correspondence on 17 March 2015.

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated March 2014) (the *National Statement*).

This letter constitutes ethical and scientific approval only.

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Human Sciences and Humanities) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics

The HREC (Human Sciences and Humanities) wishes you every success in your research.

Yours sincerely

Dr Karolyn White
Director, Research Ethics & Integrity,
Chair, Human Research Ethics Committee (Human Sciences and Humanities)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Details of this approval are as follows:

Approval Date: 24 March 2015

The following documentation has been reviewed and approved by the HREC (Human Sciences & Humanities):

Documents reviewed	Version no.	Date
Macquarie University Ethics Application Form	2.3	July 2013
Correspondence from Professor Stevenson responding to the issues raised by the HREC (Human Sciences and Humanities)		Received 17/03/2015
MQ Participant Information and Consent Form (PICF) entitled *Eating Diet and Behaviour Study (Study 1)*	1	12/12/2014
MQ Participant Information and Consent Form (PICF) entitled *Eating Diet and Behaviour Study (Study 2)*	1	12/12/2014
The Dietary Fat and free Sugar – Short Questionnaire		
Telephone Screening Questions		
Participant Questionnaire: General, Exercise (IPAQ), Sleep (PIRS 2), DASS21 and The three-factor eating questionnaire		
Chemosensory Medical History Questionnaire		
Advertisements		

Appendix 2: Verbal Paired Associates words list used in Study 1

1. Realism Entrance
2. Ruler Contrast
3. Juice Prelude
4. Curtain Subject
5. Precision Elephant
6. Leather Thicket
7. Handle Cabin
8. Summit Keyword
9. Bodywork Index
10. Business Piano
11. Fusion Storage
12. Trilogy Grant
13. Separate Penguin
14. Rider Capacity
15. Shower Patent
16. Prototype Freckle
17. Terrain Lecture
18. Counting Luggage
19. Table Legend
20. Briefcase Layout
21. Import Boarding
22. Compass Hearing
23. Habit Window
24. Stream Balcony
25. Bedding Elbow
26. Forecast Porridge

Appendix 3: Human Ethics Approval for Study 3

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23 December 2013

Professor Richard Stevenson
Department of Psychology
Faculty of Human Sciences
Macquarie University

Dear Professor Stevenson

RE: *Short term dietary, neuropsychological and physiological consequences of intake of 'Western' meals high or low in saturated fats and sugars*

Thank you for your email dated 13 December 2013 responding to the issues raised by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)).

On 13 December 2013 the Ethics Secretariat considered your correspondence and approved your application. This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007).

Details of this approval are as follows:

Reference No: 5201300817

Approval Date: 13 December 2013

This letter constitutes ethical and scientific approval only.

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
National Ethics Application Form (NEAF)	AU/1/7F65112	2008
Correspondence from Professor Stevenson addressing the HREC's feedback	No Version	13/12/2013
MQ Participant Information and Consent Form (PICF)	1	12/12/2013
Research Protocol	1	13/12/2013

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. Approval is for five (5) years, subject to the submission of annual reports.

First Annual Report Due: 1 December 2014

3. All adverse events must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Please do not hesitate to contact the Ethics Secretariat should you have any questions regarding your ethics application.

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Dr Karolyn White
Director, Research Ethics & Integrity
Chair, Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) (the National Statement) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Appendix 4: Published manuscript of Study 1 (Chapter 3)

Journal of Experimental Psychology: Animal Learning and Cognition
Psychological Association 2016, Vol. 42, No. 4, 415–428
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2329-8456/16/$12.00

A High-Fat High-Sugar Diet Predicts Poorer Hippocampal-Related Memory and a Reduced Ability to Suppress Wanting Under Satiety

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Animal data indicate that greater intake of fats and sugars prevalent in a Western diet impairs hippocampal memory and tests of behavioral inhibition known to be related to hippocampal function (e.g., feature negative discrimination tasks). It has been argued that such high-fat high-sugar diets (HFS) impair the hippocampus, which then becomes less sensitive to modulation by physiological state. Thus retrieval of motivationally salient memories (e.g., when seeing or smelling food) occurs irrespective of state. Here we examine whether evidence of similar effects can be observed in humans using a correlational design. Healthy human participants ($N = 94$), who varied in their habitual consumption of a HFS diet, completed the verbal paired-associate (VPA) test, a known hippocampal-dependent process, as well as liking and wanting ratings of palatable snack foods, assessed both when hungry and when sated. Greater intake of a HFS diet was significantly associated with a slower VPA learning rate, as predicted. Importantly, for those who regularly consumed a HFS diet, though reductions in liking and wanting occurred between hungry and sated states, the reduction in wanting was far smaller relative to liking. The latter effect was strongly related to VPA learning rate, suggestive of hippocampal mediation. In agreement with the animal literature, human participants with a greater intake of a HFS diet show deficits in hippocampal-dependent learning and memory, and their desire to consume palatable food is less affected by physiological state—a process we suggest that is also hippocampal related.

Keywords: hippocampus, diet, wanting, Western diet, memory

The rise in obesity in many countries has been linked to the increased consumption of a Western-style diet, one rich in saturated fats and refined sugars, and low in fiber, fruit, and vegetables (Drewnowski, 2007). Though this type of diet may contribute to weight gain via its palatability and energy density, it may have other effects as well. A recent animal-based model of obesity proposes that such a diet adversely impacts certain centrally controlled aspects of food intake regulation via memory and inhibition processes, which then directly contribute to weight gain (Davidson, Kanoski, Walls, & Jarrard, 2005). Specifically, diets rich in saturated fat and refined sugar impair the ability of the hippocampus to appropriately inhibit food-related memories under a sated physiological state, which subsequently promotes energy regulation and thus obesity (Davidson et al., 2005). Animals consistently show robust impairments in hippocampal-related learning and memory following a shift from standard lab chow to a diet high in fat (e.g., Greenwood & Winocur, 1996; Morrison et al., 2010), sucrose (e.g., Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney, & Corbit, 2013), and both saturated fat and refined sugars (e.g., Beilharz, Maniam, & Morris, 2014; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Tran & Westbrook, 2015). Although the animal data are substantial, there has been relatively little translation into human research. So far, it has been established that greater consumption of a saturated fats and refined sugars—a high-fat high-sugar (HFS) diet—is associated with poorer performance on hippocampal-related measures of learning and memory in children (Baym et al., 2014) and adults (Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011) and with smaller hippocampal volume in the elderly (Jacka, Cherbuin, Anstey, Sachdev, & Butterworth, 2015). These correlational findings suggest that as in animals, such a diet may impair hippocampal function across the life span.

The hippocampus may mediate several different regulatory functions in respect of food intake. These include (a) explicit

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retrieval of what has been eaten to aid conscious modulation of food intake (Higgs, 2002; Robinson et al., 2013); (b) integration of physiological signals of hunger, fullness and thirst, with memory for what has recently been eaten and drunk, to generate interoceptive states (Brannigan, Stevenson, & Francis, 2015; Brunstrom et al., 2012); and (c) state-dependent retrieval and inhibition of pleasant food-related memories (Davidson et al., 2005; Davidson, Sample, & Swithers, 2014). It is this last proposed mechanism that is of principal interest here because of its apparent importance in modulating appetite according to hunger state.

It has been suggested, again on the basis of animal data, that upon encountering food cues when hungry, pleasant food-related memories associated with the cue are excited or retrieved, thereby motivating the animal to eat that food. However, when sated, such associations are inhibited, thus reducing the incentive to consume. The regulation of appetitive behavior is therefore based on the ability of satiety cues to inhibit this association, and this ability depends on the functional integrity of the hippocampus (Davidson et al., 2005; Davidson, Sample, & Swithers, 2014). It follows then that successful long-term energy regulation involves integrating physiological states (hunger/satiety) with these memory-driven motivational states so as to facilitate or retard energy intake when encountering food cues in the environment. According to Davidson et al. (2005), diets high in fats and refined sugars disrupt this process by impairing hippocampal function. The latter would then impair the ability of satiety to inhibit pleasant food-related memories in the presence of palatable food cues, and hence the ability to modulate the incentive salience of food based upon physiolog- ical state. Although animal data support this type of model (e.g., Davidson et al., 2012; Murray et al., 2009), there is as yet no test of it in humans. The main focus of this current study is to provide such a test.

Liking a food when eating it (i.e., palatability) and wanting a food on seeing it (i.e., incentive salience) are key drivers of human eating behavior (Finlayson, King, & Blundell, 2007b). *Wanting* is hypothesized to be the consequence of an active process whereby internal cues to bodily state and external cues to food are transformed into representations with an assigned motivational value (Berridge, 1996). Generating a "want" is therefore highly dependent upon memory, with each food cue leading to the retrieval of its own particular sensory and hedonic attributes. Whereas wanting may be heavily dependent upon memory, liking is likely to be far less dependent because here consumption directly activates sensory-driven pleasure circuits (i.e., for sweetness, saltiness, fatty mouthfeel). Accordingly, wanting for a food should be strongly linked to hippocampal-related memory processes, whereas liking should not.

Another important consequence of this definition of wanting by Berridge (1996) is that the motivational value of a food should vary as a function of physiological state—a phenomenon termed *alliesthesia* (Cabanac, 1971). Although Cabanac (1971) defined this phenomenon using *pleasantness* (i.e., liking), others have since shown that changes in internal state induce greater decreases in wanting than liking when exposed to olfactory stimuli (Jiang et al., 2008) and visual stimuli (Finlayson, King, & Blundell, 2007a). According to Davidson et al., (2005), the presence a food cue activates the stored representation of that food when hungry, but is inhibited when sated. Therefore, wanting should be more sensitive than liking to changes in physiological state, since wanting is driven by the integration of physiological state and by the activation of a food-related memory (Berridge, 1996), while liking involves only the former. To see then if wanting is less effectively modulated by state in habitual consumers of a HFS diet (and changes in liking are not), we asked participants to evaluate their desire to consume and their liking for palatable snack foods (palatable food cue task) when hungry and later, after an experimental lunch, when sated. Our major prediction was that changes in wanting from a hungry to a sated state would be smaller in habitual consumers of a HFS diet than comparable changes in liking. In addition to ratings of liking and wanting, we also obtained salivary responses to these foods, which we expected to mirror changes in wanting.

To determine whether state-dependent effects on wanting and liking in the palatable food cue task were associated with perfor- mance on a hippocampal-related task, participants were also given a second test. This involved learning pairs of words—verbal paired associates (VPA)—a task that is known to be dependent upon an intact hippocampus (Baxendale, 1995; Eichenbaum & Bunsey, 1995; Karantzoulis, Scorpio, Borod, & Bender, 2011). Not only did we expect VPA performance to be poorer in frequent consum- ers of a HFS diet as predicted by our earlier work (Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011), we also expected that VPA performance would correlate with size of the state-dependent change in wanting but not liking.

Following VPA training and testing, participants were asked to engage in a series of further learning trials which involved either explicit inhibition of some VPAs and explicit rehearsal of others—the think/no think task. It has been claimed that performance on the think/no-think task is also related to the hippocampus (Anderson & Green, 2001; Anderson et al., 2004). We thus predicted that performance on this task should also be poorer in frequent consumers of a HFS diet.

A further feature of this study was our attempt to recruit participants of normal body mass index (BMI; Š25kg/m^2), as well as controlling for variation in BMI because increased BMI may affect memory recall (De Wit et al., 2016). Several other factors can affect hippocampal function. These include age (e.g., Bouchard et al., 2008), gender (e.g., Cosgrove, Mazure, & Staley, 2007), phys- ical activity (e.g., Erickson et al., 2011), sleep quality (e.g., Ri- emann et al., 2007), and depression and stress (e.g., Videbech & Ravnkilde, 2004). Furthermore, diet quality, food intake, and attitudes to food and eating have been linked with gender (e.g., Northstone, 2012), sleep quality (e.g., Chaput, 2014), physical activity (e.g., Drewnowski & Evans, 2001), and depression and stress (e.g., Appelhans et al., 2012). These possibly confounding factors were also measured in this study.

Assessment of participants' diets used a validated food fre- quency questionnaire, designed to indicate differences in intake of saturated fat and refined sugar, the Dietary Fat and Sugar Ques- tionnaire (DFS; Francis & Stevenson, 2013). In addition, we also assessed skin carotenoid levels using a spectrophotometer to de- termine fruit and vegetable intake (Stephen, Coetzee, & Perrett, 2011). This measure was expected to be negatively correlated with scores on the DFS. It also allowed us to test whether the absence of fruit and vegetables (rather than the presence of saturated fat and refined sugar) was associated with any hippocampal-related effects, on the grounds that a healthy diet may be protective.

In sum, the primary aims of the current study were to determine whether more frequent consumption of a HFS diet impairs state-dependent changes in wanting but not liking and to see whether this effect is linked to hippocampal-related processes. Secondary aims were to determine whether a hippocampal-related measure of learning and memory (VPA) was acquired more slowly in frequent consumers of a HFS diet and whether this also extended to the think/no-think task.

Method

Participants

People differ in the degree to which they eat a HFS diet. As we wished to use a correlational approach in our analyses, we needed to ensure that we had sufficient numbers of people who rarely or frequently consumed a HFS diet. To this end, we screened a large sample and recruited people only from the upper and lower quartiles of a measure designed to assess dietary intake of fats and refined sugars (see the following text). Having sampled in this way - and knowing that there would be some regression to the mean when peoples dietary habits were measured again during the study—we treated the dietary data as a continuous variable (i.e., a correlational approach) rather than grouping participants into "highs" and "lows." This decision was made because the continuous approach under these circumstances is considerably more powerful than the grouping approach (MacCallum et al., 2002; Preacher et al., 2005), as it uses all of the available information. Participants were recruited via two routes. The first involved screening the participant pool maintained by the Department of Psychology at Macquarie University using the DFS, which is a 26-item food frequency questionnaire (score range from 26 to 130) designed to identify variability in intake of saturated fat and refined sugar. The DFS has good test–retest reliability ($r = .84$ over 22 weeks) and has been validated against a full-length food frequency questionnaire and a 4-day diet diary for both saturated fat and refined sugar intake (Francis & Stevenson, 2013). Cut-offs for the DFS were similar to Francis and Stevenson (2011), with scores above 70 and below 55 being used to identify potential participants. A total of 651 undergraduates completed the DFS. Of these 267 remained as potentially eligible participants because they met all of the following criteria: (a) fell above or below the cut-offs, (b) reported a BMI between 17 and 26 (broader than the conventional criteria because this was a self-estimate and we included people of both Caucasian and Asian descent), (c) were aged between 17 and 35, and (d) consented to be approached.

The second recruitment route drew upon the broader university community. Two types of advertisement were routinely placed around campus, with one featuring fruits and vegetables and the other highly palatable snack foods. When a potential participant phoned to enquire about the advertisements, they were asked to report consumption frequencies for the seven items from the DFS that had the highest item-total correlations (soft drinks; cakes and cookies; pizza; fried chicken or chicken burgers; doughnuts, pastries, and croissants; corn chips, potato chips, popcorn with butter; french fries or fried potatoes). Participants who met age and BMI criteria and who scored below 16 or above 21 on this short-form DFS were potentially eligible to take part.

To determine whether a potentially eligible person was actually able to participate required a telephone-screening interview. This assessed any current health issues (physical or mental illness, chronic conditions, recent hospitalizations, any history of eating disorders, any head injuries, food allergies), any past health issues, and spoken English ability (i.e., for participants recruited via adverts this included leaving a voicemail message and undertaking the screening interview). Participants who reported anything beyond minor health complaints (which included asthma) or who could not adequately comprehend the interview were excluded. Eligible participants were instructed to breakfast as normal, and then refrain from eating in the 3 hr before testing so as to arrive hungry for lunch, with sessions being booked to start at either 11:00 a.m. for a 12:00 p.m. lunch or 1:00 p.m. for a 2:00 p.m. lunch. Participants were also told that they could drink water in this period but not caloric beverages and that they were not to exercise beyond their normal pattern.

In total, 97 participants completed the study. Of these, 56 were from the psychology participant pool and 41 were from the broader community. Data from 3 participants were excluded. One male participant revealed that he was diabetic and epileptic on the health-screening questionnaire administered at the start of the study. Two female participants had BMIs < 17— one of 16.2 and the other of 15.2. Although neither woman during telephone screening or on the health screening questionnaire reported having an eating disorder (or having a BMI under 17), we were concerned that this BMI might point to significant undernutrition, with unpredictable impacts on food-related behavior. The same pattern of significant findings was obtained even when these three participants were included. Demographic and other information about the 94 participants whose data were included in the reported analyses are given in Table 1.

Materials

The experimental lunch served during the study was either 350 g of beef lasagna (Woolworths select brand: total energy 1930KJ [5.5% protein, 5.5% fat, 15.0% carbohydrate, by weight]) or if they disliked lasagna (prior to consumption), 350 g of spinach and ricotta ravioli (Woolworths select brand; 1640KJ [4.6% protein, 3.7% fat, 14.9% carbohydrate, by weight]). Alongside this hot meal, participants were also presented with a plate of cookies, consisting of four chocolate Tim-Tam biscuits (total energy 1596KJ [4.6% protein, 26.9% fat, 63.9% carbohydrate, by weight]) and eight Woolworths chocolate chip cookies (total en- ergy 1744KJ [5.0% protein, 22.7% fat, 66.7% carbohydrate, by weight]).

The palatable food cue task used eight snack food items, four savory and four sweet. These were (1) a cheese and bacon ball (Fritolay), (2) a 0.5 cm^3 piece of cheddar cheese (Mainland), (3) a bbq Pringles chip, (4) a salt and vinegar Pringles chip, (5) a piece of flake chocolate (Cadbury flake bites), (6) a mini Tim-Tam chocolate biscuit (Arnotts), (7) a mini chocolate chip cookie (Arnotts), and (8) a Malteser (Mars).

The 52 words for the paired-associate tasks were selected from the lists in Nørby et al., (2010). All of the selected words were nouns with between five and nine letters, emotionally neutral and occurring in the medium to high frequency range of the Corpus of Contemporary American English. From these 52 words, 26 pairs

Table 1
Descriptive Statistics and Pearson Correlations Between Participant Characteristics, DFS (Diet) Score, and the Spectrophotometer Measure

Variable	Descriptive statistic	Variable correlate: DFS (diet)	Variable correlate: Spectrophotometry
DFS (diet) score	$M = 62.0$, $SD = 12.8$; range: 34–88		
Spectrophotometer	$M = 15.8$, $SD = 1.8$; range: 11.3–20.2	−.21×	
Gender	$n = 40$ men/54 women	.22×	−.17
Age	$M = 20.3$, $SD = 3.6$; range: 17–34	−.19	.13
BMI	$M = 22.3$, $SD = 2.6$; range: 17.2–27.9	−.15	−.02
DASS			
Depression	$M = 3.5$, $SD = 3.6$; range: 0–18	−.14	.14
Anxiety	$M = 2.9$, $SD = 2.6$; range: 0–10	−.01	.17
Stress	$M = 4.8$, $SD = 3.6$; range: 0–16	−.02	.14
Total score	$M = 11.2$, $SD = 8.1$; range: 0–35	−.05	.19
PIRS (Sleep quality)	$M = 4.7$, $SD = 1.3$; range: 2–8	−.04	.13
Activity (Min/day)	$M = 79.1$, $SD = 87.5$; range: 0–573	.14	.04
TFEQ			
Restraint	$M = 7.4$, $SD = 5.4$; range: 0–20	−.35×	.23×
Disinhibition	$M = 6.5$, $SD = 3.0$; range: 1–14	−.06	.19
Hunger	$M = 6.6$, $SD = 3.5$; range: 0–14	.16	.14

Note. DFS = Dietary Fat and Sugar Questionnaire; BMI = body mass index; DASS-21 = Depression, Anxiety, and Stress Scale; PIRS = Pittsburgh Insomnia Rating Scale; TFEQ = Three Factor Eating Questionnaire.
× $p < .05$.

were formed that were not obviously related, which was achieved by randomly generating word pairs and then having the experimenters check for relatedness (see the Appendix for selected word pairs).

Procedure

The study protocol was approved by the Macquarie University Human Research Ethics Committee, and written consent was provided by each participant. The study started with the completion of (a) a questionnaire to check adherence to the preexperimental instructions; (b) a health questionnaire to confirm the screening interview and to check for any common chronic diseases, current health, and basic medical history; (c) a brief sleep scale (the Pittsburgh Insomnia Rating Scale 2; Moul et al., 2002); (d) the Depression, Anxiety, and Stress Scale (DASS-21; Lovibond & Lovibond, 1995); and (e) a physical activity measure (IPAQ-SF; Papathanasiou et al., 2010). To assess skin yellowness and thus carotenoid levels, two readings from the palm of each hand were obtained with a CM-700D Konica-Minolta Spectrophotometer, using the $b^{\times}$ axis measure (Stephen, Coetzee, & Perrett, 2011).

Participants were then given the major study tasks in the following sequence: (a) the palatable food cue task while hungry, (b) verbal paired-associates training followed by the think/no-think task and then lunch, and (c) the palatable food cue task while sated. Each of these tasks and the lunch meal were accompanied by additional measures (detailed in the following section), most notably ratings of how hungry, thirsty, full, happy, sad, relaxed, and alert they were—in that order— on 120-mm line rating scales (anchors *not at all* and *very*). These ratings were repeated at various intervals throughout the session and are referred to as the hunger/mood ratings set.

Palatable food cue task (hungry). After completing the hunger/mood rating set, participants were instructed to place two pieces of sterile dental wadding around their submaxillary and sublingual salivary ducts (under the tongue) as well as placing one piece around each parotid duct (one each side of the upper jaw). The time elapsed from when the final piece of wadding was inserted until the time the last piece was removed was recorded. With the dental wadding in place, participants were then asked to touch, sniff and lick (in that order) each of eight snack food items presented in randomized order. Once participants had completed their interaction with all items they removed the wadding from their mouth and placed it into a bag for weighing.

After participants had rinsed their mouths with water they were presented with a fresh set of the eight snack food items, again in randomized order. Starting with the first item, participants were asked to look at it and judge how much they wanted to eat it using a 120-mm line rating scale (anchors *not at all* and *a lot*). This formed our measure of food wanting based solely upon viewing the sample. They were then asked to taste the sample after which they made two further ratings, both on 120 mm line rating scales: (1) How much did you like this food? (anchors *not at all* and *a lot*); and (2) How much more of this food would you like to eat now? (anchors *none* and *a lot*). The first of these two ratings formed our measure of liking. The second rating assessed immediate desire for more based upon sensory experience (in contrast to the wanting measure obtained prior to sampling the food that must be based upon memory). Following a water rinse, participants then repeated this process for each of the remaining snack food items.

VPA. Before participants started this phase they were asked to complete a second set of hunger/mood ratings. The VPA task started with an initial presentation block composed of 26 trials. In each trial a word pair was presented on the computer screen for 5 s (e.g., table legend). Participants were instructed to read each word pair out loud and try to learn it. In the subsequent four

training blocks only the first word of each pair was presented for 5 s (e.g., table), and participants were instructed to say out loud the (not shown) associated word. If they failed to respond within 5 s or their response was incorrect, the correct associate was presented (i.e., legend) and participants were instructed to say the pair out loud. The number of errors was recorded for each training block. The presentation order of the 26 trials was randomized in the initial presentation block and in each of the training blocks.

Think/no think task. Following completion of the VPA task, the think/no think training started. The 26 pairs used in the VPA task were randomly allocated to four sets: two practice pairs, eight baseline pairs, eight think pairs, and eight no think pairs. The two practice pairs were used to familiarize participants with the procedure. Participants were instructed that when they saw an initial word in green, they were to think of its associated word and to say it out loud (*think* word). However, if they saw an initial word in red, they were instructed to suppress thinking of the associated word and to remain silent (*no think* word). No feedback was provided. The eight think and eight no think initial words were then presented seven times each (i.e., 112 trials). These 112 trials was organized into seven blocks each composed of 16 trials, with each block composed of the eight think and eight no think initial words, presented in randomized order. On each trial the initial word was displayed for 5 s, with a 1-s intertrial interval. Partici- pants then immediately undertook the first think/no think test phase. The first word of each of the 26 pairs was presented for 5 s, all in standard black font. Participants were told to recall out loud its associated word (including the no think words). Order of presentation was random and no feedback was given. A second test occurred at the end of the study, as described later.

Lunch. Participants started by completing the third hunger/ mood ratings set. They were then instructed to eat as much of the presented food as they wished and to ask for more if they were still hungry. They were also told that all uneaten food would be thrown away. Ad libitum access to cold water was provided throughout lunch.

During the lunch period participants were told not to use electronic devices (all belongings etc., being left in the laboratory vestibule) but were allowed to read magazines provided in the test room while eating. The content of these magazines had been screened to avoid any eating-related or upsetting material. After giving participants their food, the experimenter left the test room, returning 10 min later to see if they would like any more food and to ask the participant to call out when they had finished or if they wanted more. Uneaten food was then removed for later weighing.

Palatable food cue task (sated). After completing the fourth hunger/mood ratings set, participants undertook the palatable food cue task again. This was identical to the first test in all respects, with salivation to the eight snack food items measured first, followed by evaluation (want on looking), consumption, and evaluation (like and want on tasting) of each of the eight snack food items.

Final measures. Participants started by completing the fifth and final set of the hunger/mood ratings. They were then given a delayed test for the 26 pairs learned earlier in the experiment. The test format was identical to that described above, except that a different randomized presentation order was used.

Participants then completed two questionnaires. The first was the 26-item DFS (Francis & Stevenson, 2013), so that a current measure of dietary saturated fat and refined sugar intake was available for the analysis. The second was the 51-item Three-Factor Eating Questionnaire (TFEQ), which has established reliability and validity (Stunkard & Messick, 1985) and that was used to collect data on participants' eating-related behaviors and attitudes. Finally, participants' height and weight were measured to assess BMI.

Analysis

Four sets of variables required square-root transformations so as to enable parametric analysis—the DASS-21 scores (and the total score), participant age, the energy intake measures (and total energy intake), and the activity measure from the IPAQ-SF.

On the VPA task, each participant had a percent correct score for each block and a learning rate score, calculated as Percentage Correct on Block 4 – Percentage Correct on Block 1 (VPA learning rate).

On the think/no think task scores were derived from the two test phases, the initial and the delayed test, which took place at the end of the study. On each test, three scores were computed by calculating the percent correct responses for the eight think items, the eight no think items, and the eight baseline items. A further score was also derived, reflecting the overall magnitude of think/no think-related inhibition (collapsing across both tests; [{Think + Baseline}/2] – No Think]).

Two sets of scores were computed for the palatable food cue task, one for when the test was completed hungry and one when it was completed sated. On both occasions, four measures were derived: (1) mean wanting on looking; (2) mean food liking after tasting; (3) mean want more scores after tasting; and (4) salivation rate (in g per s). For the first three scores, these were all averaged across the eight snack food items and for the fourth only an aggregate score for all items was available.

Three approaches were taken to analyze these data. The first involved descriptive statistics and zero-order correlations between the diet-related variables (i.e., DFS score and the spectrophotometer measure) and the demographic, control, interoceptive, and eating-related measures. The second approach was to analyze VPA, think/no think, and palatable food cue task data, with re- peated measures analysis of variance (ANOVA), to test for changes over time in outcome measures (i.e., VPA learning, think/no think-related inhibition, change in wanting/liking ratings with state). The third approach was to examine sources of vari- ability in the VPA, think/no think, and the palatable food cue task using stepwise regression analyses. It is this third approach that directly addresses the primary and secondary aims identified ear- lier.

The selection of predictor variables for each regression model was based on the following criteria: First, all models contained the main predictor of interest, the DFS diet score, along with basic demographic and control variables. Thus, all models started with the following predictors: age; gender; DASS-21 total score (as the three subcomponents were highly correlated); Pittsburgh Insomnia Rating Scale (PIRS) sleep score; activity score from the IPAQ-SF; Restraint score from the TFEQ; Hunger score from the TFEQ; Disinhibition score from the TFEQ; BMI; and DFS (diet) score. Second, this initial set of predictors was then included in a further regression analysis alongside the spectrophotometer measure, to

establish whether this displaced the DFS (diet) score, indicating whether it was the absence of fruit and vegetables in the diet, rather than the presence of saturated fat and refined sugar, that might be predictive of performance. Third, for the palatable food cue task regressions, amount of lunch consumed (total in kJ) and the change in hunger across lunch were added into all models, as participants varied in how much they ate and in how much hunger ratings changed across the meal. Fourth, on the two regression analyses establishing links between performance on the palatable food cue task and measures of hippocampal-related learning and memory, we included both our primary measure of hippocampal-related functioning, VPA learning rate, as well as a secondary measure, namely the think/no think related inhibition score. Finally, we note that it is generally advisable in regression to have at least five to 10 cases per predictor variable, and though all our models fell above the lower bound, a higher ratio would have been more desirable.

Results

Participant Characteristics, Lunch, Interoceptive, and Mood Measures

Participant characteristics are presented in Table 1. There was a significant association between the DFS dietary score and the spectrophotometry measure. Participants reporting diets richer in saturated fat and refined sugar tended to have less yellow skin (beta values), indicative of lower fruit and vegetable intakes. There were some significant associations between participant character- istics, and the diet and spectrophotometry measures. Female par- ticipants tended to have lower DFS scores than men, and greater dietary restraint, as measured by the TFEQ. For females the latter was associated with lower DFS score and yellower skin.

Hunger, fullness, and the lunch-related measures are detailed in Table 2. Both hunger and fullness ratings significantly changed across time, $F(4, 372) = 239.40$, $MSE = 361.32$, $p < .001$, partial eta-squared = .72, and $F(4, 372) = 276.52$, $MSE = 380.30$, $p < .001$, partial eta-squared = .75, respectively. In both cases, there were highly significant linear trends across time for decreasing hunger ($p < .001$) and for increasing fullness ($p < .001$). There were a number of significant associations between hunger and DFS score, and one with fullness, but none involving the spectrophotometer measure. Hunger ratings tended to be higher and fullness ratings lower in participants reporting a higher DFS score (i.e., more refined sugar and saturated fat).

For energy consumed at lunch, both overall, and for each food-type, there was a tendency for this to be higher in participants reporting a higher DFS score (*p*s from .061 for total energy intake, .078 for biscuits and .42 for lasagna/ravioli intake).

We also assessed changes in thirst and mood across the study. For thirst, ratings changed across the study, $F(4, 372) = 61.36$, $MSE = 492.80$, $p < .001$, partial eta-squared = .40, with progres- sively decreasing thirst (linear trend, $p < .001$). For mood ratings, happiness ratings significantly increased across the study (linear trend, $p < .001$), sadness ratings decreased (linear trend, $p < .001$), and participants also reported feeling more relaxed (linear trend, $p < .01$). There were no significant changes in alertness ratings.

VPA

A one-way repeated measures ANOVA, with Block (first, sec- ond, third, and fourth training block), entered as the within-factor, revealed a significant main effect of Block, $F(3, 279) = 327.22$, $MSE = 6.07$, $p < .001$, partial eta-squared = .78, with mean

Table 2
Descriptive Statistics for Hunger and Fullness Ratings Across the Study and for Eating-Related Variables From the Study Lunch

Time and variable	Descriptive statistic *M* (*SD*)	Variable correlate DFS (diet)	Variable correlate Spectrophotometry
Start of the study			
Hunger 1	68.1 (29.3)	.16	.14
Fullness 1	29.9 (25.5)	−.01	−.05
Prior to memory inhibition testing			
Hunger 2	64.2 (25.9)	.32×	−.07
Fullness 2	44.9 (24.9)	−.28×	.08
Prior to lunch			
Hunger 3	74.4 (26.4)	.31×	.00
Fullness 3	38.1 (22.8)	−.09	.11
Lunch consumption			
Lasagna/ravioli kJ	1799.5 (506.5)	.09	.02
Biscuits kJ	772.3 (800.2)	.20×	−.06
Total kJ	2571.8 (974.0)	.21×	−.02
Post-lunch			
Change in hunger across meal (Hunger 3—Hunger 4)	60.0 (30.9)	.19	.00
Hunger 4	14.4 (17.7)	.13	−.01
Fullness 4	95.7 (22.5)	−.13	.07
End of the study			
Hunger 5	13.5 (16.7)	.15	−.14
Fullness 5	100.0 (21.9)	−.15	.08

× $p < .05$.

percent correct score increasing linearly across blocks (significant linear trend, $p < .001$; also noting a small cubic component, $p < .01$—see Figure 1).

To determine whether VPA learning rate (Percentage Correct on Block 4 — Percentage Correct on Block 1) was related to diet, we conducted a stepwise regression analysis. The dependent variable VPA learning rate, with predictor variables, DFS (diet) score; BMI; age; gender; IPAQ-SF total activity score; DASS-21 total score; PIRS sleep score; and Restraint, Hunger and Disinhibition scores from the TFEQ. The final model was significant and is presented in Table 3, with DFS (diet) score, TFEQ Disinhibition score, and DASS-21 total score, as predictors. We then repeated this model, but now adding in the spectrophotometer score as a further predictor, but the same regression model emerged again

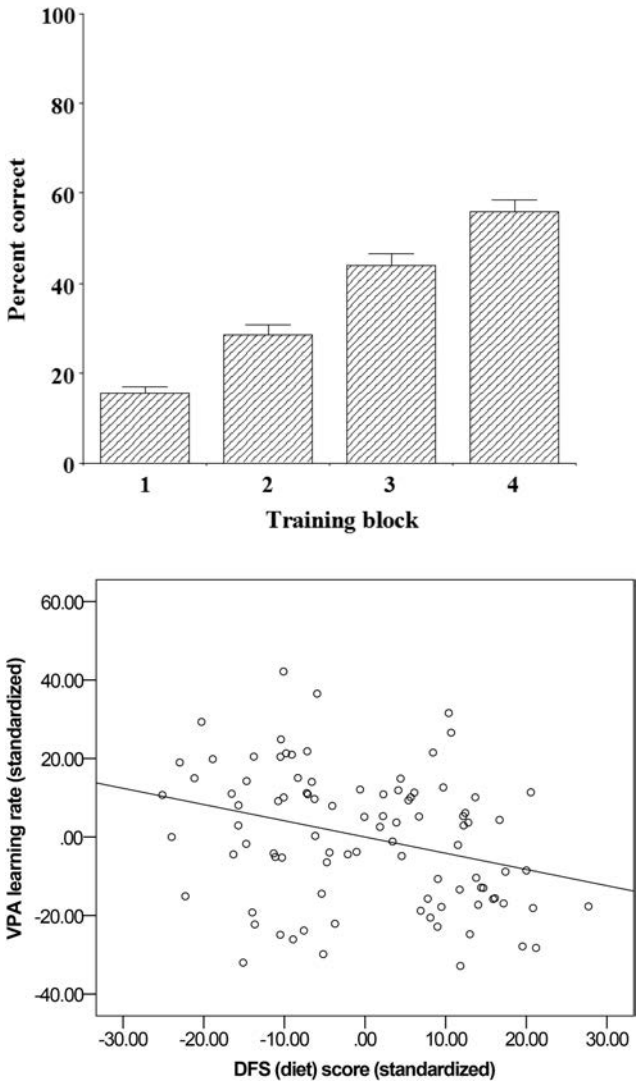

Figure 1. Top panel—Mean (and standard error) learning rate on the verbal paired-associates (VPA) task for all participants (as percentage correct) for each of the four training blocks. Bottom panel—Scatter plot of standardized Dietary Fat and Sugar Questionnaire (DFS; diet) score and standardized verbal paired-associate (VPA) learning rate (Block 4% correct — Block 1% correct) for all participants.

Table 3
Final Stepwise Regression Model Predicting Verbal Paired Associates Learning Rate (Final Training Block [4] Percent Correct Minus Initial Training Block [1] Percent Correct)

Model and predictor variable	r =	Sr =	Sr^2% =	p <
$F(3, 90) = 7.89$, $p < .001$, adjusted $R^2 = .18$ (spectrophotometer included)				
DFS (diet) score	−.29	−.28	8.1	.005
DASS-21 total	−.21	−.28	7.8	.005
TFEQ Disinhibition score	.23	.28	7.6	.005

Note. DFS = Dietary Fat and Sugar Questionnaire; DASS-21 = Depression, Anxiety, and Stress Scale; TFEQ = Three Factor Eating Questionnaire.

(i.e., the spectrophotometer score was not predictive). Overall, these findings suggest a slower VPA learning rate is associated with higher reported intake of saturated fat and refined sugar (see Figure 1).

Think/No Think Task

A repeated measures ANOVA was conducted with measure (baseline vs. think vs. no think) and time (immediate test vs. delayed test) as within factors. The analysis revealed two significant effects. First, measure, $F(2, 186) = 6.59$, $MSE = 0.25$, $p < .005$, partial eta-squared = .07, with poorest recall in the no think condition, relative to the equally trained think condition, and to the baseline condition—see Table 4. Simple contrasts revealed that the no think condition had the poorest recall, relative to the other two conditions ($ps < .002$), which did not differ. Second, time, $F(1, 90) = 9.22$, $MSE = 0.34$, $p < .005$, partial eta-squared = .09, with percentage correct recall improving slightly from the initial to the delayed test (see Table 4).

We then tested whether performance on the think/no think task (but collapsing across the initial and delayed test; see Table 4), could be predicted by participants' dietary self-reports and other variables again using stepwise regression. The dependent variable was the memory inhibition score derived from the think/no think task, with predictor variables as described above. The final model was significant with just one predictor remaining in the model, IPAQ-SF total activity score—see Table 5. Repeating this model by adding in spectrophotometer scores did not change the out- come, which indicated that larger inhibition scores were observed in participants who reported greater levels of physical activity. Finally, we note that participants varied in how much they had learned the word pairs (on the VPA task) before starting the

Table 4
Think/No Think Task Testing Scores

	Initial test	Delayed test
Measure	*M* % correct (*SD*)	*M* % correct (*SD*)
Think	65.0 (26.3)	66.3 (26.3)
No think	58.8 (26.3)	61.3 (28.8)
Baseline	65.0 (27.5)	67.5 (27.5)
Inhibition effect[a]	6.2 (14.5)	5.6 (15.7)

[a] Calculated as ([Think + Baseline]/2) — No Think.

Table 5
Final Stepwise Regression Model Predicting the Inhibition Effect (Collapsing Across the Initial and Delayed Tests) From the Think/No Think Task

Model and predictor variable	r =	Sr =	Sr^2% =	p <
$F(1, 92) = 4.25$, $p < .05$, adjusted $R^2 = .03$ (spectrophotometer included)				
Activity	.21	.21	4.4	.05

think/no think task. However, we could find no evidence that this affected participants' memory inhibition effect.

Palatable Food Cue Task

Self-report measures. Participant evaluations of the palatable foods were analyzed using a two-way repeated measures ANOVA, with state as one factor (tested hungry vs. tested sated) and measure as the other (want to eat [on looking] vs. liking [after tasting] vs. want more [after tasting]), with the data illustrated in Figure 2. The ANOVA revealed main effects of state, $F(1, 93) = 175.96$, $MSE = 546.03$, $p < .001$, partial eta-squared = .65, and measure, $F(2, 186) = 143.65$, $MSE = 109.58$, $p < .001$, partial eta-squared = .61, which were qualified by an interaction between state and measure, $F(2, 186) = 54.08$, $MSE = 46.72$, $p < .001$, partial eta-squared = .37. To determine the source of the inter- action effect, the three difference scores across state (Tested Hungry — Tested Full) for each measure (want to eat [on looking] vs. liking [after tasting] vs. want more [after tasting]) were com- pared. As suggested earlier, want to eat scores on looking at the food fell significantly more with the change of state than liking scores ($p < .001$). Want more after tasting the snack also de- creased more across state than liking scores ($p < .001$). Finally, want more after tasting scores fell further across State than want to eat on looking scores ($p < .05$). So though all evaluations declined when tested sated, this decrease was greater for both wanting ratings than for the liking rating.

We then tested our primary aim, namely whether the state-dependent difference in wanting ratings made when looking at the food, relative to the liking rating made after tasting it, could be predicted by dietary variables. In addition to the predictor variables used before, two further predictors were now included: Change in hunger across lunch and the amount of energy consumed at that meal. The final significant model, which included the DFS (diet) score, is presented in Table 6. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model. As illustrated in Figure 2, want to eat ratings—relative to liking ratings after tasting—were less affected by state in participants who consumed diets richer in saturated fat and refined sugar. To make this effect more vivid, in Figure 3 we present data (liking and wanting ratings made when hungry and replete) from just the dietary extremes of our sample—the top and bottom 20% on DFS (diet) score. As can be seen, want to eat on looking scores, relative to liking, change less across state in those who routinely eat the most saturated fat and added sugar. Thus state may be less able to moderate retrieval of pleasant food-related memories in participants who frequently consume diets rich in saturated fat and refined sugar.

Finally, we examined the sources of variability in the other major component of the Time × Measure interaction, namely the relatively larger decline in wanting more after tasting relative to liking. The same stepwise regression approach was used with the same predictor variables. The final model was significant, $F(2, 91) = 14.10$, $p < .001$, adjusted $R^2 = .22$, with two predictors remaining in the model. These were change in hunger, $Sr = .42$, $Sr^2\% = 18.1\%$, $p < .001$, and sleep quality score, $Sr = .24$, $Sr^2\% = 5.5\%$, $p < .02$. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model.

Saliva measure. Salivation rate significantly increased be- tween the hungry and sated tests from a ($M = 0.038$g/s; $SD = 0.009$) to ($M = 0.049$g/s; $SD = 0.011$), $t(93) = 12.21$, $p < .001$, $r^2 = .61$. We tested to see whether change in salivation rate

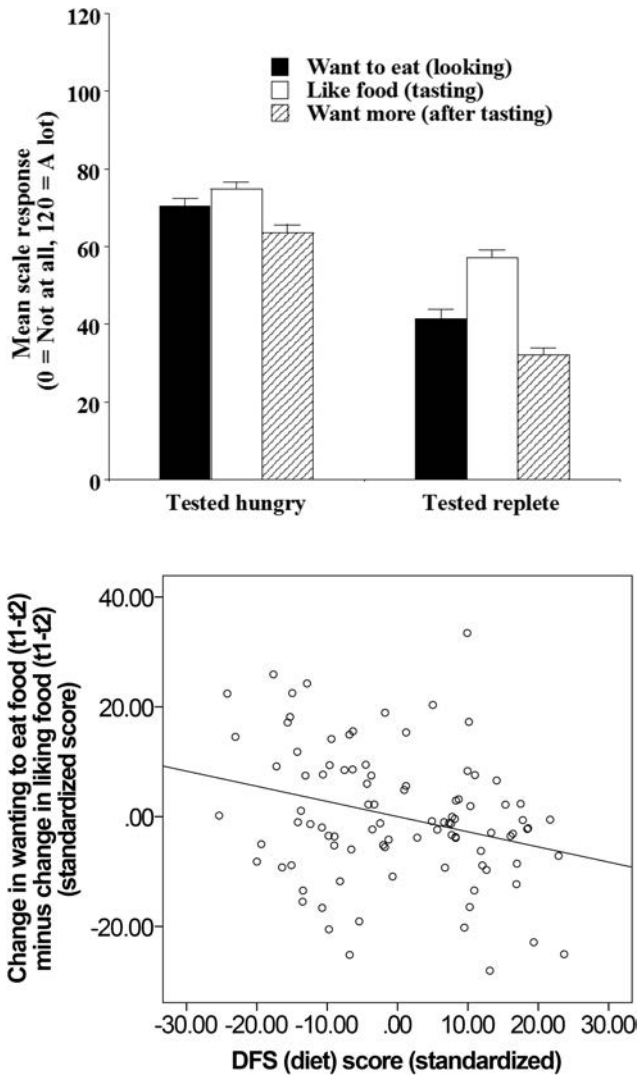

Figure 2. Top panel—Mean (and standard error) wanting (on seeing), liking, and want more ratings (after tasting) in all participants obtained before and after lunch. Bottom panel—scatter plot of standardized Dietary Fat and Sugar Questionnaire (DFS; diet) score and standardized change in wanting relative to liking across state for all participants.

Table 6
Final Stepwise Regression Model Predicting the Change in Liking Relative to the Change in Wanting to Eat Ratings Across State (Hungry Minus Full), on the Palatable Food Cue Task

Model				
Model and predictor variable	$r =$	S$r =$	Sr^2% =	$p <$
$F(3, 90) = 15.41$, $p < .001$, adjusted $R^2 = .32$ (spectrophotometer included)				
Change in hunger	.38	.43	18.5	.001
PIRS (Sleep quality)	.35	.34	11.7	.001
DFS (diet) score	−.19	−.26	6.7	.005

Note. PIRS = Pittsburgh Insomnia Rating Scale; DFS = Dietary Fat and Sugar Questionnaire.

between the hungry and sated states could be explained by any of the predictor variables used in the preceding regression analyses, but there were no significant models.

We then checked to see whether change in salivation rate across states was associated with the aggregate self-report measures (i.e., main effect of time), after partialing out the amount of energy consumed at lunch and changes in hunger across the meal. Greater salivation in the sated state (relative to the hungry state) was associated with smaller reductions in liking and wanting (i.e., main effect of time), $r_{12.34}(90) = -.22$, $p < .05$, providing some validation for the self-report ratings. The three parts of the interaction effect for the self-report data were not significantly associated with change in salivation rate between internal states (rs < .14).

Relationship Between VPA and Think/No Think Tasks and the Palatable Food Cue Task

If hippocampal-related processes contribute to participants' desire to consume food via state-dependent inhibition of food-related memories, then performance measures from the VPA and think/no think tasks should explain individual variability in changes in wanting and liking between the hungry and sated states. In addition, to the extent that such measures tap hippocampal process more directly than diet, they should displace diet-related predictors on the palatable food cue task findings. To test this, we conducted two further regression analyses, examining each major component of the Time × Measure interaction from the palatable food cue task. The primary hippocampal related predictor was VPA learning rate and the secondary predictor being think/no think inhibition score, noting that these two variables did not significantly correlate ($r = -.05$).

The dependent variable for the first regression was the difference across states between the wanting rating made when looking at the food, relative to the liking rating made when eating it. As is shown in Table 7, VPA learning rate during training was the best predictor, displacing DFS diet score from the model (contrast with Table 6). Repeating this model by adding in spectrophotometer scores led to the same outcome. Overall, this suggests that state-dependent changes in wanting scores when looking at palatable food relative to liking scores when food is actually consumed are strongly predicted by how quickly participants learned the VPAs, which in turn was shown earlier to be associated with reported dietary intake of saturated fat and refined sugar.

Finally, we examined sources of variability in the other major component of the Time by Measure interaction, namely the relatively larger state-dependent decline in wanting more after tasting, relative to liking. This regression analysis produced the same outcome as the one described earlier (an identical model—predictors change in hunger and sleep quality), with no significant involvement of either hippocampal related performance measure.

Discussion

The primary question addressed by this study was whether state-dependent reductions in wanting for palatable snack foods (relative to state-dependent reductions in liking for palatable snack foods) were as follows: (a) less affected in consumers of a HFS diet and (b) mediated by hippocampal-related processes. Consistent with expectation, the difference between wanting and liking responses between the hungry and sated states was smaller for habitual consumers of a HFS diet. We also found, again as predicted, that these diet-related impairments in wanting according to state were significantly predicted by VPA learning rate but not by the memory inhibition score from the think/no think task.

There were several important ancillary findings: (a) VPA learning rate was associated with greater consumption of a HFS diet, replicating previous findings of associations between tests sensitive to hippocampal-related function and diet in healthy young people (Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011); (b) greater consumption of a HFS diet was associated with smaller changes in hunger and fullness, that is reduced interoceptive sensitivity also as observed before (Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011); (c) greater energy intake on test lunch tended to be linked with greater HFS dietary intake (Francis & Stevenson, 2011); (d) reduced skin yellowness, indicating lower intake of fruits and vegetables, was associated with greater consumption of a HFS diet; and (e) skin yellowness was not a significant predictor of hippocampal-related processes, suggesting that the absence of fruits and vegetables was not a driving factor in diet-related cognitive performance. Finally, though we found that salivation rate was related to overall changes in wanting and liking between the hungry and sated state, it was not associated with diet or hippocampal-related processes.

Although the present findings are consistent with evidence linking diet to hippocampal function in humans (e.g., Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011; Jacka et al., 2015), it is the links between diet, hippocampal memory performance, and wanting that are of central importance. Specifically, those with a diet richer in saturated fats and refined sugars reported smaller changes in wanting scores across state relative to liking scores. Because wanting (i.e., incentive salience) has a

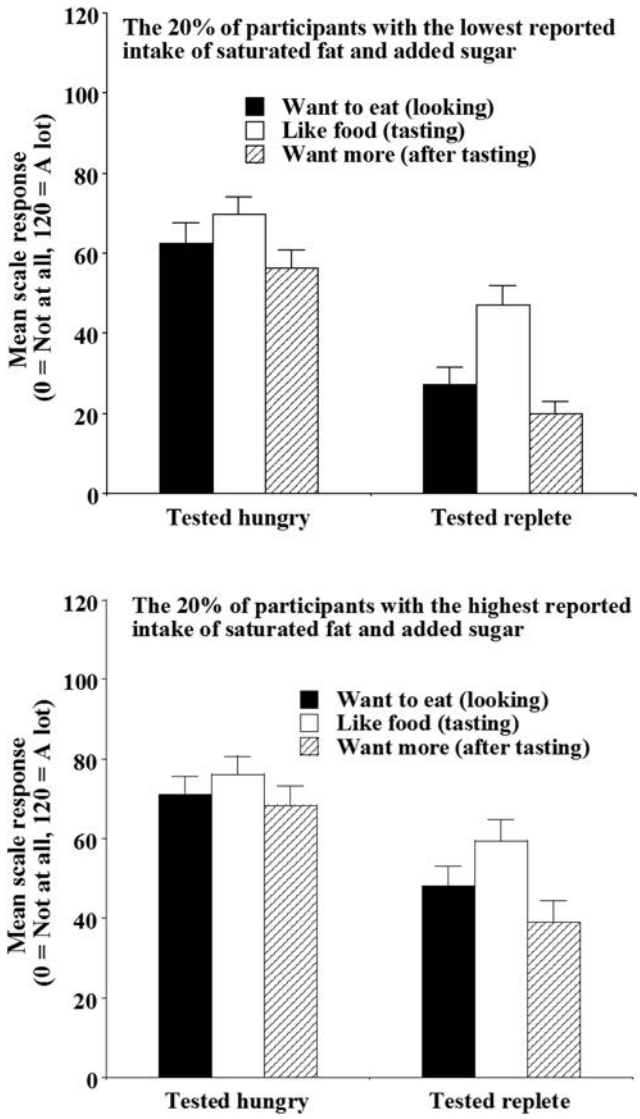

Figure 3. Top panel—Mean (and standard error) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the lowest reported intake of saturated fat and sugar, obtained before and after lunch. Bottom panel—Mean (and standard error) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the highest reported intake of saturated fat and sugar, obtained before and after lunch.

memorial component and should vary as a function of physiological state, it is plausible that it is an impairment in this process, which is driving these smaller changes in wanting relative to liking across state in HFS diet consumers. We therefore suggest that, in line with the model proposed by Davidson et al. (2005), this finding reflects poorer inhibition of pleasant food-related memo- ries when sated. We also predicted earlier that state-dependent changes in liking should be less affected by any adverse impacts to hippocampal-related learning and memory as liking is driven more by the direct sensory experience of the food (Robinson & Berridge, 2000) rather than by any memories of it. Important, the change between states was significantly larger in wanting relative to liking, and this interaction was predicted by dietary intake of fats and sugars (see Table 6) and performance on the VPA task (see Table 7)—suggesting hippocampal mediation.

One potential implication of the wanting and liking findings is that in habitual consumers of a HFS diet physiological state should have less regulatory importance, resulting in desire-driven eating whenever palatable food cues are encountered (e.g., Lowe & Butryn, 2007). Another potential implication of these findings relates to the 'vicious-circle' model of obesity (Davidson et al., 2005). Here, disruption of hippocampal inhibitory control over food-related behaviors can heighten the risk of further overconsumption of the same foods that initially contributed to hippocampal dysfunction, promoting weight gain. Findings from animals provide support for this model (Davidson et al., 2010; Kanoski & Davidson, 2010; Kanoski, Meisel, Mullins, & Davidson, 2007). The present results are consistent with the vicious circle model of obesity and may aid understanding of appetite control and overconsumption. Nonetheless, while we argue here that a diet rich in saturated fat and added sugar impairs, via hippocampal processes, the ability to use satiety to inhibit pleasant food related memories, an alternative interpretation is also plausible. Individuals more prone to palatable food intake may be more likely to eat when sated and to choose high-fat high-sugar foods. Although we sug- gest this latter possibility is plausible due to the correlational nature of our study, the former interpretation seems more likely given what is known from animal data.

An unexpected finding was that performance on the think/no think task was unrelated to HFS diet intake and to VPA learning rate. Moreover, there was also no relationship between the changes in wanting/liking across state and memory inhibition score from the think/no think test. If these processes are all mediated by the same brain area—and fMRI data suggests that memory inhibition on the think/no think task is (Anderson et al., 2004)—we would expect performance on these measures to be related. Because such relationships were not observed, one possibility is that other neural processes may be important in the think/no think task. There are two reasons for this assertion. First, although state-dependent changes in wanting/liking do not require explicit instruction to occur, the think/no think task involves explicit (i.e., strategic) direction to inhibit or rehearse stimuli. Second, the strategic nature of the think/no think task has been illustrated experimentally, as substituting an associated word instead of suppressing it, leads to markedly different memory recall when tested later (del Prete, Hanczakowski, Bajo, & Mazzoni, 2015; Racsmany, Conway, Keresztes, & Krajcsi, 2012). Nonetheless, a further alternative explanation also needs to be considered in light of the fact that fMRI data indicates that performance on the think/no think task is associated with hippocampal activation (Anderson et al., 2004). It is possible that the think/no think task may be insensitive to diet-induced affects relative to other hippocampal-related tasks (i.e., VPA). Indeed, this could be potentially important as it would imply that not all hippocampal-related measures are equally sen- sitive to diet-induced change.

The spectrophotometer findings suggest that the hippocampal-related memory performance is not linked to reduced intake of fruit and vegetables, but rather to greater consumption of a HFS diet. There are several implications from this finding. First, the inverse association between skin yellowness and scores on the DFS scale provide further external validity, as greater saturated fat

Table 7
Final Stepwise Regression Model Predicting the Change in Liking Relative to the Change in Wanting to Eat Ratings Across State (Hungry Minus Full), on the Palatable Food Cue Task, Including VPA Learning Rate and the Inhibition Score From the Think/No Think Task

Model and predictor variable	$r =$	S$r =$	Sr^2% =	$p <$
$F(4, 89) = 16.10$, $p < .001$, adjusted $R^2 = .39$ (spectrophotometer included)				
VPA learning rate	.41	.36	13.0	.001
Change in hunger	.38	.36	13.0	.001
PIRS (sleep quality)	.35	.35	12.0	.001
Age	.07	.17	2.9	.05

Note. VPA = verbal paired associates; PIRS = Pittsburgh Insomnia Rating Scale.

and sugar intake is usually associated with reduced fruit and vegetable intake (Cordain et al., 2005; Kearney, 2010). Although further research is required, this points to the potential utility of the spectrophotometer as a simple indirect measure of diet quality. Second, it suggests that it is the presence of saturated fat and added sugar—as in animals—that is problematic, rather than the absence of fruit and vegetables. This implies that a diet containing significant amounts of fruit and vegetables may not be protective against a diet that is also high in saturated fat and added sugar.

Several control variables emerged as significant predictors of either VPA learning rate, the think/no think memory inhibition score or for the change in wanting/liking scores. Although depres- sion, stress, and anxiety have all been found before to be associ- ated with hippocampal volume and/or function (e.g., Videbech & Ravnkilde, 2004), four associations were more surprising. First, physical activity was associated with the think/no think memory inhibition score. We included a measure of physical activity because this is known to increase hippocampal volume and function (Erickson et al., 2011; Pereira et al., 2007). This in turn would suggest that memory inhibition performance on the think/no think task was in fact supported by the hippocampus, something we argued earlier was not in fact the case. However, physical activity is in fact associated with improvements across many cognitive domains and brain areas, and the largest effects (on meta-analysis) are seen for tasks that involve executive function (Hillman, Erickson, & Kramer, 2008).

A second association was observed between TFEQ Disinhibi- tion score and VPA learning rate. TFEQ Disinhibition was posi- tively associated with BMI, TFEQ Restraint, and TFEQ Hunger, all of which have been found before to relate to measures sensitive to hippocampal-related measures of learning and memory (Brannigan, Stevenson, & Francis, 2015; Francis & Stevenson, 2011). Finally, we found that both increasing age and poorer sleep were associated with larger reductions in wanting (rela- tive to liking) across state, effects that were unlikely to be related to hippocampal-related processes, since VPA learning rate was also included in this model. Thus older age and poorer sleep—in the context of a young and healthy sample—reflect some other as yet unknown factors associated with better food- related memory inhibition.

We have shown here that HFS dietary intake is not only associated with poorer hippocampal-related memory performance as indexed by VPA learning rate, but also with poorer inhibition of food-related wanting when sated. Our findings suggest that hippocampal related processes are involved in energy regulation apparently in much the same way as suggested by animal models (Davidson et al., 2005; Davidson et al., 2014), irrespective or not of whether habitual consumption of a HFS diet causes (or is a consequence of) poorer hippocampal function. Although causality cannot be inferred here, the results from this study provide the first piece of evidence in humans to parallel those from animals linking a HFS diet, impaired hippocampal function, less efficient state-dependent inhibition of food-seeking behaviors and hence enhanced susceptibility to excess energy intake.

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Appendix 5: Published manuscript of Study 2 (Chapter 4)

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Research review

A systematic review of longer-term dietary interventions on human cognitive function: Emerging patterns and future directions

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a r t i c l e i n f o

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Cognitive function may be affected by long-term diet and most of the support for this idea is derived from human correlational studies and animal prescribed diet studies. To date there has been no sys- tematic examination of human experimental studies that examine whether a prescribed long-term (24 hÞ) diet can cause changes in cognitive function. Here, we review the experimental evidence of long-term changes in cognition following prescribed diet interventions. A total of 30 diet interventions were identified and reviewed. Measures of working memory, long-term memory, and attention appeared most sensitive to dietary manipulation, but there was considerable variability in outcome. Additionally, energy and fat intake manipulations tended to influence performance on these measures to the greatest degree. This review also serves to identify factors that should be considered in designing future diet- cognition studies. We also suggest a series of cognitive tests based on this review and indicate poten- tially profitable directions to take the diet-cognition literature.

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1. Introduction

Cognitive function describes a variety of processes that allow humans to perceive, evaluate, store, manipulate and respond appropriately to information from internal and external sources. Obesity, independent of its associated medical comorbidities, is significantly associated with impaired cognitive function, especially in elderly adults (Smith, Hay, Campbell, & Trollor, 2011). A review by Fitzpatrick, Gilbert, and Serpell (2013) indicated that obese individuals are impaired on measures of decision-making, planning and problem solving, with fewer difficulties on tasks of verbal fluency and learning and memory. Moreover, important links have been established between mid-life obesity and elevated risk for later onset of dementia (Fitzpatrick et al., 2009). While studies are generally supportive of the links between obesity and cognitive impairment and dementia, there are still significant inconsistencies within and across different cognitive domains (Fitzpatrick et al., 2009), suggesting some factor other than obesity might be affecting cognitive function.

While other researchers have focused on other influences on cognition such as physical activity (Hillman, Erickson, & Kramer, 2008) or micronutrients (De Jager, Dye, de Bruin, & …Wesnes, 2014), there is now accumulating evidence that cognitive func- tion may be influenced as much by diet, as by obesity itself. Diet refers to the habitual pattern of long-term intake of particular foods. Researchers readily extract from this total energy intake and typically fractionate this into energy derived from its macronutri- ents e fats, proteins and carbohydrates. We acknowledge that while others have emphasized the importance of the effects of micronutrients on cognition over a period of years (e.g. De Jager et al., 2014; Parletta, Milte, & Meyer, 2013; Otaegui-Arrazola, Amiano, Elbusto, Urdaneta, & Martínez-Lage, 2014), here we focus solely on the experimental studies that have manipulated either total energy intake, macronutrient content, or both. Since macronutrients differentially affect memory and attention at the postprandial level (e.g. Jones, Sünram-Lea, & Wesnes, 2012), then these areas of cognition may be affected by the macronutrient profile of a diet over longer periods ranging from days to months. Importantly, diet may act on particular areas of cognition in different ways, with some more important than others. Under- standing which areas of cognition are most susceptible to the ef- fects of diet may have important consequences for long-term prevention and treatment of cognitive impairment, including neurodegenerative disease. For instance, a meta-analysis by Grant (1997) on 18 community-based epidemiological studies drawn

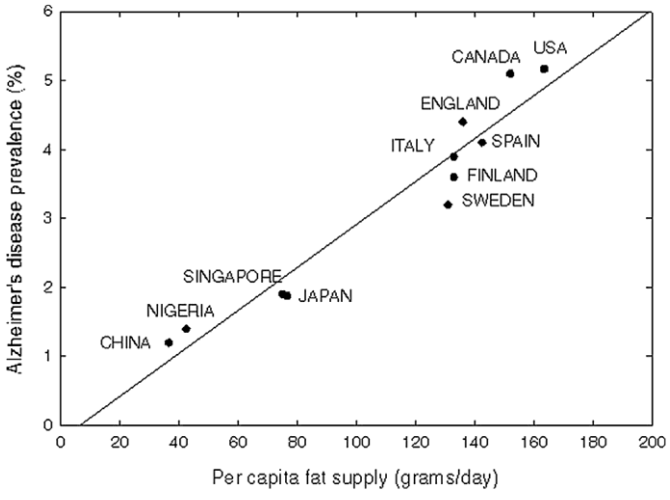

Fig. 1. Alzheimer's disease prevalence in 65 years þ population vs. fat supply.

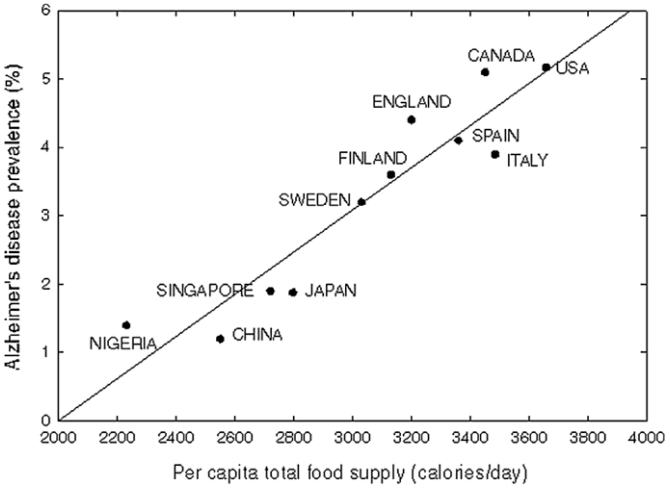

Fig. 2. Alzheimer's disease prevalence in 65 years þ population vs. total food supply.

from the total food supply data of 11 countries found a link between diet and neurodegenerative disease (See Figs. 1 and 2). Regression analyses revealed very strong positive relationships between the prevalence of Alzheimer's disease (AD), and total energy and fat intake (r^2 ¼ 0.932 and 0.880, respectively) in the population of adults 65 years or older, strongly supporting the importance of diet (especially total energy and fat intake) in the maintenance of cognition.

Taken from Grant (1997), Fig. 1 shows the scatter plot of Alzheimer's disease prevalence versus fat supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate ¼ —0.203 þ (0.0312*fat (grams/day))). Fig. 2 shows the scatter plot of Alzheimer's disease prevalence versus total food supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate ¼ —6.178 þ (0.00309*(total calories/day))). Despite potential inflation of results due to food supply data not accounting for food wastage, spoilage etc., these figures nonetheless indicate that for every per capita additional gram of fat or calorie consumed daily, one might expect an average increase of 0.03% and 0.003%, respectively, in AD prevalence in the population of adults 65 years or older. For instance, a 0.3% increase in AD prevalence would be associated with a daily increase of either 10 g of fat or 100 calories. Other researchers have similarly concluded that a diet high in saturated fats and refined sugars e the so-called "Western diet" e increases the risk of AD (Berrino, 2002), while a diet low in saturated fats and refined sugars, and high in polyunsaturated (PUFAs) and monounsaturated fats (MUFAs) e the "Mediterranean diet" decreases the risk of AD (Lourida et al., 2013). Indeed the Mediterranean diet e typically high in fish, nuts, and antioxidant-laden fruits and vegetables has been of great interest as it may be effective for weight loss maintenance (Panagiotakos, Chrysohoou, Pitsavos, & Stefanadis, 2006) and because of possibly beneficial effects on cognitive function. That saturated fat may be an independent risk factor for impaired cognition has now emerged in several correlational studies. Higher saturated fat intake is associated with: (1) impairments in speed, mental flexibility and memory in individuals older than 55 years (Kalmijn et al., 2004); (2) poorer global cognitive function and memory in older adults (Eskelinen et al., 2008); and (3) impairments in delayed memory, working memory and verbal fluency in women with type-2 diabetes (Devore et al., 2009). Part of the reason for interest in saturated fat alone and in combination with added sugar derives from the extensive animal literature examining the impact of these macronutrients on cognition. Diets rich in saturated fat and added sugar (HFS diets)

specifically impair cognitive performance associated with brain regions implicated in memory, inhibition and the regulation of food intake e the hippocampus and possibly the prefrontal cortex (Davidson, Kanoski, Walls, & Jarrard, 2005). The pre-frontal cortex is involved in inhibition and executive function (Anderson et al., 2004), while the hippocampus has a well-established role in memory function, with damage to this structure affecting memory function and interoception (Hebben, Corkin, Eichenbaum, & Shedlack, 1985). Animals show impairments in hippocampal- dependent tasks following a diet high in fat (Morrison et al., 2010), sucrose (Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney, & Corbit, 2013), and both refined sugar and saturated fat (Beilharz, Maniam, & Morris, 2013; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). In humans, cross-sectional studies have revealed that higher reported HFS intake is associated with a reduced sensitivity to internal signals of hunger and satiety and impaired performance on hippocampal-dependent memory tasks in normal-weight adults (Francis & Stevenson, 2011) and young children (Baym et al., 2014). These findings suggest that diet- induced impairments in hippocampal-related interoception and memory may precede weight gain and obesity. Dietary intake of fat and sugar, which is high in the Western diet and low in the Med- iterranean diet, could potentially be one factor in explaining the links between obesity and cognitive impairment.

While cross-sectional data have generally shown a positive relationship between consumption of an HFS diet and poorer memory function in humans, there is preliminary evidence showing that other cognitive domains including executive function might also be affected (Nyardi et al., 2014; Torres et al., 2012). Some experimental studies have shown that performance on measures of executive function improve following short-term (McMillan, Owen, Kras, & Scholey, 2011) and long-term (Martínez-Lapiscina et al., 2013a) adherence to a Mediterranean diet. Similarly, a prospec- tive cohort study of 1410 elderly adults revealed that higher adherence to a Mediterranean diet was associated with slower cognitive decline, as measured by the Mini Mental Status Examination (MMSE) (Féart et al., 2009).

Animal studies of dietecognition relationships have the major advantage of being able to demonstrate causal links between changes in cognitive performance and diet (e.g. Molteni et al., 2002). While a similar causal route could also apply to humans, most studies investigating the effects of diet on cognition have been cross-sectional (e.g. Baym et al., 2014; Francis & Stevenson, 2011), longitudinal (e.g. Eskelinen et al., 2008) or cohort studies (e.g. Barberger-Gateau et al., 2007). Correlations cannot imply causality since other extraneous factors may be involved, but research that is based on experimental evidence makes a causal inference far more plausible. To date, the relationship between diet and cognition in humans remains causally ambiguous.

The main objective of this manuscript is to review the limited experimental evidence of the link between diet and cognition in humans. We focus solely on human experimental studies that have tested the longer-term effect of diet on cognition. Many of the papers we review here were not motivated to collect cognition-related data because they had strong a priori reasons to do so (i.e., they were not premised on the animal literature referred to here), and indeed, in many cases cognitive-related data seems to have been an auxiliary aim of these studies. This review draws together the highly varied research in an effort to identify potential emerging patterns in the data linking diet to cognitive performance.

2. Method

Electronic literature searches were conducted between September 2013 and January 2014 using the following databases; PsycInfo, the Cochrane Central Register of Controlled Trials (CENTRAL), and Medline (PubMed). Manual searches were also run using smaller search engines (e.g. Google Scholar) to update the literature as much as possible. Search words represented terms utilized in other reviews in the area as well as words deemed appropriate by the authors. The following search terms were used in various combinations to find relevant articles: "diet", "dietary pattern", "energy", "macronutrient", "fat", "protein", "carbohydrate", "intake", "calori*", "sugar", " intervention", "cogniti*", "memory", "executive function", "impair*", "neurocog*", "psych*", "attention", "hippocamp*", "neurocog*", "healthy", "obese", "overweight", "lean", "BMI" and "weight". Relevant studies cited in review articles or articles identified through the search were also considered and retrieved in a manual search.

3. Inclusion and exclusion criteria

An initial search using the above search terms yielded 4141 ar- ticles. An initial screen of title and abstract of each paper was conducted, yielding a total of 87 full text articles retrieved for further review and determination of eligibility. Articles were included if researchers manipulated or advised on intake of energy and/or macronutrient content (fat, protein, or carbohydrate) for a period longer than 24 h (i.e. not postprandial), did not completely deprive participants of food, assessed cognitive function using validated measures, and tested adults only (Ç18 years) across the entire adult lifespan. Additionally, only articles written in English were considered while there were no restrictions on publication year. Application of these criteria yielded 32 research articles applying to 30 different dietary interventions (two articles were longitudinal follow-up studies). Three studies included an addi- tional group that altered diet and exercise (Martin et al., 2007; Smith et al., 2010) or deprived energy completely (Lieberman et al., 2008), so only the findings from the appropriate diet manipulation groups were used.

Across the literature, the groups of individuals tested vary significantly (e.g. obese adults, frail elderly, or healthy men only), but these have been grouped together here for practical reasons. We posit that any potential differences between groups in cognitive performance associated with age or health status are of minor importance to the overall pattern since the magnitude, but not the direction, is likely to vary between different groups of individuals. Indeed, some groups may be more vulnerable to dietary changes than others, but the highly varied nature of the current literature makes it difficult to discern any meaningful pattern. Due to the inadequate reporting of cognitive outcomes and their effect sizes, as well as a distinct lack of nutritional breakdown of each diet in some studies, this paper provides a qualitative review of the experimental evidence of the link between diet and cognition. The effect sizes of cognitive outcomes and nutritional information of each diet will be reported when possible. The summary tables in this review were constructed and organized based on intended dietary targets of each study (e.g. low fat) rather than reported dietary intakes, since in many cases dietary adherence varied. For instance, despite imposing restrictions only on carbohydrate intake, Krikorian et al. (2012) reported significant differences in total energy intake between groups and over the intervention period.

4. Findings by cognitive domain

Broadly, the review has been organized into two sections based on cognitive domains: (1) memory (working, long-term verbal, and long-term visual-spatial memory) and (2) other cognitive domains (global cognitive function, executive function, attention, &

Table 1
Summary of effects of diet interventions on working and long-term memory.

Intervention		Study	Sample population	Duration (days)	Change in energy (%)	Effect on memory		
						Working memory	Visual-spatial	Verbal LTM
Energy intake	Decrease	Wardle et al. (2000)*	n = 105 middle-aged adults	84	—17	-	-	No change
		Bryan and Tiggemann (2001)	n = 42 overweight women	84	—20	No change	-	↑
		Makris et al. (2013)*	n = 47 obese adults	168	—25	-	-	No change
		Martin et al. (2007) †	n = 24 overweight	168	—25	↑	No change	No change
		Witte et al. (2009)	n = 19 overweight elderly	84	—30	No change	-	↑
		Halyburton et al. (2007)* †	n = 93 obese adults	56	—30	↑	-	-
		Pearce et al. (2012)	n = 44 obese with type 2 diabetes	56	—30	No change	-	-
		Cheatham et al. (2009)*	n = 28 overweight	180	—30	No change	-	-
		Brinkworth et al. (2009)* †	n = 64 obese adults	365	—30	↑	-	-
		Kretsch et al. (1997)	n = 14 women	105	—50	-	-	↑
Protein	Increase	Lindseth et al. (2011)	n = 45 young men	4	0	No change	No change	-
		Van Der Zwaluw et al. (2014)	n = 65 frail elderly	168	NR	No change	-	No change
Fat	Decrease	Bayer-Carter et al. (2011)	n = 11 healthy elderly	28	0	-	↑	No change
			n = 14 elderly with mild cognitive impairment	28	0	-	↑	No change
		Nilsson et al. (2013)	n = 44 healthy adults	28	0	-	-	↑
		Wardle et al. (2000)*	n = 52 middle-aged adults	84	—17	-	-	No change
	Increase	McMillan et al. (2011)	n = 12 young women	10	NR	↓	↑	↑
		Lee et al. (2015)	n = 23 young women	10	NR	↓	↑	↓
		Martínez-Lapiscina et al. (2013b)	n = 190 elderly adults	2373	NR	↑	↑	↑
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	No change	No change	-
		Lindseth et al. (2011)	n = 45 young men	4	0	↑	No change	-
		Holloway et al. (2011)	n = 16 healthy men	5	0	↓	-	No change
		Edwards et al. (2011)	n = 20 healthy men	7	0	No change	-	No change
		Bayer-Carter et al. (2011)	n = 9 healthy elderly	28	0	-	No change	No change
			n = 15 elderly with mild cognitive impairment	28	0	-	No change	No change
		Witte et al. (2009)	n = 20 overweight elderly	84	0	No change	-	No change
		Wardle et al. (2000)*	n = 53 middle-aged adults	84	—17	-	-	No change
		Halyburton et al. (2007)* †	n = 48 obese adults	56	—30	↑	-	-
		Brinkworth et al. (2009)* †	n = 32 obese adults	365	—30	↑	-	-
Carbohydrate	Decrease	D'Anci et al. (2009)*	n = 9 women	21	NR	↓	↓	No change
		Makris et al. (2013)*	n = 22 obese	730	—25	-	-	No change
		Cheatham et al. (2009)*	n = 16 overweight	180	—30	No change	-	-
		Krikorian et al. (2012)*	n = 12 older adults	42	—41	-	-	↑
	Increase	D'Anci et al. (2009)*	n = 10 women	21	NR	No change	No change	No change
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	No change	No change	-
		Lindseth et al. (2011)	n = 45 young men	4	0	No change	No change	-
		Smith et al. (2010)	n = 38 obese adults	120	0	No change	-	No change
		Krikorian et al. (2012)*	n = 11 older adults	42	—6	-	-	No change
		Makris et al. (2013)*	n = 25 obese adults	168	—25	-	-	No change
		Halyburton et al. (2007)* †	n = 45 obese adults	56	—30	↑	-	-
		Cheatham et al. (2009)*	n = 12 overweight	180	—30	No change	-	-
		Brinkworth et al. (2009)* †	n = 32 obese adults	365	—30	↑	-	-
		Ngandu et al. (2015)	n = 591 elderly adults	730	NR	-	-	No change

Summary of the effects of dietary change on various domains of memory. Findings have been sub-categorized according diet manipulation, degree of energy restriction (if any), and duration of diet, respectively. Significant improvements are represented by an upwards arrow (↑). Significant impairments are represented by a downwards arrow (↓). Studies that do not measure the relevant cognitive domain are represented with a dash (—). † indicates that changes in these studies may be due to methodological shortcomings, such as a practice effect. * denotes diet study manipulated both energy and macronutrient content. NR = Not reported.

information processing speed). Of the diet intervention studies reviewed here, 23 assessed memory and 31 assessed other cogni- tive domains. This split is made on both organizational grounds, but also because memory processes, and especially long-term ones are of special interest, given the human and animal literature mentioned above.

5. Memory

While it has been established that memory tasks are most sensitive to macronutrient intake at the postprandial level (Hoyland, Lawton, & Dye, 2008), the longer-term experimental evidence has not been reviewed. We have divided the following section into three sub-components e working memory, visual-spatial memory, and long-term verbal memory. Working memory refers to the system used to keep things in mind while performing complex tasks such as reasoning, comprehension and learning (Baddeley, 2012). Visual-spatial memory is responsible for recording information about one's environment and its spatial orientation. While working memory persists only for around 30 s, long-term verbal memory involves storage and retrieval of information from several minutes to decades. Additionally, long-term verbal and visual spatial memory systems appear to be mediated chiefly by the hippocampus (Van Petten, 2004), and may be particularly susceptible to diet-induced damage (Walsh & Emerich, 1988) and thus requires more detailed consideration. The effects of diet on these sub-components of memory have been summarized in Table1.

5.1. *Working memory*

To date, research has only studied the impact of decreases in energy intake on working memory (WM), while the impact of increasing energy intake is unknown. Research has yielded mixed

findings. A 30% energy restricted diet (6300 kJe6600 kJ/day) either high (45%) or low (4%) in carbohydrate content led to improvements in numerical WM (digit span backwards) after 8 weeks (Halyburton et al., 2007) and 1 year (Brinkworth, Buckley, Noakes, Clifton, & Wilson, 2009). A common measure of numerical working memory storage capacity, digit span backwards requires participants to recall a series of digits in reverse order of initial presentation. Since numerical WM performance did not vary as a function of macronutrient manipulation at both time points, the restriction in energy intake likely explains this improvement. However, in the absence of an appropriate control group, it was unclear whether the improvements in WM were due to the restricted energy intake or due to repeated administration of the test (practice effect).

Martin et al. (2007) found that non-numerical WM performance improved following a six-month 25% energy restricted diet (6500 kJ/day) and a low energy diet (3700 kJ/day, but effect sizes were small ($h^2 < 0.07$). Since there was a significant effect of time and WM performance in the diet group did not differ from the control group, improvement over time likely reflected a practice effect. Indeed, other studies involving similar energy restrictions (Bryan & Tiggemann, 2001e20%; Pearce, Noakes, Wilson, & Clifton, 2012e30%; Witte, Fobker, Gellner, Knecht, & Flöel, 2009e30%) and even of longer duration (Cheatham et al., 2009e30%) did not find any significant changes in WM performance.

There is only limited evidence that WM performance is influ- enced by dietary macronutrient content. Working memory is un- affected by changes in protein (Lindseth et al., 2011; Van der Zwaluw et al., 2014), while there have been mixed findings with carbohydrate intake. The processing of carbohydrates affects short- term glycemic control and cognition (Benton et al., 2003) and may influence long term cognition and brain function since some brain areas, such as the hippocampus, have insulin receptors (Stangl & Thuret, 2009). Glycemic index (GI) ranks carbohydrates according to their effect on blood glucose levels. Cheatham et al. (2009) found that varying dietary GI did not affect WM in healthy overweight adults over six months [High GI (Energy (E): 7900 kJ; Protein (P): 20%; Fat (F): 20%; Carbohydrate (C): 60% (GI ¼ 85.6)) vs. Low GI (E: 7900 kJ; P: 30%; F: 30%; C: 40% (GI ¼ 52.4))]. Similarly, Smith et al. (2010) found no changes in WM following adherence to the high carbohydrate Dietary Approaches to Stop Hypertension (DASH) diet (E: 8209 kJ; P: 19%; F: 28%; C: 55%) relative to a usual diet control group.

Severe restriction of carbohydrates may have deleterious effects on WM. Although the nutritional information was not reported, D'Anci, Watts, Kanarek, and Taylor (2009) compared a three-week low-carbohydrate diet based on the Atkins (1998) program to a high-carbohydrate diet based on the American Dietetic Association (ADA) recommendations (E: 8368 kJ; P: 18%; F: 29%; C: 55%). Following a week of severe carbohydrate restriction, low carbohy- drate dieters recalled fewer digits on the digit backwards task compared to the ADA dieters, while there were no differences in the less cognitively demanding digit forwards task. Importantly, the difference in WM performance between the energy-matched diets was likely due to the severe restriction of carbohydrate since diet- induced impairments were not evident following the reintro- duction of carbohydrates at weeks 2 and 3 of the diet (D'Anci et al., 2009).

Since the low carbohydrate Atkins-like diet (D'Anci et al., 2009) was also high in total fat, it may be that increasing total fat, rather than decreasing carbohydrate content was responsible for the im- pairments in WM. However, this seems unlikely since no differ- ences were found in WM performance when comparing a high fat to a high carbohydrate diet. Halyburton et al. (2007) compared the effects of a high-fat, low-carbohydrate diet ((E): 6636 kJ/day; (P): 33%; (F): 61% (21% Saturated fat (SFA)); (C): 4%) to a high-carbohydrate, low-fat diet (E: 6319 kJ/day; P: 23%; F: 26% (5.6% SFA); C: 45%) on WM in overweight and obese participants over a period of 8 weeks. Improvements in numerical WM were evident in both groups after 8 weeks (Halyburton et al., 2007) and remained stable at 1-year follow-up (Brinkworth et al., 2009). Despite this, the trajectory of cognitive change did not vary between diet groups, suggesting that the restriction in energy intake, and not carbohy- drate or fat intake, was likely driving this improvement.

Working memory in other studies was unaffected by increases in total fat intake (Edwards et al., 2011; Lieberman et al., 2008). No changes in WM were reported following 2.5 day diets high in carbohydrates (E: 11784 kJ; P: 1%; F: 0%; C: 99%) or carbohydrates and total fat (E: 11796 kJ; P: 1%; F: 26%; C: 73%), suggesting that changes in either carbohydrate or total fat intake do not affect WM (Lieberman et al., 2008). Likewise, Edwards et al. (2011) placed twenty men on a ketogenic high-fat low-carbohydrate (Atkins- style) diet (E: not reported; P: 24%; F: 74%; C: 2%) for 7 days, and found no significant changes in numerical WM performance rela- tive to baseline performance following 3 days on a low-fat high-carbohydrate diet (E: not reported; P: 22%; F: 17%; C: 61%). Interestingly, a subsequent study with an improved randomized controlled cross-over design with a 2-week wash-out period in between, as well as 3 days on a standardized diet prior to each 5 day test diet found some changes in WM (Holloway et al., 2011). Speed of memory index, a composite score derived from WM and recognition scores, was significantly slower after healthy men were fed a high fat diet for 5 days (E: not reported; P: 26%; F: 70%; C: 4%) relative to an isoenergetic low-fat diet (E: not reported; P: 26%; F: 24%; C: 50%). However, caution should be taken since the individual component scores of WM performance were not reported and another related composite score e 'quality of WM' related to the ability to hold information temporarily in the articulatory loop and the visuo-spatial sketchpad e was unchanged following the high fat diet.

Meanwhile, a comprehensive study by Lindseth et al. (2011) reported that fat may improve WM. Lindseth et al. (2011) gave participants diets either high in fat (E: not reported; P: 22%; F: 56%; C: 22%), protein (E: not reported; P: 56%; F: 22%; C: 22%), or car- bohydrates (E: not reported; P: 22%; F: 22%; C: 56%), or a "balanced" control diet (E: not reported; P: 15%; F: 35%; C: 50%), for four days each in a randomized, counterbalanced cross-over design. Nu- merical WM performance, as measured by the Sternberg short- term memory test (Sternberg, 1966) varied as a function of diet. Specifically, response times on this memory test were faster for participants fed the high-fat diet, especially for higher memory loads but remained unchanged in other diets. One potential confound in this study was that participants completed the cognitive tests within 2 h of their final meal, suggesting partici- pants were tested in a postprandial state. Improvements in mem- ory performance in the high-fat diet condition may have reflected postprandial improvement following fat ingestion e a finding in agreement with other postprandial studies (Fischer, Colombani, Langhans, & Wenk, 2001; Hoyland et al., 2008).

A further factor may be the type of fat rather than total fat intake. Higher reported adherence to two different Mediterranean diets high in PUFAs and MUFAs and low in saturated fats e improved numerical WM performance relative to a control group in middle-aged adults after 6.5 years (Martínez-Lapiscina et al., 2013b). However, others have found impairments in numerical WM performance following Mediterranean diet adherence in fe- males after 10 days (Lee et al., 2015; McMillan et al., 2011). The reasons for these discrepancies are unknown, but may be related to the duration of each diet intervention (i.e. 10 days versus 6.5 years). Additionally, the effects of various types of fat remains hard to gauge since studies investigating the effects of various fat types on

WM have thus far failed to report any pertinent nutritional information, despite reporting successful adherence to the Mediterranean diet (Lee et al., 2015; Martínez-Lapiscina et al., 2013b; McMillan et al., 2011). Another study by Witte et al. (2009) failed to find changes in WM performance in elderly adults after a 3 month diet where the ratio of unsaturated fats to saturated fats was doubled, making the picture a little less clear.

In sum, there are mixed findings around WM. Significant changes in WM were reported in 3/7 with changes in energy intake, 0/2 studies with changes in protein, 5/10 studies from changes in total fat, and1/7 studies from changes in carbohydrates. Thus, few consistent changes in WM performance were evident, except some evidence that fat (and fat type) may be important here. Addition- ally, some tests may be more sensitive to dietary change than others, since numerical WM tests appeared to be more sensitive to dietary change than their non-numerical equivalents.

5.2. Visual-spatial memory

Only one diet intervention study have investigated the effects of energy restriction on visual-spatial memory. Martin et al. (2007) found no changes in performance on the Benton Visual Retention Test (BVRT) after a 30% energy reduction over 3 or 6 months. Thus, in agreement with human correlational data (Redman et al., 2008), visual-spatial memory function appears unaffected by changes in dietary energy intake.

Performance on tests of visual-spatial memory did not change following a brief four-day diet high in total fat (E: not reported; P: 22%; F: 56%; C: 22%), protein (E: not reported; P: 56%; F: 22%; C: 22%), or carbohydrates (E: not reported; P: 22%; F: 22%; C: 56%; Lindseth et al., 2011). Likewise, Lieberman et al. (2008) found that fat did not impact performance on the delayed spatial matching-to-sample task. Nonetheless, four other studies have found significant changes in visual-spatial memory following changes in dietary fat intake. Bayer-Carter et al. (2011) compared the effects of a four week high fat (>25% saturated fat), high GI (>70) diet or a low fat (<7% saturated fat), low GI (<55) diet on the Brief Visuospatial Memory Test (BVMT) in elderly adults with and without mild cognitive impairment. In three learning trials, the participant views the stimulus page for 10 s and is asked to draw as many of the figures as possible in their correct location both immediately and following a 25-min delay. Bayer-Carter et al. (2011) reported that delayed visual memory improved in participants with and without amnestic mild cognitive impairment following the low fat, low GI diet (E: 9088 kJ; P: 15%; F: 25%; C: 60% (GI ¼ 55)) relative to the high fat diet (E: 8581 kJ; P: 15%; F: 45%; C: 40% (GI ¼ 70)). That is, de- creases in saturated fat and GI load were associated with improved delayed visual recall in both cognitively impaired adults and healthy controls, while improvements in memory were not evident at immediate recall or in the group given the high fat, high GI diet. Importantly, this dietary intervention was designed as a weight- maintenance macronutrient manipulation and changes in mem- ory performance were therefore due to changes in diet and unre- lated to energy intake. It is unclear if the improvements in memory were driven by decreases in total fat intake, saturated fat intake, the glycemic load of the diet or some combination of these changes. Nonetheless, these findings did reveal that improvements in visual- spatial memory associated with the low-fat diet were prevented by increases in saturated fats and GI load, implying that diet was a significant environmental factor modulating memory. In agree- ment with this, 6.5 years adherence to a Mediterranean diet high in PUFAs and MUFAs from extra virgin olive oil consumption led to improvements in visual-spatial performance on the both immedi- ate and delayed memory recall of the visual-spatial ReyeOsterith Complex Figure task (ROCF) in 285 elderly individuals (Martínez-Lapiscina et al., 2013b). Likewise, McMillan et al. (2011) found that higher reported adherence to this diet improved reaction time on the spatial Corsi Block task in young females after 10 days (McMillan et al., 2011), while Lee et al. (2015) found a trend towards significance on the same task in young females after 10 days when tested in a cross-over design.

For carbohydrate intake, the findings have been mixed. Lieberman et al. (2008) reported no effect of carbohydrate content (E: 9566 kJ; P: 1%; F: 0%; C: 99%) or carbohydrates and total fat (E: 11796 kJ; P: 1%; F: 26%; C: 73%), on delayed spatial matching-to- sample performance over 2.5 days, while D'Anci et al. (2009) found that the complete removal of dietary carbohydrates impaired visuospatial memory after 1 week, and these impair- ments were ameliorated with the reintroduction of dietary carbo- hydrate in subsequent weeks. That is, on the visual-map task, low carbohydrate dieters correctly placed fewer items during immedi- ate recall and made more incorrect placements during delayed recall. Interestingly, it suggests that complete removal of dietary carbohydrates, but not other macronutrients, significantly impairs memory, suggesting a unique role of dietary carbohydrate intake. However, as no nutritional information about the diet was re- ported, these findings must be interpreted with caution.

Except for diets that altered fat content, there was no consistent pattern in visual-spatial memory performance across the diet intervention studies, since significant effects were reported in 0/1 studies from changes in energy intake, 0/1 studies from changes in protein, and 1/3 studies from carbohydrates. Four out of six studies found changes in visual-spatial memory after changes in fat. The evidence suggests a possible beneficial effect of *fat*, noting that the type of fat may be critical here e for example, a Mediterranean diet. In summary, visual-spatial memory performance was improved by decreases in total fat content, as well as increases in PUFAs and MUFAs, but not by changes in intake of energy or other macronutrients.

5.3. Long-term verbal memory

Restrictions in energy intake have been reported to have either no effect on verbal memory (Makris et al., 2013; Martin et al., 2007; Wardle et al., 2000) or to improve performance (Bryan & Tiggemann, 2001; Kretsch, Green, Fong, Elliman, & Johnson, 1997; Witte et al., 2009). Notably, none of the diet intervention studies have reported impairments in verbal memory following energy restrictions.

Martin et al. (2007) found no significant changes in performance on a word recall task [Rey Auditory Verbal Learning Test (RAVLT)] at 3 months or 6 months following an intervention with either a 25% energy-restricted diet based on American Heart Association recommendations (Ç30% total fat) or a low-energy diet derived from a liquid formula (E: 3565 kJ; P: 36%; F: 12%; C: 52%). The RAVLT evaluates rate of learning, learning strategies, interference, differences between encoding and retrieval, and retention of information. In the RAVLT, participants are given a list of 15 unrelated words repeated over five different trials and are asked to repeat immediately. Another list of 15 unrelated words are given and the participant must again repeat the original list of 15 words immediately and again after a 30 min delay. Overall, mixed linear models found no consistent pattern of verbal memory change emerged during the trial and the degree of energy restriction was not associated with change in cognitive performance (*Cohen's d < 0.08*). Similarly, Makris et al. (2013) reported no changes in word recall performance following reductions of up to 25% in energy intake after 24 weeks. Verbal memory performance was also unaffected by reductions in energy by 20% in adults with elevated serum cholesterol over 12 weeks (Wardle et al., 2000).

In contrast, other researchers have found improvements in verbal memory following energy restriction. First, Kretsch et al. (1997) found that immediate word recall memory improved significantly by 24.4% relative to baseline in overweight women (no nutritional information was reported in this study). Second, par- ticipants were less vulnerable to interference effects and more accurate in their recall following restrictions in energy intake by 20% for twelve weeks (Bryan & Tiggemann, 2001). Specifically, free recall intrusions on the RAVLT were greater in the control group than in the diet group, indicating some positive effect of energy restriction on verbal memory recall. Lastly, Witte et al. (2009) found that, after reducing energy by 30% for twelve weeks, elderly adults remembered more words and made fewer mistakes on the RAVLT compared to baseline performance and this effect was moderate to large (*Cohen's d* ¼ 0.66).

Increases in dietary protein intake have no effect on long-term verbal memory in frail elderly adults after 24 weeks (E: 7500 kJ; P: 16%; F: 35%; C: 44%; Van der Zwaluw et al., 2014). Increases in total fat did not affect verbal memory in males (Edwards et al., 2011; Holloway et al., 2011) or elderly adults (Bayer-Carter et al., 2011), while reductions in total (25%) and saturated fat (7%) intake had no effect on verbal memory in elderly adults (Bayer-Carter et al., 2011). Nevertheless, Nilsson, Tovar, Johansson, Radeborg, and Björck (2013) found some preliminary evidence that a diet low in saturated fat (<6%) (E: 9866 kJ; P: 19%; F: 31%; C: 50%) designed to reduce markers of inflammation associated with metabolic syndrome enhances verbal memory. Overweight middle-aged adults given a diet low in saturated fat (<6%), but high in polyunsaturated (8%) and monounsaturated fats (13%) improved verbal recognition memory performance on the RAVLT relative to a control diet (E: 9657 kJ; P: 15%; F: 30%; C: 55%; Nilsson et al., 2013). Despite overall increases in performance scores associated with repeated test administration, greater improvements in memory were significantly associated with reported diet adherence. These findings hint at the potential to reverse or alter the trajectory of verbal memory impairments in middle-aged adults using dietary intervention. Importantly, it also suggests that the type of fat may be important since there were no differences in total fat intake between the diet and control groups.

Other studies designed to increase PUFA and MUFA intake yielded improvements in verbal memory, with better performance on Verbal Paired Associates (Martínez-Lapiscina et al., 2013b) and fewer errors in immediate and delayed word recall (McMillan et al., 2011). By comparison, Lee et al. (2015) observed better word recognition in the control group, while the remaining studies manipulating fat type have found no discernible change in verbal memory (Wardle et al., 2000; Witte et al., 2009). Interestingly, the studies reporting significant changes in verbal memory (Lee et al., 2015; Martínez-Lapiscina et al., 2013b; & McMillan et al., 2011) also failed to report the nutritional content at the end of their respective interventions, making any conclusions about the relationship between diet and verbal memory performance problematic.

Limiting carbohydrate intake was found to affect verbal memory in one study. Krikorian et al. (2012) reported that, in older adults with mild cognitive impairment, moderate reductions in dietary carbohydrates (E: 4339 kJ; P: 27%; F: 60%; C: 13%), improved performance on the verbal paired associates task (*Cohen's f* ¼ 0.26) after six weeks relative to a high carbohydrate diet (E: 6653 kJ; P: 15%; F: 35%; C: 50%). Given that the low carbohydrate group also consumed significantly less energy over the intervention period, it is unclear whether changes were due to reductions in carbohydrate intake, energy intake, or some combination of both. Meanwhile, other intervention studies have failed to find any change in verbal memory performance following restrictions in dietary carbohy- drates from three weeks (D'Anci et al., 2009) up to twenty-four weeks (Makris et al., 2013). Makris et al. (2013) reported no changes in word recall following a high carbohydrate (E: 6276 kJ; P: 15%; F: 30%; C: 55%), or low carbohydrate diet following the guidelines of *Dr. Atkins' New Revolution* (Atkins, 1998) (nutritional information not provided) for 2 years, showing that carbohydrate content did not affect memory. Training sessions at baseline to familiarize participants with the memory tasks may have plateaued scores preventing any further improvement in memory perfor- mance (ceiling effect). Similarly, Smith et al. (2010) found no changes in verbal paired associate learning following 4 month adherence to a high carbohydrate DASH diet (E: 8209 kJ; P: 19%; F: 28%; C: 55%) and Ngandu et al. (2015) found no differences between diet and control groups in verbal memory after a 2 year high car- bohydrate diet (E: NR; P: 15%; F: 30%; C: 50%).

Diet intervention studies reveal no consistent effect of diet on long-term verbal memory since significant effects were found in 3/ 6 studies from changes in energy intake, 0/1 studies from changes in protein, 4/9 studies from changes in total fat, and 1/5 studies from changes in carbohydrates. Verbal memory was improved to varying degrees by reductions in energy intake and changes to fat type (but not necessarily fat content). While the fat-related findings look disappointing, several studies hinted at potential benefits associated with varying intake of fat type in healthy adults. In agreement with this, a review found that verbal memory perfor- mance, more than any other cognitive domain, is acutely affected at the postprandial level (Hoyland et al., 2008).

5.4. *Concluding remarks on memory*

The research from diet intervention studies suggests three conclusions: (1) there is notable variation in outcomes across all cognitive domains and diets; (2) reductions in energy intake and dietary fat appear beneficial to long-term memory function especially among overweight and obese adults, although this effect was not always clear (see Table 1); and (3) changes in dietary fat, especially towards a more healthful Mediterranean pattern may benefit multiple types of memory.

6. Other cognitive domains

In the following part of the review, we examine diet interven- tion studies that have measured performance on non-memory based tasks. These have been broadly categorized into four cogni- tive domains: global cognitive function, executive function, atten- tion, and information processing speed. First, we discuss tests of global cognitive function (e.g. MMSE), which are typically used to estimate the severity and progression of cognitive impairment, thus making it an effective tool to track an individual's cognitive function over time. Second, we examine executive function e a multifaceted construct consisting of a set of higherorder processes that allow individuals to make choices and to engage in purposeful, goal-directed and future-oriented behavior. Long-term energy regulation may require planning and self-regulation to balance food consumption behaviors with the ability to suppress or inhibit those behaviors. Moreover, optimal cognitive function depends not only on the ability to retrieve information when it is needed, but also on the ability to inhibit retrieval of information when it is not needed. Third, we investigate the effects of diet on attention, including sub-tests of sustained attention and divided attention. Finally, information processing refers to ability to direct mental focus to relevant information in order to process it rapidly and efficiently, as well as make accurate and appropriate decisions based on current information and/or pre-existing knowledge. We have made an effort to classify the various tests according to the major functional areas of responses and for most, this was possible.

Many others, however, involve several functions while few tests measure a single cognitive construct. For instance, the Trail Making Test (TMT) parts A and B e complex tests of attention involving a response speed component may also tap into executive function. In this way, their assignment to a particular domain was somewhat arbitrary but was based heavily on the recommendations of Lezak, Howieson, Bigler, and Tranel (2012).

6.1. Global cognitive function

Global cognitive function refers to overall or general cognitive performance tapping into various neural networks and brain regions. It includes multiple domains such as attention, memory, language, orientation and motor skills. Because of this, measures of global cognitive function are typically used as screening tools to detect general cognitive status of individuals. Nonetheless, a total of seven studies have examined the effects of changes in energy or macronutrients on global cognitive function, and are detailed below.

The effects of energy intake on global cognitive function have been explored by only two studies. Aquilani et al. (2008) showed that a protein-energy supplementation program that boosted energy intake by 22% (E: 6477 kJ; P: 17%; F: 36%; C: 47%) improved global cognitive function (MMSE) in cognitively impaired sub-acute stroke patients relative to baseline performance but not relative to the control group (E: 4640 kJ; P: 14%; F: 35%; C: 58%). Nevertheless, this finding should be interpreted with caution since significant changes were found in a $\log_{10}$ transformed MMSE score within the supplemented group only and not between groups, while there were no significant differences in the raw MMSE score in either group. By comparison, only one study has found that restricting energy resulted in improvements in global cognitive function in cognitively unimpaired adults. Siervo et al. (2012) found improvements on MMSE scores and the Short-Portable Mental Status Questionnaire following 40% energy restriction over 4 months in middle aged adults (E: 6761 kJ; P: 27%; F: 25%; C: 53%), and in healthy older adults (E: 5845 kJ; P: 27%; F: 25%; C: 53%). Taken together, these limited findings suggest that changes in energy may be important for global cognitive function, but research is lacking. Increases in protein did not change MMSE scores in younge old (65e74 years) type-2 diabetes subjects (Ciarambino, Ferrara, Castellino, Paolisso, & Giordano, 2011) and frail elderly subjects (Van der Zwaluw et al., 2014), while two other studies (Aquilani et al., 2008; Jakobsen, Kondrup, Zellner, Tetens, & Roth, 2011) found improvements in global cognitive function following in- creases in protein. As mentioned previously, the $\log_{10}$ transformed improvements in MMSE scores from Aquilani et al. (2008) should be viewed with caution. Moreover, since Aquilani et al. (2008) altered both macronutrient and energy content in one group while the control group received neither treatment, it is difficult to attribute any improvements in cognition to one dietary factor. Jakobsen et al. (2011) found significant improvements on the orientation score of the Addenbrooke Cognitive Examination e a test typically used to detect gross cognitive impairments. It is, however, likely inappropriate to use this test to detect improve- ments in cognitive performance in a sample population of healthy young males without any pre-existing cognitive impairments. One key long-term prevention trial found improvements in global cognitive function following a Mediterranean diet with no change in total energy intake (Martínez-Lapiscina et al., 2013a). They compared two Mediterranean diets e one supplemented with 1 L/week Extra Virgin Olive Oil [MedDiet þ EVOO] or supplemented with 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts) [MedDiet þ Nuts] e to a control low- fat diet. Although there were no differences in energy intake within and between diet and control groups, MedDiet groups did show strong adherence to the MedDiet guidelines, which have been described in detail elsewhere (Zazpe et al., 2008). Despite a lack of nutritional information at the end of the trial, reported adherence to both MedDiets improved cognitive status (MMSE) relative to the control diet in a 6.5-year follow-up in 522 elderly adults (Martínez-Lapiscina et al., 2013a) and a random subsample (n ¼ 285) within the same time period suggesting a robust finding (Martínez- Lapiscina et al., 2013b). Another study using a 'brain preservation' diet with the target of two fruit portions daily, three leafy green vegetable portions daily, five fish portions weekly, and avoidance of salty foods did not improve MMSE scores in elderly adults over 33 months (Kwok, Lam, Sea, Goggins, & Woo, 2012). Again, without detailed nutritional information, the relationship between diet and global cognitive function cannot be properly established.

Another comprehensive 2 year high carbohydrate (50%) multi-domain intervention program (diet, exercise, cognitive training, and vascular risk monitoring) reported improvements in perfor- mance on the Neuropsychological Test Battery in adults 60e77 years (Ngandu et al., 2015). In this program, 591 participants were advised to consume a diet with 10e20% of daily energy from pro- teins, 25e35% daily energy from fat (<10% from saturated plus trans fatty acids, 10e20% from monounsaturated fatty acids, and 5e10% from polyunsaturated fatty acids [including 2$5e3 g/day of omega- 3 fatty acids]), 45e55% daily energy from carbohydrates (<10% from refined sugar), 25e35 g/day of dietary fiber, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Although dietary adherence was not recorded at the time of this review, at the end of the 2 year intervention period, a modified intention to treat analysis found that improvement in the NTB total score was 25% higher for the intervention group than in the control group (Ngandu et al., 2015). Unfortunately, since the diet intervention group also increased physical exercise, cognitive training, social activity, and intensive monitoring and management of metabolic and vascular risk factors, it is difficult to know which intervention type was most beneficial to cognitive function. One may speculate that it is likely some combination of the above, but future research should aim to isolate them to better understand the most important and useful interventions for cognitive and clinical outcomes.

Overall, global cognitive function remained relatively unaffected across the diet intervention studies, since significant changes were evident in only 2/2 studies that altered energy intake, and 4/7 studies altering macronutrient content. The findings of two macronutrient studies (Aquilani et al., 2008; Jakobsen et al., 2011) are somewhat questionable. Few diet studies have found significant changes in global cognitive function, suggesting that either 1) these tasks are insensitive to changes in diet, or 2) the neuropsycholog- ical constructs underlying these tasks are not affected by changes in diet. Given the gross nature of the multi-domain cognitive test batteries, it is likely that these tests are insensitive to dietary in- terventions. For instance, the MMSE is typically used as a screening tool of cognitive impairment and was not intended to test treat- ment success. It may be that tasks of greater difficulty, which create a higher cognitive load, may be required to detect changes following dietary manipulations. Importantly, changes in test per- formance lack the specificity to determine which cognitive domain may be affected.

6.2. Executive function

Generally speaking, executive function is the ability to respond in an adaptive manner to novel situations. It is the most complex of cognitive domains that includes complex higher order thinking processes related to planning, problem solving, verbal reasoning, inhibition, mental flexibility, or set-shifting. It has been proposed

that the type of diet one consumes may augment total energy intake or interfere with inhibitory processes resulting in excess energy intake and weight gain (Davidson et al., 2005). To date, there is little human experimental evidence to substantiate this claim. Only three studies have investigated the long-term effects of energy intake on inhibition using either the Stroop task, or a modified food-Stroop task using food-related cues. The Stroop task is a measure of inhibition e the ability to suppress automatic and habitual responses or behaviors. Bryan and Tiggemann (2001) re- ported significant improvements in Stroop reaction time in both the 20% energy restricted and control groups, likely reflecting a practice effect. Two other studies reported promising changes in Stroop performance. Specifically, percentage of correct responses on the Stroop task improved over time following 25% energy re- striction for 24 weeks (Makris et al., 2013), while more severe en- ergy restrictions up to 80% for 4 weeks led to improvements in number of words read on the Stroop task (Wing, Vazquez, & Ryan, 1995). Despite also manipulating carbohydrate content, both studies showed improvements in the Stroop task over time regardless of carbohydrate content, suggesting energy restrictions likely contributed to these improvements. However, in the absence of an appropriate control group (i.e., one that did not alter their diet but completed the task at the same time points), it is difficult to determine if improvements in Makris et al. (2013) and Wing et al. (1995) were due to repeated administration or a genuine conse- quence of energy restriction. Additionally, it may be that the impact of energy restriction on tasks of inhibition is greater with increasing duration or magnitude of energy restriction, but this remains unexplored. As it stands, it appears that tasks of inhibition are susceptible to changes in energy intake.

Other tasks of executive function have shown no changes as a result of energy restriction. Reductions in energy intake ranging from 10% to 75% did not impact performance on executive function measures such as: (1) Self-Ordered Pointing Task or verbal fluency in women after 20% restriction over 12 weeks (Bryan & Tiggemann, 2001); (2) the Wisconsin Card Sorting Task in middle-aged adults after 25% restriction over 24 weeks (Makris et al., 2013); (3) or tasks of grammatical reasoning in healthy overweight adults after 30% restriction over 6 months (Cheatham et al., 2009). Thus, except for measures of inhibition, there is little evidence to suggest that energy intake affects executive function across various populations. Addi- tionally, there appears to be no dosage effect based on the pattern of findings, with changes in executive function performance no more likely to occur with greater energy restriction (see Table 2).

Much like energy intake, measures of inhibition have presented some changes associated with diet manipulation. Jakobsen et al. (2011) found improved reaction time and fewer errors on the Go/ No Go task after a three week high protein diet (E: 7485 kJ; P: 35%; F: 15%; C: 50%) relative to a control diet (E: 7085 kJ; P: 17%; F: 16%; C: 67%). The Go/No Go task is a reaction time task of behavioral inhibition and typically involves choosing one of two outcomes across multiple trials: one in which participants are required to make a motor response (go), and another requires participants to withhold a response (no-go). Importantly, the significant differ- ences in reaction time persisted even after accounting for baseline differences. On another task of inhibition, Stroop performance improved significantly following the high carbohydrate ADA diet (E: 8368 kJ; P: 18%; F: 29%; C: 55%) relative to a low-carbohydrate diet (nutritional information unavailable; D'Anci et al. (2009)). Specifically, participants on the ADA diet responded faster to non- food words over test sessions e an effect not evident in the low carbohydrate group. This difference may reflect a reduction in food pre-occupation. Despite this, D'Anci et al. (2009) concluded that, due to the inconsistent nature of responses in the low carbohydrate group, it is unclear why or how diet improved Stroop performance. Likewise, the reasons for the discrepancy in findings between the Stroop task and Go/No Go task are currently unknown, but may be related to task sensitivity or difficulty associated with the different tasks of inhibition. Other studies found no changes in Stroop per- formance following increases or decreases in fat intake (Bayer- Carter et al., 2011), protein intake (Van der Zwaluw et al., 2014), or carbohydrate intake (Makris et al., 2013; Smith et al., 2010).

Improved performance on other executive function tasks has been reported in a small number of studies following shifts in di- etary macronutrient content. For instance, a 6.5 year diet trial (n ¼ 522) found improvements in executive function (Clock Drawing Task) after adherence to a Mediterranean diet supple- mented with extra-virgin olive oil (Martínez-Lapiscina et al., 2013a). A subsequent article using a random subsample (n ¼ 285) detected improvements in verbal fluency in the Mediterranean diet group relative to the control group, using a logistic regression model adjusting for multiple confounders (Martínez-Lapiscina et al., 2013b). Meanwhile, Ngandu et al. (2015) reported an 83% improvement in executive function performance relative to a con- trol group following a 2 year high carbohydrate diet (E: NR; P: 15%; F: 30%; C: 50%) in adults 60e77 years. One study that varied fat and carbohydrate content failed to find improvements in grammatical reasoning scores over a 2.5 day intervention period (Lieberman et al., 2008), but given the relatively short intervention period this finding is not surprising. The results of varying macronutrient content on executive function has yielded inconsistent findings. One problem is that some studies have altered only macronutrient content, while others have also altered energy intake to varying degrees. Despite this, there was no clear pattern of results across studies when this was taken into consideration.

Executive function tasks not involving inhibition remained relatively unaffected across the diet intervention studies, since significant effects were found in 0/3 studies from changes in energy intake, 0/1 studies from changes in protein, 2/4 studies from changes in total fat, and 1/6 studies from changes in carbohydrates. Tasks of greater difficulty, which create a higher cognitive load, may be required to detect changes following dietary manipulations. Indeed, tasks of inhibition appeared to show some sensitivity to changes in energy intake in 2/3 studies, while only 2/6 studies with macronutrient manipulations showed improvements in inhibition. A summary of the various diets and their effects on executive function can be found in Table 2. Another important point of consideration is that significant improvements in performance were mostly evident in reaction time measures within these tasks of inhibition. The effect of dietary intervention on reaction time will be discussed in detail in the next section.

6.3. Attention

Most everyday activities depend on intact mechanisms for directing attention, dividing attention when necessary, and sus- taining attention until an activity is complete. Likewise, successful performance of many cognitive tests requires sustained and focused attention. Here, we have divided tasks according to the classifications by Lezak et al. (2012), including general measures of attention, and more specific measures including divided attention and sustained attention tasks. Divided attention occurs when we are required to perform multiple tasks at the same time and attention is required for successful performance on all tasks at hand (e.g. Trail making task part B (TMT-B)), while measures of sustained attention typically involve sequential presentation of stimuli over a period of time with instructions to indicate when target stimuli is perceived (e.g. digit vigilance task).

The majority of energy restriction studies (Cheatham et al., 2009; Kretsch et al., 1997; Makris et al., 2013; Martin et al., 2007;

Table 2
Summary of effects of diet interventions on other cognitive domains.

Intervention		Study	Sample population	Duration (days)	Change in energy (%)	Effect on other cognitive domains			
						Global cognitive function	Executive function	Attention	Information processing speed
Energy Intake	Decrease	Wardle et al. (2000)*	n = 105 middle-aged adults	84	—17	-	-	↓	No change
		Bryan and Tiggemann (2001) †	n = 42 overweight women	84	—20	-	↑	↑	-
		Martin et al. (2007)	n = 24 overweight	168	—25	-	-	No change	-
		Makris et al. (2013)*	n = 47 obese	168	—25	-	↑	No change	-
		Halyburton et al. (2007)* †	n = 93 obese	56	—30	-	-	-	↑
		Pearce et al. (2012)	n = 44 obese with type 2 diabetes	56	—30	-	-	No change	No change
		Witte et al. (2009)	n = 19 overweight elderly	84	—30	-	-	No change	-
		Cheatham et al. (2009)*	n = 28 overweight	180	—30	-	No change	No change	No change
		Brinkworth et al. (2009)*	n = 64 obese	365	—30	-	-	-	No change
		Siervo et al. (2012)	n = 21 middle and old aged	116	—40	↑	-	↑	-
		Kretsch et al. (1997)	n = 14 women	105	—50	-	-	No change	↓
		Buffenstein et al. (2000) †	n = 9 overweight women	28	—66	-	-	-	↑
		Wing et al. (1995)*	n = 21 overweight women	28	—80	-	↑	↑	-
	Increase	Aquilani et al. (2008)	n = 24 elderly	21	+22	↑	-	-	-
Protein	Decrease	Ciarambino et al. (2011)	n = 52 overweight with T2DM	28	0	No change	-	-	-
	Increase	Van der Zwaluw et al. (2014)*	n = 65 frail elderly	168	NR	No change	No change	No change	↑
		Jakobsen et al. (2011)	n = 11 healthy men	21	0	↑	↑	No change	No change
		Aquilani et al. (2008)	n = 24 elderly	21	+22	↑	-	-	-
Fat	Decrease	Bayer-Carter et al. (2011)	n = 11 healthy elderly	28	0	-	No change	No change	No change
			n = 14 elderly with mild cognitive impairment	28	0	-	No change	No change	No change
		Nilsson et al. (2013)	n = 44 healthy adults	28	0	-	-	↑	-
		Wardle et al. (2000)*	n = 52 middle-aged adults	84	—17	-	-	↓	No change
	Increase	McMillan et al. (2011)	n = 12 young females	10	NR	-	-	No change	No change
		Lee et al. (2015)	n = 23 young females	10	NR	-	-	No change	No change
		Martínez-Lapiscina et al. (2013a)	n = 390 elderly subjects	2373	NR	↑	↑	-	-
		Martínez-Lapiscina et al. (2013b) ˆ	n = 190 elderly subjects	2373	NR	↑	↑	No change	-
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	-	No change	No change	No change
		Holloway et al. (2011)	n = 16 healthy men	5	0	-	-	↓	-
		Edwards et al. (2011)	n = 20 healthy men	7	0	-	-	↓	↓
		Bayer-Carter et al. (2011)	n = 9 healthy elderly	28	0	-	No change	No change	No change
			n = 15 elderly with mild cognitive impairment	28	0	-	No change	No change	No change
		Kwok et al. (2012)	n = 149 elderly care subjects	990	0	No change	-	-	-
		Wardle et al. (2000)*	n = 53 middle-aged adults	84	—17	-	-	↓	No change
		Halyburton et al. (2007)* †	n = 48 obese	56	—30	-	-	-	↑
		Brinkworth et al. (2009)*	n = 32 obese	365	—30	-	-	-	No change
Carbohydrate	Decrease	D'Anci et al. (2009)*	n = 9 overweight women	21	NR	-	No change	↑	-
		Makris et al. (2013)*	n = 22 obese	168	—25	-	No change	No change	-
		Cheatham et al. (2009)*	n = 16 overweight	180	—30	-	No change	-	No change
		Krikorian et al. (2012)*	n = 12 older adults	42	—41	-	-	No change	-
		Wing et al. (1995)* †	n = 11 overweight women	28	—80	-	-	↑	-
	Increase	D'Anci et al. (2009)*	n = 10 overweight women	21	NR	-	↑	↓	-
		Ngandu et al. (2015)	n = 591 elderly adults	730	NR	↑	↑	-	↑
		Lieberman et al. (2008)	n = 27 healthy adults	2	0	-	No change	No change	No change
		Smith et al. (2010)	n = 38 obese	120	0	-	No change	↑	-
		Krikorian et al. (2012)*	n = 11 older adults	42	—6	-	-	No change	-
		Makris et al. (2013)*	n = 25 obese	168	—25	-	No change	No change	-
		Halyburton et al. (2007)* †	n = 45 obese	56	—30	-	-	-	↑
		Cheatham et al. (2009)*	n = 12 overweight	180	—30	-	No change	-	No change
		Brinkworth et al. (2009)*	n = 32 obese	365	—30	-	-	-	No change
		Wing et al. (1995)* †	n = 21 overweight women	28	—80	-	-	↑	-

Note: Sample populations derived from diet groups only. Significant improvements are represented by an upwards arrow (↑). Significant impairments are represented by a downwards arrow (↓). Studies that do not measure the relevant cognitive domain are represented with a dash (—).† indicates that changes in these studies may be due to methodological shortcomings, such as a practice effect. Studies that manipulate both energy and macronutrient content are marked with an asterisk (*). (ˆ) Martínez-Lapiscina et al. (2013b) used a random subsample of 285 subjects from the total pool of 522 subjects used in Martínez-Lapiscina et al. (2013a). NR = Not Reported.

Pearce et al., 2012; Witte et al., 2009) have failed to show any changes in performance on the tasks of attention (see Table 2 for a detailed breakdown of findings). Three studies report improve- ments in attention (Bryan & Tiggemann, 2001; Siervo et al., 2012; Wing et al., 1995), while only one study found impairments in attention following energy restriction (Wardle et al., 2000). For instance, adults with elevated serum cholesterol given either a 20% energy restricted low fat or iso-energetic Mediterranean diet over 12 weeks performed significantly worse on the Bakan vigilance task of sustained attention than the waitlist control group (Wardle et al., 2000). The reasons for this difference in performance remain unknown.

Attention, as measured by the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) improved after twelve weeks in both the 20% energy restricted diet group and the usual-diet control group, while performance on the Trail Making Task part A (TMT-A) and part B (TMT-B) remained un- changed (Bryan & Tiggemann, 2001). Since improvements in Digit

Symbol Coding occurred in both groups, the effect likely resulted from repeated administrations of the test and not a consequence of the energy restriction. Siervo et al. (2012) reported that a 40% energy restriction over 4 months improved performance on the TMT- A and TMT-B in middle aged adults (E: 6761 kJ; P: 27%; F: 25%; C: 53%), and on the TMT-B only in healthy older adults (E: 5845 kJ; P: 27%; F: 25%; C: 53%). The Trail Making Task involves connecting 25 consecutive targets that are all numbers in sequential order (1, 2, 3, etc.) (TMT-A), and that alternate between numbers and letters (1, A, 2, B, etc.) (TMT-B). Improvements in cognition may be a potential consequence of energy restriction and its associated weight loss. Indeed, a meta-analysis by Siervo et al. (2011) found that weight loss was associated with better performance on TMT-B, especially in older adults, suggesting that excess weight may be a risk factor for cognitive decline. Importantly, there may be sample pop- ulations who are particularly vulnerable to excess weight, and correspondingly, restrictions in energy intake.

The influence of macronutrients on attentional performance is as yet fully understood. Increased protein content has no effect on sustained attention (Jakobsen et al., 2011) or TMT-A and TMT-B performance (Van der Zwaluw et al., 2014). By comparison, Wing et al. (1995) reported greater improvement in TMT-B perfor- mance in an energy restricted high carbohydrate group (E: 2486 kJ; P: 33%; F: 14%; C: 53%) relative to an iso-energetic low carbohydrate group (E: 2469 kJ; P: 35%; F: 58%; C: 7%). Subsequent analyses showed that this was due to baseline differences in performance on this task and not a result of the diet intervention, since performance in subsequent weeks was equivalent. Thus, it is likely that energy restriction (or even repeated administrations), and not differences in carbohydrate content, drove improvements in TMT-B perfor- mance. Three other studies also report no effect of carbohydrate content on measures of attention (Krikorian et al., 2012; Lieberman et al., 2008; Makris et al., 2013). Meanwhile, D'Anci et al. (2009) showed that, for women who self-selected two weight-loss diet regimens e a low-carbohydrate diet (nutritional information not available) or a <30% fat, weight maintenance ADA diet for 3 weeks e the low-carbohydrate group showed reduced response time on the Continuous Performance Task, while it increased for the ADA dieters. That is, a diet with reduced carbohydrates improved response times in the last 10 min of a 15 min task, indicating better sustained attention. Likewise, Smith et al. (2010) found that par- ticipants on the high carbohydrate DASH diet (E: 8209 kJ; P: 19%; F: 28%; C: 54%), relative to usual diet controls (E: 8765 kJ; P: 17%; F: 37%; C: 46%), exhibited better performance (*Cohen's d ¼ 0.44*) on the Ruff 2 and 7 s Selective Attention Test e a test of the difference between automatic and controlled detection that provides infor- mation on attentional capacity. Improvements in the DASH diet group were comparable to an 8.3-year improvement in automatic detection speed and a 9.6-year improvement in controlled detec- tion speed, while the control group exhibited relatively smaller improvements, with a 0.6-year improvement in automatic detec- tion speed and a 3.6-year improvement in controlled detection speed. Certainly, this test of attentional capacity has been shown to differentiate between right and left-side brain lesions (Ruff, Niemann, Allen, Farrow, & Wylie, 1992).

Some studies have revealed adverse effects of increased total fat intake on measures of attention. Males performed significantly worse on tasks measuring focused and sustained attention following a five day high fat (70%) diet compared to an isoenergetic low fat (24%) diet (Holloway et al., 2011). Likewise, sedentary males given a high fat, low carbohydrate diet for seven days exhibited impairments in the Rapid Visual Processing Speed (RVIP) task of sustained attention compared to performance on a low fat control diet (Edwards et al., 2011). Wardle et al. (2000) also found im- pairments in sustained attention following either a low-fat or a Mediterranean diet, but since these diets were also energy restricted, the exact role of fat content is difficult to determine. In the same way, changes in other tasks of attention were not signif- icant and the reasons for the absence of improvement following reductions in fat may be related to the lack of dietary target adherence. Wardle et al. (2000) reported that, despite different dietary fat targets in the low fat and Mediterranean diet groups, MUFA and PUFA intakes were equivalent, while total fat intake had decreased relative to the control group (statistics not reported).

Nilsson et al. (2013) reported that reducing the intake of satu- rated fat by 7% and increasing PUFA and MUFA intakes by 8% and 13%, respectively, significantly increased correct responses and decreased reaction time on a test of selective attention after four weeks (Nilsson et al., 2013). Importantly, they reported no signifi- cant no changes in total fat intake. It is unclear if improvements in attention were related to the reduction of saturated fats or the commensurate increase in PUFAs and MUFAs. One study found that neither increases nor decreases in total and saturated fat intake had any effect on attention (TMT-A) in elderly adults with or without MCI (Bayer-Carter et al., 2011), while other studies involving in- creases in PUFA and MUFA intake found no changes in attention (Lee et al., 2015; Martínez-Lapiscina et al., 2013b; McMillan et al., 2011), leaving this question unanswered.

Hence, as it stands, there is some evidence that attention is influenced by energy intake and fat content, but this remains to be seen given the paucity of research. Overall, significant changes in attention were found in 4/10 studies from changes in energy intake, 0/2 studies from changes in protein, 4/9 studies from changes in fat, and 3/6 studies from changes in carbohydrates. Indeed, there was no clear direction in the pattern of findings and, given the sub- stantial variability in findings and the lack of reported statistics, this is not surprising.

64. *Information processing speed*

Many cognitive tasks require sufficient information processing speed for relevant operations to be executed within the time allowed. Speed of information processing constitute the basic di- mensions of attention since how much the attentional system can process at once depends on how fast it operates. The speed at which information is processed, typically measured by reaction time tests, is a relatively direct means of measuring processing speed and understanding the nature of attentional deficits.

Information processing speed, typically measured by reaction time tasks, was unchanged in four energy restriction studies (Brinkworth et al., 2009; Cheatham et al., 2009; Pearce et al., 2012; Wardle et al., 2000), while the remaining three reported some interesting changes across various processing speed tasks. Buffenstein, Karklin, and Driver (2000) found that a four-week energy restricted diet (3347 kJ/day) was associated with improve- ments in a complex reaction time, while simple reaction time was unaffected relative to baseline performance. However, there was no control group and the researchers did suggest that the improve- ment might have been a 'practice effect' (Buffenstein et al., 2000). Another study revealed that the minimum amount time to identify a target stimulus over progressively shorter time intervals (i.e. in- spection time task) improved following a 30% energy restriction over 8 weeks (Halyburton et al., 2007). However, performance on this task returned to baseline levels when tested at 1 year (Brinkworth et al., 2009). Only one study reported impairments in processing speed following energy restriction. A 50% energy- restricted weight reducing diet for obese pre-menopausal women impaired simple reaction time after 15 weeks (Kretsch et al., 1997). Compared to baseline, simple reaction time on the finger tapping task was significantly slower at the end of energy restriction

(—5.2%) and continued to slow further during the 3-week weight stabilization period (up to —10.9% slower). Of particular importance was the finding that reaction time performance did not readily improve following the restoration of energy intake to maintain weight. The reasons for this lack of reversibility remain unclear.

One study indicated that dietary protein may provide some benefit for processing speed in the elderly. Specifically, reaction time improved more (68 ms) in frail elderly adults supplemented with protein and energy relative to a non-isoenergetic placebo group (18 ms) given a supplement containing no protein (Van der Zwaluw et al., 2014). Since participants did not compensate for the additional protein supplementation, the authors concluded that increasing protein intake (from 1.0 kg/b-w to 1.4 kg/b-w) was responsible for the improvements in processing speed. It should be noted that, despite reduced energy intake in both groups (excluding the supplement), the additional energy intake from the supplement program was not reported, making it difficult to determine the degree of energy restriction. In contrast, Jakobsen et al. (2011) found no improvements in reaction time in young men following increases in dietary protein over 3 weeks. It may be that additional dietary protein may benefit elderly adults, who likely have age-related cognitive impairments relative to their younger counterparts.

There are mixed findings with respect to the relationship be- tween processing speed and fat and carbohydrate content. Edwards et al. (2011) reported that sedentary males given a high fat, low carbohydrate diet for seven days exhibited impairments in simple reaction time compared to performance on a low fat control diet. Ngandu et al. (2015) found that improved processing speed in adults 60e77 years after a 2 year high carbohydrate diet (E: NR; P: 15%; F: 30%; C: 50%) was 150% higher than the control group. It may be processing speed has a positive and inverse relationship with carbohydrate and fat content, respectively. In a test of this, Halyburton et al. (2007) reported improved performance on a speed of processing task following an energy restricted diet either high in fat or carbohydrate diet over eight weeks, but showed greater improvement over time in the high-carbohydrate, low-fat diet (E: 6319 kJ/day; P: 23%; F: 26% (5.6% SFA); C: 45%) relative to a low carbohydrate/high fat diet (E: 6636 kJ/day; P: 33%; F: 61% (21% SFA); C: 4%). Adding to the mixed pattern of findings and despite greater improvements in inspection time in the former over the latter (h^2 ¼ *0.04*), change in performance scores were positively correlated with percentage of energy from fat (r ¼ 0.23), saturated fat (r ¼ 0.21) and MUFA (r ¼ 0.23) and negatively associated with carbohydrate intake (r ¼ —0.21), suggesting a favorable role of fat on processing speed (Halyburton et al., 2007). Interestingly, at 1-year follow-up, speed of processing decreased to baseline levels in both diet groups (Brinkworth et al., 2009). The reasons for these discrepancies are unclear, but may be related to the restriction in energy rather than the macronutrient content of either test diet.

Other studies involving changes in total fat content or relative ratios of fat types (e.g. Mediterranean diet) failed to find differences in information processing speed after dietary change (Lee et al., 2015; Lieberman et al., 2008; McMillan et al., 2011; Wardle et al., 2000). Likewise, most studies have failed to find any long-term benefit of changing dietary carbohydrate intake on performance on measures of reaction time or other measures of processing speed (Cheatham et al., 2009; Lieberman et al., 2008).

Overall, there have been mixed findings across the diet inter- vention studies, since significant changes were found in 3/7 studies from changes in energy intake, 1/2 studies from changes in protein, 2/7 studies from changes in fat, and 2/5 studies from changes in carbohydrates. Despite these inconsistent findings, there is some evidence of an inverse relationship between processing speed and energy intake, while carbohydrate may have a positive relationship with processing speed. However, given the inconsistencies in findings across studies, as well as the inter-dependency of processing speed measures with other measures of cognitive func- tions, it is as yet unclear whether measures of processing speed are sensitive to changes in diet.

6.5. *Concluding remarks on other cognitive domains*

Based on the experimental findings, tasks of global cognitive function appeared insensitive to dietary alteration. Executive function e particularly tasks involving inhibition e showed promising changes in the presence of energy restriction. Measures of attention and processing speed presented quite varied findings, occasionally in opposite directions. Across the various domains, changes to energy intake and fat content appeared most impactful, but once again the pattern is not entirely clear.

7. Summary of findings

Of the 32 published articles relevant to 30 different diet interventions, 27 studies found significant changes in cognition following dietary manipulation. Briefly, despite notable variation in outcomes across all cognitive domains and diets, the literature indicates that reductions in energy intake and dietary fat appear beneficial to all types of memory function and measures of attention, while changes in dietary fat, especially towards a more healthful Mediterranean pattern may benefit multiple types of memory. Interestingly, although verbal memory did not show consistent changes following diet interventions, medium to strong effects were found following changes in energy intake (Witte et al., 2009) or fat intake (Nilsson et al., 2013). Based on the findings, information processing speed appeared insensitive to dietary alteration, while executive function showed some changes, noting that these were mostly apparent in tasks of inhibition. Meanwhile, working, visual-spatial, verbal memory and measures of attention evidenced some changes after diet manipulations (see Fig. 3). Across the various domains, changes to energy intake and fat content appeared most impactful (see Fig. 4), but given the vari- ability in findings, this effect is not robust.

8. Discussion

The focus of this manuscript was to review the experimental evidence of the relationship between diet and cognition. Overall, there was some evidence that both memory performance and attention were affected by changes in dietary energy intake and fat intake. Measures of attention, working, visual-spatial and long- term memory appeared most sensitive to changes in macronu- trient content, with large but inconsistent effects found in verbal memory. Most notably, performance on tasks of longer-term memory appeared to be influenced by changes in energy and fat intake e an idea is consistent with animal data, which have found impairments in hippocampal-dependent learning and memory following an energy-rich HFS diet (Beilharz et al., 2013; Davidson et al., 2013; Jurdak & Kanarek, 2009; Molteni et al., 2002). One potential explanation of this pattern of results might be that diet might affect specific brain regions associated with performance on these various measures (Kallus, Schmitt, & Benton, 2005; Monti, Baym, & Cohen, 2014; Vuoksimaa et al., 2013), but this has yet to be tested experimentally.

Any causal inference about the relationship between diet and cognition would be supported substantially by related physiological changes. Research on the potential physiological mechanisms involved in diet-induced cognitive changes may provide some insight into which dietary components are important. Moreover,

the criteria for establishing causality (e.g. the BradfordeHill criteria) includes a biological gradient e greater exposure should generally lead to greater incidence of the effect. A small number of studies have explored various mechanisms including insulin (Witte et al., 2009), ketones (Makris et al., 2013), and inflammation (Nilsson et al., 2013; Witte et al., 2009). These potential mecha- nisms mediating the relationship between diet and cognition have been discussed in detail elsewhere (see; Francis & Stevenson, 2013; Parletta et al., 2013). Briefly, the experimental evidence has demonstrated a negative relationship between verbal memory performance and insulin following decreases in energy (Witte et al., 2009), carbohydrates (Krikorian et al., 2012) and fat, (Nilsson et al., 2013) indicating a significant role of glucoregulatory processes in mediating the relationship between diet and memory function. Additionally, improvements in memory performance were signifi- cantly associated with reductions in inflammatory markers following decreases in energy (Witte et al., 2009) and fat intake (Nilsson et al., 2013). Levels of ketones e a metabolite from fat in the absence of dietary carbohydrate and upon depletion of glycogen stores ewere positively correlated with verbal memory performance (r ¼ 0.45) in response to a relatively brief period of carbohydrate restriction (Krikorian et al., 2012). WM and executive function were not affected by the level of dietary carbohydrate e supporting the notion that carbohydrate restriction affects long- term memory via ketone metabolism.

8.1. Recommendations for future studies

The findings from experimental studies to date have been inconclusive. A reasonable argument can be made that this is in part due to substantial variability in the designs of diet interventions. In the studies reviewed here multiple designs were employed, including between subjects (23 studies), within-subjects (2 studies), or mixed designs such as randomized cross-over trials (5 studies). Within-subjects and mixed designs offer a practical approach to diet manipulation, since fewer subjects are required with subjects serving as their own controls. However, if diet has a long-lasting or persistent effect on cognition, then a within-subjects or mixed design would be inappropriate and may confound identification of causality. Thus, from an experimental standpoint, a between subjects design is recommended to better isolate the effects of diet on cognition and to avoid carry-over or interference between diet conditions.

The reviewed studies varied dramatically in their dietary interventions making it difficult to compare their findings. Some experimental studies administered stringent and clear diet guidelines (Bayer-Carter et al., 2011; Nilsson et al., 2013), while others did not (Bryan & Tiggemann, 2001; Ciarambino et al., 2011). Ideally, well-defined dietary guidelines on what participants are allowed to consume during the intervention period should be provided to standardize test conditions. Alternatively, individually tailored dietary plans that ensure macronutrient proportions, while also giving each person their required daily energy intake will likely improve overall dietary compliance and is also recommended for future studies. It may also be worthy of consideration to increase the variety of foods available within a dietary intervention as a means of increasing diet compliance. Few diet intervention studies accounted for major confounds including physical activity, stress levels or sleep patterns. Indeed, accounting for these sources of variance can influence diet effects. For instance, Smith et al. (2010) found that improvements in cognition associated with diet compliance were attenuated when variables of physical activity were accounted for statistically. Consequently, researchers should be aware of and account for major confounds including stress, alcohol and caffeine intake, and sleep and physical activity habits. Long-term benefits of diet should, presumably, be easier to observe after longer periods of time (e.g. Martínez-Lapiscina et al., 2013a, 2013b). Importantly, the amount of time it takes for dietary intake to affect cognition depends on various factors including, but not limited to the area of cognition being tested, the absolute and relative macronutrient intake in the diet, adherence to the diet, and sample population. Although some researchers have taken these factors into consideration to varying degrees, one important caveat of diet research that remains unclear relates to the earliest occur- rence of cognitive changes. Indeed, it may be worthy of consider- ation to determine the minimum amount of time to observe significant changes in cognitive function, which will likely reduce the amount of time and resources required from both researchers and participants. A fortunate consequence of this may be increased diet adherence and reduced attrition. Most studies found signifi- cant changes in various cognitive domains even at short time pe- riods (Edwards et al., 2011; Holloway et al., 2011; Lee et al., 2015; Lindseth et al., 2011; McMillan et al., 2011), while no changes were reported after a 2 day diet intervention (Lieberman et al.,

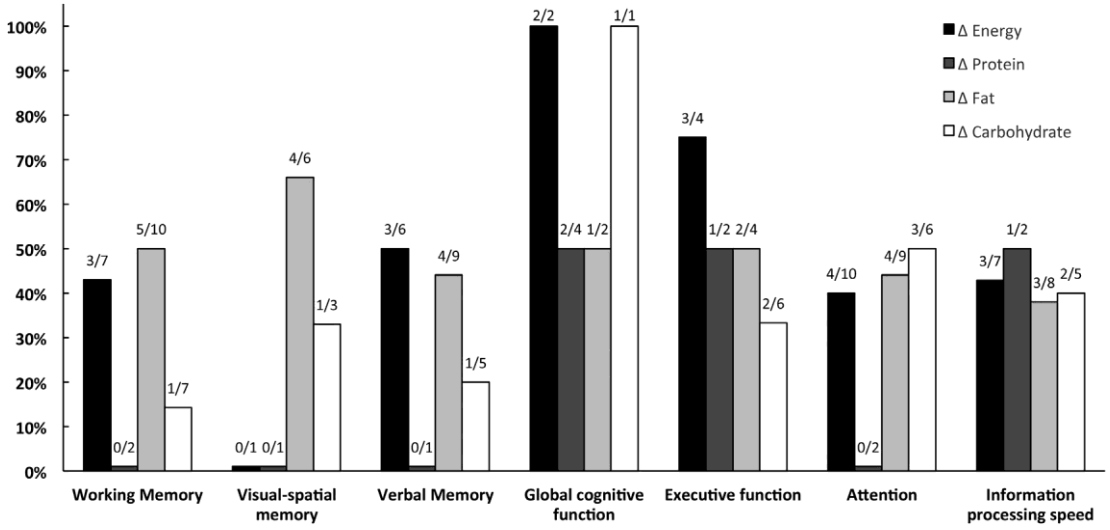

Fig. 3. A summary of the pattern of results showing the number of studies with significant changes in each cognitive domain with respect to the total number of studies within each domain, sub-categorized by diet type. All tasks of memory appear to show some changes after diet manipulation, while non-memory tasks present mixed findings.

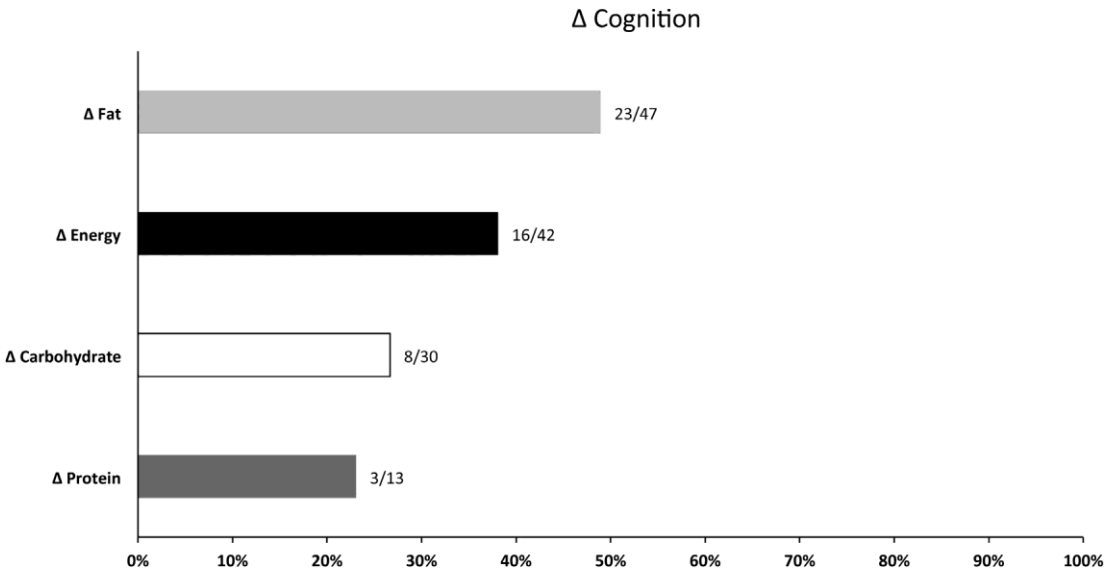

Fig. 4. A summary of the pattern of results showing that, across the various cognitive domains, fat and energy intake appear to be most impactful on cognitive change (regardless of direction), while carbohydrate and protein appear to have minimal impact. Here, it appears that changes in fat and energy intake affect various areas of cognition (memory and non-memory) more so than changes in protein and carbohydrates.

2008), suggesting that cognitive changes occur after 5 or more days (e.g. Holloway et al., 2011). However, the experimental studies revealed no clear pattern of results in relation to duration of diet. The reason for this inconsistency is unclear, and the minimum duration for a diet to affect cognition remains unknown.

The abundance of potential validated cognitive tasks available to researchers means that cognitive tasks can be combined and tailored to the specific requirements or hypotheses of the study. It has been previously recognized that there is no definitive guide for the selection of cognitive tests within the field of diet research (Wesnes, 2010). A failure to detect an effect of a diet on cognition may due to a true absence of cognitive change, or it may reflect poor sensitivity in the chosen cognitive tasks. Cognitive tasks that measure an appropriate function with low sensitivity will not likely demonstrate the expected effect of a diet intervention. Moreover, the difficulty of the cognitive task may determine its sensitivity to changes in diet (Hoyland et al., 2008). Thus, cognitive tasks of increasing difficulty should be used to detect the subtle effects of diet interventions, while alternate (or parallel) forms of the same task will also serve to reduce practice effects, and minimize vari- ability in task performance. The absence of alternate forms of a cognitive task greatly limits its utility in diet research in which the principal goal is to detect change.

Studies should aim to assess multiple cognitive domains to correctly interpret findings (Schmitt, Benton, & Kallus, 2005). The assessment of various cognitive domains may provide insight into the specificity of a diet-induced effect, as well as potentially determining the primary source and sequence of cognitive changes. Also, the optimal functioning of one domain may depend on the quality of another related domain. For instance, Tam and Schmitter- Edgecombe (2013) found that performance on a visual-spatial task (BVMT) was dependent on the quality of processing speed in healthy older adults. Changes in processing speed could influence performance on this task, but this can only be established if tests of processing speed are performed concurrently. Consensus about which cognitive tests to use has not been reached, but in order to satisfactorily compare studies, measures should be consistent and only changed with sufficient justification. Caution should be taken in developing series of cognitive tasks, since a lengthy battery can lead to fatigue and diminished motivation. An extensive battery has the potential to determine a wide range of effects and to determine if some domains are more sensitive to dietary change than others. Based on the findings in this review, we recommend a cognitive battery including a measure of numerical WM (e.g. digit span), a free word recall task of verbal memory (e.g. RAVLT), visual-spatial memory (e.g. ROCF), attention (e.g. RVIP), and inhibition (e.g. Go/No Go task). The items on this battery have been derived from thorough examination of the most sensitive cognitive tasks used in diet intervention studies (see Fig. 3 for a summary).

An interesting point to take into consideration is that particular subsets of macronutrients may differentially affect cognition, but this has not been well explored. Without an appropriate break- down of the types of macronutrients, it is difficult to conclude how specific components of a diet impact cognition. For instance, knowing the total carbohydrate intake does not inform us of the relative or absolute intake of simple or complex carbohydrates, which may prove vital since simple and complex carbohydrates differentially influence short-term cognitive performance (Benton et al., 2003) and may have long-term consequences. Based on the findings of the experimental studies, we speculate that decreases in energy intake by at least 20% may be sufficient to observe changes in cognitive performance, especially in memory tasks. Increases in fat greater than 30% may affect cognition, noting that fat type might be important here. The findings around protein and carbohydrates are mixed, but the degree of dietary manipulation will likely be dependent of the goals of the study.

It is worth noting that there may be populations more vulner- able to the effects of diet change. The cognitive impairments associated with increased weight have been well documented (e.g. Smith et al., 2011), and while the arrow of causality has yet to be determined, obese subjects may benefit most from dietary inter- vention that improves both weight loss and cognitive outcomes. A meta-analysis by Siervo et al. (2011) found that weight loss was associated with better performance on TMT-B, especially in older adults, supporting the notion that excess weight may be a risk factor for cognitive decline. Likewise, populations with existing impairments might see improvements in cognition, but the most sensitive cognitive domains have yet to be established. Recent

research has sought to use dietary interventions to enhance the cognitively impaired (e.g. Aquilani et al., 2008) or as a means of primary prevention of pathological cognitive aging (e.g. Martínez-Lapiscina et al., 2013a). These diets typically move away from one pattern of diet intake (e.g. the Western diet), to one associated with better health outcomes (e.g. the Mediterranean diet). To date, the majority of studies have improved cognitive performance following adherence a Mediterranean-like diet (Lee et al., 2015; Martínez-Lapiscina et al., 2013a, 2013b; McMillan et al., 2011). On the other hand, there is very little experimental evidence that shifting away from the Mediterranean diet towards the Western diet leads to impaired cognitive function, with only a few studies testing the effects of a high fat diet (Bayer-Carter et al., 2011; Edwards et al., 2011; Holloway et al., 2011; Lindseth et al., 2011). It would be interesting to investigate the effects of long-term consumption of a Western-like diet on cognitive function, but such long-term RCTs may be harmful and potentially unethical. One way around this complication is to group participants retrospectively, but no human studies exist to date. It may be that a Western diet high in fat and sugar has little effect on cognition in humans, but these effects remain relatively unexplored. Notably, no human studies have as yet examined if the effects of diet on cognitive function are reversible, which could be crucial in determining the role of diet in cognitive function.

8.2. Potential for remediation

Diet interventions may provide a practical approach to enhancing cognition, although such an approach would be well advised to wait until dietecognition relationships are considerably better understood. There is accumulating evidence that the ratio of various fats may be important. The ratio of omega-6 to omega-3 polyunsaturated fats, which may be up to 15 times higher in a typical Western diet (Simopoulos, 2008), is linked to cognitive decline later in life (Loef & Walach, 2013). To date, only one experimental study measured this ratio and found memory im- provements associated with its decrease (Nilsson et al., 2013). Meanwhile, the Mediterranean diet e one high in PUFAs and MUFAs may be effective for both weight loss maintenance (Panagiotakos et al., 2006) and improvements in cognition, espe- cially in older individuals. For instance, adherence to the Mediter- ranean diet for 6.5 years improved global cognitive performance (scores on MMSE and Clock Drawing Task) compared to a low-fat control diet (Martínez-Lapiscina et al., 2013a). Indeed, deter- mining the absolute changes in saturated, monounsaturated and polyunsaturated fats (as well as their relative ratios) associated with improved memory is essential since the relative intake of omega-6 to omega-3 fatty acids is positively associated with cognitive decline and incidence of dementia (Loef & Walach, 2013).

8.3. Conclusions

This is the first review of the experimental evidence of diet-induced changes in cognitive function. In summary, there was a trend showing that memory and attention were most sensitive to changes in energy and fat intake, but no consistently clear dietary effect was found since many studies yielded results in the opposing direction. Unfortunately, there is a paucity of high-quality long-term RCTs testing diet-induced changes in cognitive function. In order to strengthen the knowledge base, there is a clear need for better quality RCTs in the diet intervention literature to determine the causative role of diet in cognitive function. Future experimental research should aim to account for important confounds (e.g. physical activity levels), administer distinct and well-controlled dietary interventions and determine optimal diet duration. Diet intervention studies should also aim to report all pertinent nutritional information as well as the relevant statistical data. We will have a much clearer understanding of our current position and where the diet-cognition literature is headed once the findings have been compiled and analyzed quantitatively (i.e., a meta-analysis).

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