The effects of high-fat, high-sugar, and high-fat high-sugar diets on hippocampal-dependent spatial and contextual memory

Author:
Abbott, Kirsten

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Kirsten Nicole Abbott

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CARE AND USE OF ANIMALS

The experiments presented in this thesis conformed to the guidelines on ethical use of animals maintained by the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (7th Edition), and all procedures were approved by the Animal Care and Ethics Committee at the University of New South Wales. All efforts were made to minimise both suffering and the number of animals used.

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Gladding, J. M., **Abbott, K. N.,** Antoniadis, C. P., Stuart, A., & Begg, D. P. (2018). The effect of intrahippocampal insulin infusion on spatial cognitive function and markers of neuroinflammation in diet-induced obesity. *Frontiers in endocrinology*, *9*, 752.

Reichelt, A. C., Loughman, A., Bernard, A., Raipuria, M., **Abbott, K. N.,** Dachtler, J., ... & Moore, R. J. (2018). An intermittent hypercaloric diet alters gut microbiota, prefrontal cortical gene expression and social behaviours in rats. *Nutritional neuroscience*, 1-15.

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Abbott, K.N., Morris, M.J., & Westbrook, R.F. (2017). The effect of a high-sugar diet on context-dependent memory and neuroinflammation in rats. Poster presented at UNSW Brain Sciences Conference. Sydney, Australia.

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List of Abbreviations

ABS	Australian Bureau of Statistics
AD	Alzheimer's Disease
AIHW	Australian Institute of Health and Welfare
ANOVA	Analysis of Variance
ApoE e4	ε4 allele of the apolipoprotein E gene
ATT	Abdominal Adipose Tissue
ATSI	Aboriginal and Torres Strait Islander
AUC	Area Under the Curve
BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
BGL	Blood Glucose Level
BL	Baseline
BMI	Body Mass Index
BTACT	Brief test of Adult Cognition by Telephone
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
CANTAB	Cambridge Neuropsychological Test Automated Battery
CD	Control Diet
CDR	Cognitive Drug Research computerized assessment battery
CNS	Central Nervous System
CPFC	Context Pre-exposure Fear Conditioning
CVD	Cardiovascular Disease
DALYs	Disability-Adjusted Life Years
DG	Dentate Gyrus
DS	Digit Span
DSM-IV	Diagnostic and Statistical Manual 4th edition
ELISA	Enzyme Linked Immunosorbent Assay
EC	Entorhinal Cortex
EF	Executive Function
Expt	Experiment
FFQ	Food Frequency Questionnaire
GFAP	Glial Fibrillary Acidic Protein

GI	Glycaemic Index
GPA	Grade Point Average
GTT	Glucose Tolerance Test
HbA1c	Haemoglobin A1c
HDL	High Density Lipoprotein
HOMA	Homeostatic Model Assessment
hs-CRP	high-sensitivity C-reactive protein
HS	High-Sugar
HFFruc	High-fat High Fructose
HF	High-Fat
HFHS	High-Fat High-Sugar
HFruc	High fructose
HVLT	Hopkins Verbal Learning Test
IL-1β	Interleukin-1Beta
ITT	Insulin Tolerance Test
IQ	Intelligence Quotient
kcal	Kilocalories
KD	Ketogenic Diet
LDL	Low Density Lipoprotein
LEC	Lateral Entorhinal Cortex
LM	Logical Memory
LPP	Lateral Perforant Pathway
MCI	Mild Cognitive Impairment
MEC	Medial Entorhinal Cortex
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MPP	Medial Perforant Pathway
mRNA	messenger Ribonucleic acid
MUFA	Mono-Unsaturated Fatty Acid
MWM	Morris water maze
NAFLD	Non-Alcoholic Fatty Liver Disease
NCCD	Noncommunicable Chronic Disease
NES	Neuropsychological Evaluation System

NHMRC	National Health and Medical Research Council
NP	Neuropsychological
PP	Perforant Pathway
PR	Place Recognition
PUFA	Poly-Unsaturated Fatty Acid
QUICKI	Quantitative Insulin Sensitivity Check
RAM	Radial Arm Maze
RAVLT	Rey Auditory Verbal Learning Test
RAWM	Radial Arm Water Maze
RI	Retention Interval
SA	Spontaneous Alternation
SBP	Systolic Blood Pressure
SES	Socioeconomic Status
SFA	Saturated Fatty Acid
SSB	Sugar-Sweetened Beverage
TA	Temporoammonic (pathway)
TC	Total Cholesterol
TGLs	Triglycerides
TNF-α	Tumour Necrosis Factor-Alpha
Unsat	Unsaturated
w/w	Weight by weight
WAIS-III	Wechsler Adult Intelligence Scale 3rd edition
WAIS-5	Wechsler Adult Intelligence Scale 5th Edition
WC	Waist Circumference
WHO	World Health Organisation
WHR	Waist-to-Hip Ratio
WISC-III	Wechsler Intelligence Scale for Children 3rd Edition
WISC-5	Wechsler Intelligence Scale for Children 5th Edition
WISC-R	Wechsler Intelligence Scale for Children Revised
WMS-IV	Wechsler Memory Scale 4th Edition
WMS-R	Wechsler Memory Scale Revised
WRAT-III	Wide Range Achievement Test 3rd edition
WRAT-4	Wide Range Achievement Test 4th Edition

WRAT-R   Wide Range Achievement Test Revised

VO_{2max} maximal oxygen consumption

YRBSS   Youth Risk Behaviour Surveillance Survey

Chapter 1: Introduction

1.1. Global Food Trends: The Modern Diet

The past 50-years or so has been characterised by a considerable increase in per capita energy intake that is likely to continue for many years to come (Kearney, 2010). At the global level, per capita energy intake has steadily increased from 2196 kilocalories (kcal) per person per day in 1961 to 2884 kcal per person per day in 2013 (Figure 1.1; Roser & Ritchie, 2013). However, this trend differs when per capita energy intake is considered at a regional level; both North and South America have experienced a steady increase in energy intake between 1961 and 2013; in Western Europe and Oceania regions, such as Australia and New Zealand, average daily energy intake has remained relatively constant; and in Eastern Europe the energy intake in 2013 is comparable to that in 1961, despite there being a noticeable decrease in intake during the 1990s. The greatest increase in per capita energy intake is observed in Asia and Africa; indeed, while the per capita energy intake of developed regions, such as Northern America and Europe, has consistently been higher than that in developing regions, this gap has been slowly reducing since 1961 (Roser & Ritchie, 2013).

The global increase in energy intake is thought to be driven by three major food trends. The first is a change in dietary patterns (Baker et al., 2020; Drewnowski, 2018; Monteiro, Moubarac, Cannon, Ng, & Popkin, 2013). Nutritional guidelines for a healthy diet prescribe high intake of nutrient dense foods, such as fruits and vegetables, whole grains, and lean protein, as well as avoidance of or minimal consumption of so-called discretionary foods (Herforth et al., 2019; e.g. Australian Institute of Health and Welfare [AIHW], 2018 and United States Dietary Guidelines Advisory Committee, 2010). These are foods that are low in micronutrients but high in saturated fats, trans fats, and refined sugars. However, epidemiological research indicates that few individuals consume a diet

in line with these recommendations. For example, the most recent comprehensive survey of dietary patterns in Australia found that less than 10% of the population consume a healthy diet, with men and women of all ages not meeting recommended intake of fruits, vegetables, whole grains, and lean meats (Australian Bureau of Statistics [ABS], 2015). Furthermore, discretionary foods were regularly consumed and contributed to 35% and 41% of the total daily energy intake for adults and children, respectively. Similar dietary intake patterns have been reported in North America (Steele, Popkin, Swinburn, & Monteiro, 2017), South America (Parra et al., 2019; Rivera et al., 2016), the United Kingdom (Rauber et al., 2020), the Pacific Islands (Sievert, Lawrence, Naika, & Baker, 2019), and upper- and middle-income Asian countries (Baker & Friel, 2014).
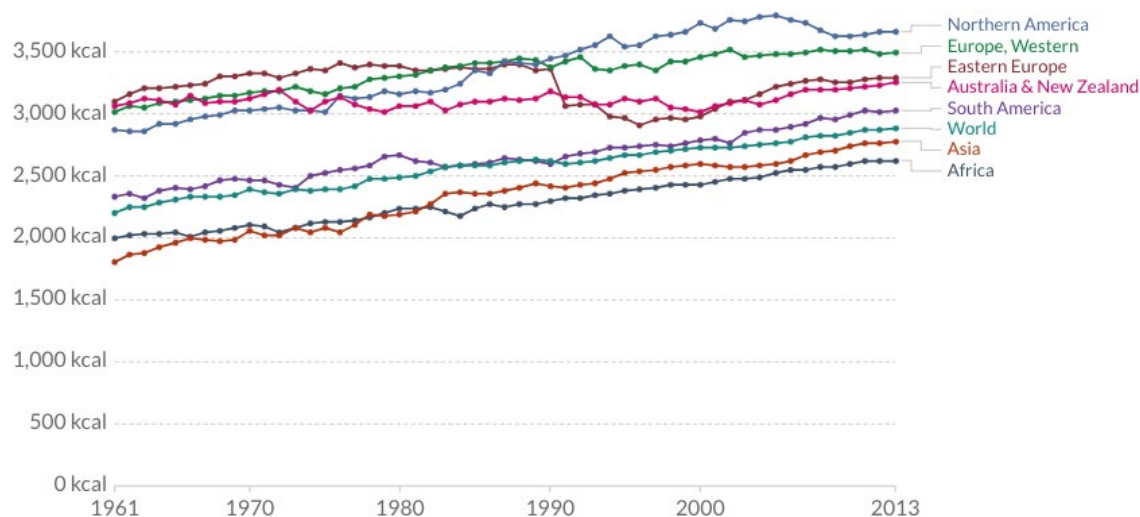
Figure 1.1. Average energy intake measured as kilocalories consumed per person per day by world region between 1961 and 2013. Figure taken from Roser and Ritchie (2013).

While the trend toward increased consumption of discretionary foods has been observed at a global level, the transition has been most notable in developing nations (Kearney, 2010). Many researchers have described a significant shift away from traditional diets to diets that are high in fat and sugar, a so-called "Westernisation" of dietary patterns, in regions including the Middle East (Golzarand, Mirmiran, Jessri,

Toolabi, Mojarrad, & Azizi, 2012), low-income Asian countries (Pingali, 2007; Soon & Tee, 2014), Latin America (Rozowski, Castillo, & Moreno, 2005), and Mediterranean countries (De Silva, Bach-Faig, Quintana, Buckland, de Almeida, & Sarra-Majem, 2009; Vareiro et al., 2009). Such findings indicate that discretionary foods are displacing the consumption of micronutrient-dense foods, particularly fruits and vegetables (Aburto, Pedraza, Sánchez-Pimienta, Batis, & Rivera, 2016; Koiwai et al., 2019; Sui, Wong, Louie, & Rangan, 2017; Wiggins & Keats, 2017), in both developed and developing nations. Moreover, correlational research across the lifespan demonstrates that increasing consumption of discretionary foods is associated with higher total daily energy intake and malnutrition (Bowman et al., 2004; Paeratakul, Ferdinand, Champagne, Ryan, & Bray, 2003; Schmidt et al., 2005).

The second food trend driving increased per capita energy intake is the dramatic increase in food portion sizes, especially in recent decades (Steenhuis & Poelman, 2017). Increased portion size has been observed both inside and outside of the home (Nielsen & Popkin, 2003). The largest increase in portion size has occurred in fast food establishments; not only have the size of products increased since their original introduction, but larger, super-sized portions have been added to many fast food menus (Rolls, 2003; Steenhuis, Leeuwis, & Vermeer, 2010; Young & Nestle, 2003). Discretionary foods are also being marketed in larger portion sizes in both supermarkets and convenience stores (French, Story, & Jeffery, 2001; Young & Nestle, 1995, 2003) Furthermore, there is now evidence that the increased portion size is also accompanied by an increase in the caloric content of many discretionary foods (Tran, Moran, & Bleich, 2019). Experimental research demonstrates that providing individuals with larger portion sizes results in increased food consumption, and thus greater energy intake, than when smaller portions of the same foods are served. This so-called "portion size effect" occurs

in adults whose weights are "normal" and in those who are overweight (Rolls, Morris, & Roe, 2002; Rolls, Roe, Kral, Meengs, & Wall, 2004), as well as in children (Kling, Roe, Keller, & Rolls, 2016; Smith, Conroy, Wen, Rui, & Humphries, 2013).

The final factor contributing to increasing per capita energy intake is the variety and the hyper palatability of discretionary foods (Johnson & Wardle, 2014). Many discretionary foods that fall into one category (e.g. biscuits, potato chips) come in a large variety of shapes, textures, and flavours. Such variety promotes overconsumption through sensory-specific satiety mechanisms. The phenomenon of sensory-specific satiety, whereby the palatability or the hedonic value of a food declines across its consumption (Rolls, Rolls, Rowe, & Sweeney, 1981), has been observed in people, regardless of sex, age, or body weight status (Brondel et al., 2007; Rischel, Nielsen, Gamborg, Møller, & Holm, 2016; Snoek, Huntjens, Van Gemert, De Graaf, & Weenen, 2004), and other animals such as laboratory rodents (Rolls, 1986). Sensory-specific satiety can be partially removed by altering properties (e.g. flavour, texture) of the same food or presenting a different type of food. Evolutionarily, sensory-specific satiety is thought to function as an adaptation that promotes variety in the diet, leading to consumption of a wide range of nutritionally-balanced foods. However, the variety of discretionary foods means that this adaptation has been hijacked, becoming maladaptive. Furthermore, the high-fat and sugar content of discretionary foods renders them hyper palatable and rewarding (Levine, Kotz, & Gosnell, 2003; Yanovski, 2003), even over riding sensory-specific satiety mechanisms (McCrickerd & Forde, 2016). Thus, variety in combination with the hyper palatability of discretionary foods promotes consumption beyond our energy requirements.

The aforementioned changes in global food consumption patterns are argued to largely be a consequence of globalisation (Kennedy, Nantel, & Shetty, 2004; Qaim, 2017) and the resultant modifications in food production and supply chains (Bentham et al.,

2020; Gouel & Guimbard, 2019; Qaim, 2017). For example, there have been notable modifications to agriculture and manufacturing practices, improvements in storage and transportation, and more efficient retailing and marketing in the last 50-years (Borusiak, & Pierański, 2017; Kennedy et al., 2004). Moreover, economic changes, such as increased income and urbanisation, and social drivers, such as rural to urban migration, have also contributed to changes in dietary practices. A detailed examination of these processes is beyond the scope of the present thesis and can be found elsewhere (e.g. Baker et al., 2020; Costa-Font & Mas, 2016; Kearney, 2010; Kennedy et al., 2004; Popkin, 2001). However, one of the most significant consequences of globalisation and the resultant changes in food systems is that food, and in particular discretionary food, has become increasingly affordable and accessible in both developing and developed nations (Zobel, Hansen, Rossing, & von Scholten, 2016). The affordability and accessibility of discretionary foods will be discussed separately in the following sections.

1.1.1. Affordability

The term affordability refers to the low cost and convenience of discretionary foods when compared to nutrient-dense foods. It has long been established that food cost directly influences diet quality (James, Nelson, Ralph, & Leather, 1997; Darmon & Drewnowski, 2015). Experimental research demonstrates that consumers will purchase fewer items when food prices rise and more items when food prices drop (Andreyeva, Long, & Brownell, 2010; see Epstein et al., 2012). For example, Privitera, Gillespie, & Zuraikat (2019) found that adults provided with pre-paid debit cards and told to purchase any food were more likely to select energy dense foods when they were inexpensive relative to nutrient dense foods, but more likely to select micronutrient-dense foods when the prices were reversed. However, recent decades have seen discretionary foods become inexpensive relative to micronutrient-dense foods, particularly in developing nations

(Drewnowski, 2010; Headey & Alderman, 2019); this is likely due to micronutrient-dense foods becoming more expensive and discretionary foods becoming less expensive (Bachewe & Minton, 2019; Capacci, Mazzocchi, & Shanker, 2012; Jones, Conklin, Suhrcke, & Monsivais, 2014; Wiggins, Keats, & Han, 2015). For example, correlational research demonstrates an inverse relationship between price and energy density of foods sold in fast food restaurants (Wellard, Havill, Hughes, Watson, & Chapman, 2017) and supermarkets (Darmon, Briend, & Drewnowski, 2004). Furthermore, discretionary foods are almost twice as likely as nutrient-dense foods to be on sale (Riesenberg et al., 2019; Furey et al., 2019; Zorbas et al., 2019), which increases the likelihood of their purchase (Bell, Chiang, & Padmanabhan, 1999; Hawkes, 2009). For example, McPoland, Furey, and McLaughlin (2020) found that 76.5% of adult respondents in a quantitative survey reported that they more readily purchased confectionary and snack foods when they were on sale. In terms of convenience, many discretionary foods are either fully prepared or partially prepared (De Boer, McCarthy, Cowan, & Ryan, 2004), requiring less time and effort for their consumption than nutrient dense foods (Darmon, Briend, & Drewnowski, 2004; Patel & Rathod, 2017). In an increasingly time-poor global society, consumer demand for pre-prepared or easy to prepare foods has dramatically increased (Harris & Shiptsova, 2007; Jekanowski, Binkley, & Eales, 2001; Osman et al., 2014; Verma & Chawla, 2020). Thus, discretionary foods are highly desirable to consumers as they require minimal time investment, but also because they can be consumed with minimal physical or mental effort (Buckley, Cowan, & McCarthy, 2007; Park & Capps, 1997; Sheely, 2008).

1.1.2. Accessibility

It is now easy to access discretionary foods. Firstly, there has been a dramatic increase in both the number and density of supermarkets, convenience stores, and fast

food outlets in developed and developing nations (Reardon, Timmer, Barrett, & Berdegue, 2003). This has resulted in so-called "food deserts", regions that contain plentiful access to food but with few food options that are nutritious or fresh (Beaulac, Kristjansson, & Cummins, 2009). Secondly, consumers are now able to purchase discretionary foods in an increasing number of locations. Such foods are not only stocked by traditional food retailers, but are also available at sporting arenas, newsagents, vending machines, and petrol stations (Lucan et al., 2018). Moreover, online delivery services provided by supermarkets and restaurants and the ever-increasing number of delivery apps, such as Uber and Deliveroo, have dramatically increased in the last 15-years such that people can now access discretionary foods at the click of a button (Statistica, 2020). As a result, discretionary foods are readily available where people live, work, go to school, exercise, socialize, and engage in sport and other activities. Thirdly, there has been a trend toward extended trading hours of many food retailers, particularly those that offer discretionary foods that can be purchased and immediately consumed. Many supermarkets are open for 16+ hours/day (Borusiak & Pierański, 2017), and convenience stores and fast food retailers provide 24-hour/day services. For example, 90% of convenience stores in the United States operate 24-hours/day (National Association of Convenience Stores, 2020). Finally, the increasing rate of urbanization observed around the world, but particularly in developing nations, has resulted in an increased proportion of individuals living in urban areas (Seto & Ramankutty, 2006). Research in developing countries demonstrates that rural living is associated with increased consumption of healthy and traditional foods when compared to urban living, primarily as a result of increased accessibility to high-fat and sugar food products in the urban environments (d'Amour, Pandey, Reba, Ahmad, Creutzig, & Seto, 2020; Downs et al., 2012; Sievert et al., 2019; Wang et al., 2015).

A growing body of literature demonstrates that the increased accessibility to discretionary foods has changed dietary intake patterns (Pan & Zinkhan, 2006; reviewed in Fleischhaker, Evenson, Rodriguez, & Ammerman, 2011). For example, the last four decades has been characterized by increased consumption of food purchased away from the home (Guthrie, Lin, & Frazao, 2002; Kant & Graubard, 2004; Lachat et al., 2012), which is associated with increased consumption of discretionary foods and decreased intake of nutrient-dense foods such as fruits and vegetables (Boutelle, Fulkerson, Neumark-Sztainer, Story, & French, 2007; Davis & Carpenter, 2009; Fraser, Edwards, Cade, & Clarke, 2010). Furthermore, cross-sectional research demonstrates that increased access to convenience stores and fast food outlets is associated with poor diet quality and less healthy dietary habits (Lind, Jensen, Glümer, & Toft, 2016; Moore, Diez Roux, Nettleton, Jacobs, & Franco, 2009). This trend is observed across the lifespan (Bowman, Gortmaker, Ebbeling, Pereira, & Ludwig, 2004; Boone-Heinonen et al., 2011; He, Tucker, Gilliland, Irwin, Larsen, & Hess, 2012; Shareck, Lewis, Smith, Clary, & Cummins, 2018), and is particularly noticeable in low socioeconomic communities (Livingstone et al., 2017; Pearce, Blakely, Witten, & Bartie, 2007) and ethnic minorities (Dunn, Sharkey, & Horel, 2012; Hickson et al., 2011).

1.2. Global Food Trends and Noncommunicable Chronic Diseases

The last half century has been characterized by a significant rise in prevalence of non-communicable chronic diseases (NCCDs), such as obesity, type 2 diabetes, cardiovascular disease, and some cancers (World Health Organization [WHO], 2018a). The rise in NCCDs is recognized as a significant contributor to global burden of disease. Epidemiological research in adults living in both developing and developed countries shows that morbidity and mortality arising from NCCDs exceeds that from

communicable diseases (Abegunde, Mathers, Adam, Ortegon, & Strong, 2007; WHO, 2018b; Wu et al., 2015). For example, NCCDs were responsible for 71% of the 57 million deaths that occurred globally in 2016 (WHO, 2018a). Moreover, increasing rates of NCCDs have been observed in children and adolescents (AIHW, 2005; Dalwood, Marshall, Burrows, McIntosh, & Collins, 2020), leading to health issues in adulthood and reduced life expectancy (Di Cesare et al., 2019).

The speed at which NCCD prevalence has increased in recent decades implies that it cannot be due to changes in the human genome and, therefore, must be due to environmental factors. There are many such factors, but the shift in global food trends to a so-called Western diet is thought to be the most significant contributor (Danaei et al., 2009; Jayedi, Soltani, Abdolshahi, & Shab-Bidar, 2020; Malik et al., 2010; Popkin, 2006; Rauber et al., 2018). Consistent with this proposal, research in traditionally hunter-gatherer communities demonstrates that NCCDs are rare in individuals that adhere to their traditional paleolithic diet (Froment, 2001; Lindeberg, Eliasson, Lindahl, & Ahrén, 1999; O'Dea, White, Sinclair, 1988). Contrastingly, communities that have transitioned to a Western-style diet have significantly increased rates of NCCDs. For example, research conducted with Aboriginal and Torres Strait Islander (ATSI) communities in rural Australia that have transitioned to a Western-style diet across the past 20-years had greater rates of NCCDs than those that adhered to their traditional diets (O'Dea, Spargo, & Nestel, 1982). Furthermore, rates of NCCDs diminished in the ATSI peoples who returned to their traditional diets (O'Dea, 1984). Together, this evidence supports the hypothesis that the environmental factor of diet, rather than genetic factors, contributes significantly to NCCDs.

A recently published meta-analysis has demonstrated the relationship between poor dietary intake and NCCDs (Afshin et al., 2019). Health data collected between 1990

and 2017 from 195 countries were used to estimate the proportion of disease-specific burden attributable to dietary factors. The analysis revealed that suboptimal diets were responsible for 10.9 million deaths, or 22% of deaths among adults, and 255 million disability-adjusted life years (DALYs), or 16% of DALYs among adults. The analysis further revealed that 50% of deaths and 34% of DALYs were attributed to the consumption of discretionary foods. These figures highlight that diet-related NCCDs are a significant, albeit preventable, contributor to the global burden of disease and premature death.

Of particular concern is the well-established relationship between increasing intake of discretionary foods and the increasing prevalence of people who are overweight and obese over the last 40-years (Kopp, 2019; Malik, Willett, & Hu, 2013; Mozaffarian, Hao, Rimm, Willet, & Hu, 2011; Popkin, 2001). The most common measure of overweight and obesity is the Body Mass Index (BMI). The WHO (2006) categorise individuals with BMI > 25 kg/m^2 as overweight and BMI > 30 kg/m^2 as obese. The global rates of obesity have nearly tripled since 1975 (WHO, 2021) and obesity is now recognised as a global pandemic (Popkin, Adair, & Ng, 2012). For example, current global prevalence estimates are that at least 1.9 billion adults are overweight, of whom 650 million are obese. In Australia, data collected in the most recent Australian health survey (ABS, 2015) indicated that approximately 36% of the adult population were overweight and 28% were obese, and that 20% of children and adolescents were overweight and 7.4% were obese.

The accumulation of body fat in overweight and obese individuals has a detrimental effect on physical health. Epidemiological studies have demonstrated a positive association between BMI and risk of NCCDs, including metabolic disorders (Alexander, Landsman, & Grundy, 2008; Han, Freskens, Lean, & Seidell, 1998),

cardiovascular disease (CVD; Katagiri, Yamada, & Oka, 2007), non-alcoholic fatty liver disease (NAFLD; Loomis et al., 2016), and some cancers (Renehan, Zwahlen, & Egger, 2015). Increased BMI is also associated with reduced life expectancy (National Health and Medical Research Council [NHMRC], 2013). Experimental dietary manipulation in animal models of obesity has demonstrated that increased body fat is associated with metabolic disturbances and NAFLD (Buettner, Schölmerich, & Bollheimer, 2007). Such findings resemble those which are observed in humans consuming high-fat and sugar diets, and thus provides more direct evidence of a causal association between dietary intake, obesity, and NCCDs.

1.3. Modern Diet and Cognitive Function: Epidemiological Research

Regular consumption of discretionary foods has a detrimental effect not only on physical health but also on cognitive function across the lifespan (see Beilharz, Maniam, & Morris, 2015; Burrows, Goldman, Pursey, & Lim, 2017a; Yeomans, 2017). The following sections provide an overview of the evidence linking obesity or the excessive intake of fat and/or sugar with cognitive impairment.

1.3.1. Obesity and Cognitive Impairment

A growing body of literature highlights an inverse association between obesity and cognition that is present across the lifespan (Prickett, Brennan, & Stolwyk, 2015 for systematic review; Table 1.1.). Academic performance is negatively associated with obesity in children and adolescents (Caird et al., 2011). Cross-sectional research demonstrates poorer academic performance in standardized tests of reading and mathematics in overweight and obese students than in normal-weight students attending elementary school, high school, and university (Datar, Strum, & Magnabosca, 2004; Li, Dai, Jackson, & Zhang, 2008). A recent meta-analysis that included 60 cross-sectional

studies examined the relationship between BMI and academic performance in students aged four to 34-years (He, Chen, Fan, Cai, & Huang, 2019). The analysis revealed a negative association between BMI and academic performance. It also found that this association was larger in American and European than Asian samples; however, this difference in effect size between world regions may be an artefact of using BMI as a measure of adiposity, as BMI has been shown to be a poor indicator of body fat percentage in Asian samples (WHO, 2004).

Associations between obesity and global cognitive function have also been observed in children and adolescents (Smith, Hay, Campbell, & Trollor, 2011). For example, in a nationally representative sample of eight to 16-year-old children and adolescents living in North America, BMI was negatively associated with general cognitive ability that was assessed using standardised tests of cognitive function (Li et al., 2008). Similarly, in a sample of 400 adolescents aged 12 to 15-years, cognitive function assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) was reduced in participants whose BMI placed them in the obese range when compared to participants whose BMI placed them in the overweight or normal range (Meo et al., 2019).

A relationship between obesity and global cognitive impairment has also been reported in adults. One of the earliest demonstrations of this relationship was reported by Sørensen, Sonne-Holm, Christensen, & Krèiner-Møller (1982). Data from 4,525 young Danish males, collected at time of their draft to national service, revealed that those who were obese had significantly poorer cognitive performance on a standardized intelligence test than those who were of normal weight. In the Framingham Heart Study, Elias and colleagues (2003) examined cognitive functioning in a sample of middle-aged and elderly males (n = 551) and females (n = 872) using the Kaplan-Albert Neuropsychological Test

Battery. Cognitive function was significantly reduced in obese participants when compared to non-obese participants for both males and females. However, the relationship between obesity and cognition only remained significant in males after controlling for age, CVD risk factors, and education. Finally, longitudinal research has demonstrated that a BMI in the overweight or obese range in middle-aged adults was associated with poorer cognitive ability and steeper rate of cognitive decline in old age (e.g. Dahl et al., 2010, 2013; Hassing, Dahl, Pedersen, & Johansson, 2010; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009)

Much of the research examining the relationship between obesity and cognitive function has examined domain specific deficits in cognition (Smith et al., 2011; Prickett et al., 2015). Evidence from children and adults has shown associations between obesity and impairments in visuospatial organisation and visuospatial memory. For example, Li and colleagues (2008) found that the BMI of eight to 16-year-old children was negatively correlated with visuospatial organisation, as measured by the block design subtests of the Wechsler Intelligence Scale for Children Revised (WISC-R), which remained significant after controlling for socioeconomic variables, physical activity, blood pressure, and serum lipid profiles. Similarly, Elias et al. (2003) found a negative relationship between BMI and visuospatial memory using the Visual Reproduction subtest of the Wechsler Memory Scale (WMS) in adult males aged 55 to 88-years, which remained significant after controlling for CVD risk factors.

Deficits in language and both verbal learning and memory have also been observed in obese adults. For example, Elias and colleagues (2003) found that increased BMI was associated with reduced verbal episodic memory, assessed using the Logical Memory (LM) subtest from the WMS, and reduced language ability, indexed by performance in a word fluency task that requires participants to name as many words as

they can that start with a particular letter in one minute. Gunstad et al. (2006), Cook et al. (2017) and Hartanto and colleagues (2018, 2019) assessed verbal learning and memory in healthy adults, aged from 21 to 80-years, 18 to 35-years, and 32 to 84-years, respectively, used a word learning task. The task assessed learning of unrelated words across repeated trials, free recall of the learned words at a short and long delay, and recognition of the learned words from word pairs. The findings were impairments in learning, memory recall, and recognition in overweight and obese adults when compared to normal weight adults (Gunstad et al., 2006); poorer verbal memory in obese adults when compared to normal-weight adults (Cook et al., 2017); and a negative association between memory recall and BMI (Hartanto & Yong, 2018; Haranto et al., 2019). These results remained significant after controlling for demographics, SES, and various health covariates that included: neurological disease and CVD (Gunstad et al., 2006); depression symptoms, physical activity, systemic inflammation, and omega-3 fatty acid index (Cook et al., 2017); and diabetes, hypertension, stroke, and smoking status (Hartanto & Yong, 2018; Hartanto et al., 2019).

Finally, executive functioning, at both a global and domain specific level, has been shown to be negatively associated with BMI in both children and adults. For example, Laurent et al. (2020) found a negative relationship between BMI and performance in the Wisconsin Card Sorting Test and the Matrix Reasoning subtest of the WISC 5th edition, indicating reduced abstract reasoning, working memory, and cognitive flexibility, in nine to 10-year-old children. Similarly, Meo et al. (2019) showed that performance on the Attentional Set Shifting and Intra-Extra Dimensional Set Shift tasks of the CANTAB, which measure cognitive flexibility and attention, was significantly poorer in obese than normal-weight 12 to 15-year-old students. In adults, healthy young women aged 18 to 35-years had poorer performance in a Go/No-go task when compared

to normal-weight participants, indicating poorer behavioural inhibition (Cook et al., 2017). This difference remained significant after controlling for depression symptoms, physical activity, systemic inflammation, and omega-3 fatty acid index as co-variates. Gunstad and colleagues (2007) found that visual working memory was poorer in obese/overweight adults than normal weight adults, as well as a negative association between BMI and visual working memory. Notably, the association remained significant when the data from young (21 to 50-years) and older (50 to 80-years) participants was examined separately, indicating the significant results were not driven by the performance of older adults but rather was present across both age groups. Finally, global executive functioning, as measured by a validated neuropsychological test battery, has been shown to be inversely associated with BMI in adults aged 21 to 82-years (Gunstad et al., 2007).

While obesity is associated with a number of cognitive impairments, evidence from cross-sectional research suggests that even in the absence of obesity, increased levels of adipose tissue are associated with cognitive deficits in all age groups. For example, experimental research in children aged seven to nine-years demonstrated an association between different adipose tissues and a selective impairment in hippocampal-dependent memory (Khan et al., 2015a). In this study, participants completed a computerised task that involved two separate study and test blocks. One of the blocks assessed hippocampal-independent item memory; participants first studied individual creatures and at test were required to identify the previously studied creature from a line-up that contained one familiar and two novel creatures. The other block assessed hippocampal-dependent relational memory; participants first studied creatures paired with a unique scene background and at test were required to select the creature that had been paired with a given scene from an array of three creatures. One of the creatures had been studied with the scene and two had been studied with a different scene; thus,

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familiarity across the creatures was matched. Khan et al. found that hippocampal-dependent relational memory was negatively associated with both total abdominal AT and subcutaneous abdominal AT, measured using Dual Energy X-Ray Absorptiometry (DEXA); however, there were no associations between hippocampal-independent item memory and either measure of AT.

Correlational research in children and adults has demonstrated associations between adiposity and academic performance, as well as impairments in a number of cognitive domains. For example, visceral AT has been shown to be negatively correlated with reading and writing ability in pre-school aged children (Khan et al., 2020). Similarly, abdominal AT was negatively associated with reading, spelling, and mathematical ability in seven to nine-year-old children, and the combination of whole-body AT and abdominal AT was inversely associated with performance on a Go/No-Go task, indicating that increasing levels of AT were associated with poor behavioural inhibition (Kamijo et al., 2012)

In young, middle-aged, and older adults, waist circumference (WC) and waist-to-hip ratio (WHR), which provide estimates of abdominal adipose tissue (Hu, 2008), have been associated with impaired memory and executive function. For example, in a sample of adults aged 23 to 98-years, WC and WHR were negatively associated with scores on the Mini-Mental State Examination (MMSE) and with performance on neuropsychological tests assessing visuospatial organisation, abstract reasoning, and working memory (Dore, Elias, Robbins, Budge, & Elias, 2008). These associations remained significant after controlling for demographic factors and components of metabolic syndrome; however, only the associations between WC and WHR with abstract reasoning remained significant after controlling for physical activity levels. Similarly, in a sample of adults aged 32 to 84-years, WC and WHR, but not BMI, were negatively

associated with performance on neuropsychological tests assessing verbal episodic memory and executive functioning (Hartanto & Yong, 2018). Finally, Hartanto et al. (2019) found that WHR and BMI were negatively correlated with episodic memory and executive functions in adults aged 33 to 84-years. They further found that WHR, but not BMI, was predictive of decline in episodic memory in all age groups over a nine-year period, and predictive of decline in executive function in young (33 to 45-years) and middle-aged (46 to 55-years) adults, but not older (56+ years) adults, over the same time period.

Chapter 1

Table 1.1. Summary of experimental details from epidemiological studies that have examined the relationship between obesity and/or adiposity measures and performance across a number of cognitive domains. (ATT = Abdominal Adipose Tissue; BMI = Body Mass Index; BTACT = Brief test of Adult Cognition by Telephone; CANTAB = Cambridge Neuropsychological Test Automated Battery; CVD = Cardiovascular Disease; DS = Digit Span; EF = Executive Function; IQ = Intelligence Quotient; MMSE = Mini-Mental State Examination; NP = Neuropsychological; WC = Waist Circumference; WHR = Waist-to-Hip Ratio; WAIS-III = Wechsler Adult Intelligence Scale 3rd edition; WISC-5 = Wechsler Intelligence Scale for Children 5th Edition; WISC-R = Wechsler Intelligence Scale for Children Revised; WMS-R = Wechsler Memory Scale Revised; WRAT-III = Wide Range Achievement Test 3rd edition; VO$_{2max}$ = maximal oxygen consumption).

Author	Participants (sample size)	Measure of Adiposity	Test(s) Administered (test battery)	Cognitive Domain Assessed	Covariates or Confounding Variables	Major Findings
Bleiweiss-Sande et al. (2019)	Children (n = 868) aged 8 to 10-years	BMI	DS-forward	Short-term memory	Confounders: age, sex, race/ethnicity, maternal and paternal education level, breakfast consumption on the day of the tests, BMI for age Z-score, and physical activity.	No association between BMI and score.
			DS-backward	Working memory		No association between BMI and score.
			Stroop colour-word task	Attention and behavioural inhibition (EF)		Higher BMI was significantly associated with lower Stroop test score.
			Massachusetts Comprehensive Assessment System develop by the Massachusetts Department of Elementary and Secondary Education.	Academic performance	Confounders: age, sex, race/ethnicity, maternal and paternal education level, BMI for age Z-score, and physical activity.	Higher BMI was significantly associated with numeracy score.

Study	BMI measure	Task	Domain	Covariates/Cofounders	Results
Cook et al. (2017)	Adults (n = 299) aged 18 to 35-years; females only. Participants had no medical conditions as obese and did not use medication regularly (oral contraceptive pill and asthma medications were allowed). BMI. Used to group participants as obese (BMI ≥ 30 kg/m²) and normal weight (BMI 18.5 – 24.9 kg/m²)	Go/No-Go Test (IntegNeuro)	Cognitive control (EF)	Covariates: systemic inflammation, omega-3 index (O3I), depression symptoms, and physical activity.	Significantly poorer performance by obese than normal-weight participants.
		Continuous Performance Task (IntegNeuro)	Attention (EF)		Significantly poorer performance by obese than normal-weight participants.
		Attention Switching Task and Choice Reaction Time (IntegNeuro)	Information processing		No differences between obese and normal-weight.
		List Learning Task, DS-forward, and DS-backward (IntegNeuro)	Verbal memory		Significantly poorer performance by obese than normal-weight participants.
		Maze Test (IntegNeuro)	Visuospatial working memory (EF)		No differences between obese and normal-weight.
Datar et al. (2004)	Children (n = 11,192) aged 5 to 6-years BMI	Standardised reading and maths tests as part of the elementary school curriculum conducted at beginning of school day, physical activity	Academic performance	Cofounders: socioeconomic factors (race/ethnicity, mother's education, annual family income), hours of television watching per school day, physical activity, potential confounds.	BMI negatively correlated with baseline test scores for maths and reading. Association between BMI and math score remained significant after controlling for sociodemographic factors and potential confounds.

Study	Sample	Predictor	Test battery	Cognitive domain	Method	Results
					parent-child interaction, and child birth weight. First grade scores were additionally controlled for baseline scores.	Differences detected at baseline remained at the end of first grade.
			kindergarten (baseline scores) and end of first grade.			Significant negative correlation with both WC and WHR. Associations remained significant at step 1 and 2 of regression analysis.
Dore et al. (2008)	Adults (n = 917) aged 23 to 98-years with no history of stroke, or dementia, no active dialysis treatment, and no chronic alcohol abuse.	WC and WHR	Test battery that includes subtests from the WMS-R, WAIS-III, and Halstead-Reitan NP Test Battery	Global composite	Simple correlations followed by regression analysis. Co-variates in multiple regression analysis: age, sex, education, and number of prior cognitive examinations at step 1; smoking (cigarettes per week), the ratio of triglycerides to high density lipoprotein cholesterol (TG/HDL-C), CVD, systemic inflammation, systolic blood pressure, depressed mood, and blood glucose in step 2; physical activity in step 3.	Significant negative correlation with both WC and WHR. Associations remained significant at step 1 and 2 of regression analysis.
				Verbal memory		Significant negative correlation with both WC and WHR. Neither association remained significant after regression analysis.
				Visuospatial organisation		Significant negative correlation with both WC and WHR. Associations remained significant at step 1 and 2 of regression analysis.
				Working memory (EF)		Significant negative correlation with both WC and WHR. Associations remained significant at step 1 and 2 of regression.
				Scanning and tracking (EF)		Significant negative correlation with both WC and WHR. Associations remained significant at step 1 and 2 of regression.

Study	Sample	Measure	Cognitive domain	Results
Elias et al. (2003)	Adults aged 55 to 88-years with no history of stroke, dementia, or CVD. No differences between normal-weight and overweight participants, who were Male participants (n = 551).	Average BMI (mean of 10 measurements taken across 20-years). Kaplan-Albert Neuropsychological Test Battery consisting of subtests from the WAIS, WMS, and Multilingual Aphasia Examination. MMSE Tests administered 4 to 6-years after final BMI measurement.	Abstract reasoning (EF)	Significant negative correlation with both WC and WHR. Association for WC remained significant at step 1, 2, and 3 of regression. Association for WHR not significant after regression.
			Cognitive function	Significant negative correlation with both WC and WHR. Association for WC remained significant at step 1 of regression. Association for WHR not significant after regression.
			Visuospatial memory	Obese males performed significantly worse than non-obese males. No differences in females.
			Verbal memory	No differences between obese and non-obese for males or females.
			Verbal episodic memory	Obese males performed significantly worse than non-obese males. No differences in females.
			Attention & Concentration (EF) Covariates: age, education level, occupational level, CVD risk factors (alcohol consumption, smoking, serum cholesterol, and type 2 diabetes).	Obese males performed significantly worse than non-obese males. No differences in females.

Study	Participants	Measure	Test	Cognitive domain	Covariates	Results
	Female participants (n=872). combined into a "non-obese" group			Verbal fluency (EF)		Obese males performed significantly worse than non-obese males. No differences in females.
				Concept formation (EF)		No differences between obese and non-obese for males or females.
				Total test score		Obese males, but not females, had significantly reduced scores than their non-obese counterparts.
Gunstad et al. (2006)	Adults (n = 486) aged 21 to 80-years with no history of neurological disorders, head injury, CVD, or diabetes.	BMI	List learning task	Verbal learning, recall, and recognition memory	Covariate: age.	Obese participants had reduced learning, recall, and recognition when compared to overweight or normal-weight participants. No differences between overweight or normal-weight. Younger performance significantly better for learning, recall, and recognition. No interaction between BMI and Age.
Gunstad et al. (2007)	Adults (n = 400) aged 20 to 82-years with no	BMI	DS-forward (IntegNeuro) Choice Reaction Time (IntegNeuro)	Attention	Covariates: estimated IQ, years of education, sex, and self-reported levels of depression, anxiety, and stress.	Negative correlation between BMI and performance on all tests. In MANCOVA, effect of age on all tests (younger outperform

Author	Sample	Predictor	Tasks	Domain	Analysis	Results
	history of neurological disorders, head injury, CVD, or diabetes.		Switching of Attention-number (IntegNeuro)			older). Effect of BMI on all tests except DS-forward (Overweight/obese poorer performance than normal-weight). No Age x BMI interaction.
			Attention-number (IntegNeuro)		Separate MANCOVA for attention and executive functioning using the independent variables BMI and age group (20 to 50-years, and 51+ years).	Negative correlation between BMI and performance on all tests.
			Visual Memory Span (IntegNeuro)			In MANCOVA, effect of age on all tests (younger outperform older). Effect of BMI on all tests except switching of attention (Overweight/obese poorer performance than normal-weight). No Age x BMI interaction.
			Verbal interference (IntegNeuro)	Executive function		
			Switching of Attention- letter/number (IntegNeuro)			
			Maze errors (IntegNeuro)			No Age x BMI interaction.
Hartanto & Yong (2018)	Adults (n = 3,712) aged 32 to 84-years	BMI and WHR	DS-backward, Categorical fluency, Number series, Backward counting, Stop and go switch task (BTACT)	Executive function	Covariates in multiple regression models: Model 1: age, sex, education, household income, and subjective social status. Model 2: hypertension, diabetes, stroke, total number chronic diseases in previous 12-months,	Significantly associated with BMI in model 1, but not in models 2, 3 and 4. Significantly associated with WHR in models 1, 2, 3 and 4. No interactions between BMI and age, nor BMI and sex.
			Immediate and delayed word list recall (BTACT)	Episodic memory		Significantly associated with BMI in model 1 but not in models 2, 3 and 4.

				smoking status, alcohol intake, physical activity.	Significantly associated with WHR in models 1, 2, 3 and 4.
				Model 3: Big 5 personality traits	No interactions between BMI and age, nor BMI and sex.
Hartanto et al. (2019)	Adults (n = 2,652) aged 33 to 84-years (M_{age} = 55). Cognitive tasks measured at time point 1 and 2. BMI and WHR measured at time 1 and 2.	DS-backward, Categorical fluency, Number series, Backward counting, Stop and go switch task (BTACT)	Executive function	Model 4: self-perceived obesity	Time 1: negatively correlated with BMI and WHR measured at time 1, and negatively correlated with WHR measured at time 2. Time 2: no correlation with BMI and WHR at time 2.
				Confounders: age at assessment, sex, education attainment, and household income.	Time 1: negatively correlated with BMI and WHR measured at time 1. No correlation at time 2.
		Immediate and delayed word list recall (BTACT)	Episodic memory	Covariates: smoking history, alcohol abuse, hypertension, diabetes status, and stroke.	Time 2: negatively correlated with WHR measured at time 1, and no correlation with BMI and WHR measured at time 2.
		Composite of all tests	Global cognitive function		Time 1: negatively correlated with WHR measured at time 2.

	Sample	Adiposity measure	Task	Cognitive domain	Covariates / Confounders	Findings
						Time 2: no correlation with BMI and WHR measured at time 1 or time 2.
Kamijo et al. (2012)	Children (n = 126) aged 7 to 9-years	BMI; AAT; percent whole body fat mass (%WBFM)	Go/No-Go task	Cognitive control		Significant negative associations between weight measures and No-Go performance for BMI, %WBFM, and AAT.
			Reading, Spelling, Arithmetic sections from WRAT-III	Academic performance	Confounders: age, sex, SES, IQ, and fitness (VO$_{2max}$ percentile).	Significant negative associations between (1) %WBFM and scores for reading and spelling (2) AAT and scores for reading, spelling, and arithmetic (3) BMI and scores for spelling and arithmetic.
Khan et al. (2015a)	Children (n = 126) aged 7 to 9-years	Percent whole-body fat mass (%WBFM); total AAT; subcutaneous AAT; visceral AAT.	Computerised memory task.	Hippocampal-dependent recognition memory (RM) & hippocampal-independent item memory (IM)	Covariates: age, sex, pubertal timing, IQ, aerobic fitness (VO$_{2max}$ percentile), and BMI for age Z-score. Dependent variables: behavioural accuracy and preferential disproportionate viewing (PDV).	Behavioural accuracy: (1) Children with BMI in normal range: no association between adiposity measures and RM or IM. (2) Children with BMI in overweight/obese range: all measures of adiposity negatively correlated with RM. Total AAT was predictive of RM. Subcutaneous AAT negatively correlated with IM.

Khan et al. (2015b)	Children (n = 150) aged 7 to 10-years.	BMI	Colour-shape switching paradigm: homogenous trials - all trials required a response based on one dimension (colour or shape) alone.	Cognitive control: behavioural inhibition	Confounders: age, sex, SES, IQ, aerobic fitness (VO$_{2max}$ percentile), and BMI for age Z-score.
			Colour-shape switching paradigm: heterogeneous trials - trials required selection of the dimension (colour or shape) that they were required to respond to, and then respond accurately based on this dimension.	Cognitive control: behavioural inhibition, working memory, and cognitive flexibility	Dependent variables: Accuracy of responding and reaction time.

PDV:

No associations between adiposity measures and RM or IM in children with BMI in normal range, or BMI in overweight/obese range.

Children with BMI in obese range had a higher global switch cost* for accuracy compared to children with BMI in normal range.

BMI was positively correlated with global switch cost* for accuracy.

Global switch cost: Difference in performance between homogenous and heterogeneous trials.

Study	Participants	Measure	Test/Task	Outcome	Findings
Khan et al. (2020)	Children (n = 57) aged 4 to 5-years overweight (BMI ≥ 25 kg/m²) and normal weight (BMI 18.5 – 24.9 kg/m²)	BMI and VAT	Woodcock-Johnson Test of Early Cognitive and Academic Development	Academic performance	VAT negatively correlated with early academic skills and expressive language. Early academic skills significantly reduced in children in overweight/obese range compared to children in normal range.
Laurent et al. (2020)	Children (n = 4,524) aged 9 and 10-years-old	BMI	Wisconsin Card Sorting Test	Abstract reasoning & cognitive flexibility (EF)	Confounders: age, sex, ethnicity/race, intracranial volume, handedness, and puberty status. Negative correlation between score and BMI.
			Flanker task	Response inhibition (EF)	BMI not correlated with score.
			List Sorting Task	Working memory (EF)	Negative correlation between score and BMI.
			Matrix reasoning subtest (WISC-5)	Abstract problem solving (EF)	Negative correlation between score and BMI.
Li et al. (2008)	Children	BMI	Reading and arithmetic sections (WRAT-III)	Academic performance	Confounders in hierarchy regression: age and gender at step 1; ethnicity, Significantly reduced in children in obese range when compared to

Study	Participants	Grouping criteria	Measure	Domain	Covariates	Results
	(n = 2,519) aged 8 to 16-years-old	Used to group participants as obese (BMI ≥ 30 kg/m²) and normal weight (BMI 18.5 – 24.9 kg/m²)	Block design subtest (WISC-R)	Visuospatial organisation	education level, marital status of the family head, family income, and dwelling condition at step 2; hours of television watching per day, physical activity, blood pressure, serum total cholesterol and triglycerides, iron deficiency, anxiety, child behaviour, and social skills at step 3.	children in normal range at step 1; not significant at steps 2 and 3.
			DS subtest (WISC-R)	Attention & working memory (EF)		Significantly reduced in children in obese range when compared to children in normal range at step 1; not significant at steps 2 and 3.
			Composite of block design and DS subtest scores	Cognitive function		Significantly reduced in children in obese range when compared to children in normal range at steps 1, 2, and 3. Composite scores significantly reduced in children in obese range when compared to children in normal range at steps 1, 2, and 3.
Meo et al. (2019)	Children (n = 400) aged 12 to 15-years-old; males only.	BMI used to group children as severely obese (BMI ≥ 35 kg/m²), obese, (BMI 30-34.99 kg/m²) or non-obese (BMI < 25 kg/m²).	Spatial recognition memory task (CANTAB)	Visuospatial memory		No difference between severely obese and non-obese groups, nor between obese and non-obese groups.
			Attention switching task (CANTAB)	Attention & cognitive flexibility (EF)		Significantly reduced in severely obese group and obese group when compared to non-obese group.
			Intra-extra dimensional set shift (CANTAB)	Cognitive flexibility (EF)		Significantly reduced in severely obese group when compared to non-obese group. No difference between obese and non-obese groups.

1.3.2. Dietary Fat and Cognitive Impairment.

A relationship between dietary fat intake, independent of body weight, and cognition has been reported in children, adolescents, and adults (Table 1.2.). However, the direction of the association appears to be dependent on the type of fat consumed. Cross-sectional research in children and adolescents provides evidence that fat intake is associated with academic performance. For example, 10 and 11-year-old Canadian children with low caloric intake from fruits and vegetables combined with high caloric intake from saturated fatty acids (SFAs) were more likely to fail standardised assessment of reading and writing abilities (Florence, Asbridge, & Veugelers, 2008). However, in a sample of 3,666 children and adolescents aged 6 to 16-years, Zhang, Hebert, and Muldoon (2005) found that increased intake of poly-unsaturated fatty acid (PUFA) was associated with lower odds ratio of poor reading performance, but there was no evidence of an effect of total fat, SFA, or mono-unsaturated fatty acid (MUFA) intake on mathematic or reading ability. They also found that attention and memory function, assessed using a digit-span task, was positively correlated with PUFA intake but negatively correlated with cholesterol intake, and that replacing SFA with 5% energy from PUFA resulted in a lower odds ratio for poor performance on the digit-span task. These results remained significant after controlling for a number of SES and health-related factors, including BMI and physical activity.

An association between fat intake and cognition has also been reported in correlational research conducted in children. For example, Baym and colleagues (2014) found evidence of a relationship between different types of fat and hippocampal-dependent cognition in a sample of children aged seven to nine-years in the computerised task used by Khan et al. (2015a) described above. Specifically, they found that omega-3 fatty acid intake was positively associated with accurate responding on hippocampal-

dependent recognition memory trials, but SFA intake was negatively correlated with accurate responding on both recognition memory trials and hippocampal-independent item memory trials. These associations remained significant after controlling for demographic factors, SES, intelligence quotient (IQ), pubertal timing, and aerobic fitness. However, when the data from male and female children were assessed separately, the associations remained significant for the male but not the female children.

In another study from the same research group, Khan and colleagues (2015b) demonstrated an association between different types of fat intake and impairments in various cognitive tasks in a sample of 150 children aged seven to 10-years. In this study, children completed a computerised colour-shape switching task that required them to shift their attention to a specific feature (shape or colour) of a cue (a toy figurine) located in the centre of a computer screen and execute a response according to the rule assigned to that cue. Homogenous sets included trials that required students to respond based on either the shape (e.g. respond on left button if square, right button if circle) or colour (e.g. respond on left button if blue, right button if green) dimension only, and thus assessed behavioural inhibition. For trials in heterogeneous sets, children were required to first identify the dimension for responding based on the pose of the toy on the screen (e.g. arms up, sort by shape; arms down, sort by colour) and then provide a response based on the rule assigned to the cue; thus, heterogeneous sets assessed working memory and cognitive flexibility in addition to behavioural inhibition. Khan et al. found that higher intake of saturated fats was associated with increased reaction time on heterogeneous trials, and cholesterol intake was associated with poorer ability to switch between dimensions in heterogeneous sets. They further found that the difference in response accuracy between homogenous and heterogeneous trials increased with higher intake of total fat, SFA, and cholesterol. Furthermore, these results remained significant after

adjusting for demographic factors, SES, IQ, and BMI. Together, the results suggest that higher fat intake impaired performance on tasks that required greater executive control.

Correlational research in adults provides evidence of a relationship between fat intake and cognition at both a global and domain-specific level. For example, Ding and colleagues (2014) found that adults aged 18 to 65-years who consumed 29% or more energy from fat had significantly reduced global cognitive function when compared to those who consumed 20% or less energy from fat. Zhang, McKeown, Muldoon, and Tang (2006) reported a negative association between total energy intake from fat and visuomotor speed, MUFA intake and processing speed, and cholesterol intake and verbal working memory in adults aged 20 to 59-years. Finally, in a sample of 38 women aged 25 to 45-years, habitual intake of SFA and trans fats, as well as a high saturated to unsaturated fat ratio, was associated with impairments in visuospatial ability and verbal recognition memory after controlling for age, physical activity levels, and IQ (Gibson, Barr, & Jeanes, 2013). These associations were not mediated by total energy intake, and there was no association found between intake of carbohydrates and performance on any neuropsychological test. This suggests that the associations were specific to fat intake, rather than the dietary intake pattern per se.

Finally, correlational and prospective studies in middle-aged and older adults have demonstrated associations between dietary intake of different types of fat, and global cognitive function, global cognitive decline, and increased risk of mild cognitive impairment (Eskelinen et al., 2008; Morris et al., 2004; Ortega et al., 1997). For example, in a sample of 5,084 adults aged 65-years and older, Okereke et al. (2012) found that higher intake of SFA was associated with a significantly faster rate of decline in verbal episodic memory, assessed using the East Boston Naming Test, and global cognitive function, assessed using the Telephone Interview for Cognitive Status, across a four-year

period. Conversely, lower intake of SFA and higher intake of MUFA was positively correlated with favourable global cognitive function over the four-years. Notably, the change in global cognitive function in adults in the highest quintile of SFA intake was equivalent to five to six additional years of aging, whereas the change in adults in the highest quintile of MUFA intake was equivalent to six to seven fewer years of aging. These results remained significant after controlling for BMI, and a number demographic and health factors. These findings are partially supported by a recent systematic review and meta-analysis of nine studies that included a total of 23,402 participants aged 55-years or older, which reported that higher intake of SFA was associated with increased risk of cognitive impairment, however found no evidence of an association between total fat or unsaturated fat intake and cognition (Cao et al., 2019).

Table 1.2. Summary of experimental details from epidemiological studies that have examined the relationship between dietary fat intake and performance across a number of cognitive domains. (AD = Alzheimer's Disease; ApoE ε4 = ε4 allele of the apolipoprotein E (APOE) gene; BMI = Body Mass Index; CANTAB = Cambridge Neuropsychological Test Automated Battery; CVD = Cardiovascular Disease; DS = Digit Span; FFQ = Food Frequency Questionnaire; LM = Logical Memory; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MUFA = Mono-Unsaturated Fatty Acid; NES = Neuropsychological Evaluation System; PUFA = Poly-Unsaturated Fatty Acid; SBP = Systolic Blood Pressure; SES = Socioeconomic Status; SFA = Saturated Fatty Acid; WHR = Waist-to-Hip Ratio; IQ = Intelligence Quotient; WISC-R = Wechsler Intelligence Scale for Children Revised; WRAT-R = Wide Range Achievement Test Revised).

Author	Participants (sample size)	Dietary Intake Measure	Test(s) Administered (test battery)	Cognitive Domain Assessed	Covariates or Confounding Variables	Major Findings
Baym et al. (2014)	Children (n = 52) aged 7 to 9-years.	152-item Youth-Adolescent FFQ.		Hippocampal-dependent recognition memory (RM) & hippocampal-independent item memory (IM)	Confounders: age, sex, SES, IQ, pubertal timing, fitness (VO_{2max} percentage).	Behavioural accuracy: RM positively correlated with omega-3 intake. RM and IM negatively correlated with SFA intake.
		Jointly completed by participants and their primary caregiver.	Computerised memory task.		Correlations adjusted for BMI for age Z-score.	
		Responses used to calculate total energy intake, dietary lipids intake, and carbohydrates intake.			Data analysed separately for males and females, and collapsed across sex.	PDV: No significant correlations.
				Dependent variables: behavioural accuracy and preferential disproportionate viewing (PDV)		Males vs Females: Behavioural accuracy associations significant for male participants but not female participants.

Study	Population	Dietary assessment	Cognitive assessment		Adjustments	Findings
Ding et al. (2018)	Adults (n = 777) aged 18 to 65-years, free from cancer, psychiatric disorders, organ failure, alcohol abuse, cerebral infarction, severe brain injury, medications for psychiatric or neurological disease.	34 item semi-quantitative FFQ. Responses used to group participants into quartiles according to percentage of energy intake from fat.	MoCA and MMSE.	Cognitive function.	MCI defined by the following criteria: MoCA≤13 and MMSE≤20 for illiteracy; MoCA≤19 and MMSE≤23 for participants with 1 to 6-years of education; and MoCA≤24 and MMSE≥27 for participants with ≥7-years of education.	Fat intake in the third and fourth quartile (> 29% total energy from fat) had significantly poorer cognitive function than individuals in the lowest quartile (<20% total energy from fat). Total energy intake was positively associated with risk for developing mild cognitive impairment.
					Scores adjusted for age, sex, education, total energy intake, BMI, education, total energy intake, and hyperlipidaemia.	
Eskelinen et al. (2008)	Adults (n = 1,341) aged 65 to 79-years at time of cognitive assessment and free from dementia.	Semi-quantitative FFA. Dietary assessment occurred approx. 21-years prior to	MMSE / Mayo Clinic AD Research Center criteria for clinically diagnosing MCI.	MCI / Global cognitive function	Scores adjusted for: age, sex, education, time between diet assessment and follow-up in model 1; additional adjustments for ApoE e4	High total fat and SFA intake were associated with an increased risk of MCI. No effect of PUFA or MUFA intake. Significantly lower scores in participants with high total fat and high SFA intake compared to participants with low intake. No effect of PUFA or MUFA fat intake.

Study	Participants	Dietary assessment	Cognitive test	Cognitive domain	Covariates	Findings
	Subset of participants (n = 82) had MCI at time of cognitive testing	cognitive assessment. Responses used to calculate total fat, SFA, MUFA, and PUFA intake. Participants group as low intake (1st and 2nd tertile) and high take (3rd tertile).	Immediate word recall test	Episodic verbal memory	carrier status and CVD risk factors (smoking status, SBP), cholesterol intake, and BMI in model 2.	No effect of fat intake.
			Category fluency	Semantic memory		No effect of fat intake.
			Stroop test	Executive function		Significantly lower scores in participants with high SFA intake compared to participants with low intake. No effect of PUFA or MUFA fat intake.
			Task by Einstein et al. (1992)	Prospective memory		No effect of fat intake.
Florence et al. (2008)	Children (n = 4,589) aged 9 to 10-years	Responses used to calculate a Diet Quality Index-International (DQI-I) score. Modified Youth-Adolescent FFQ.	Reading and writing abilities (Elementary Literacy Assessment developed by the Nova Scotia Department of Education)	Academic performance	Covariates: overweight/obesity risk (defined by BMI), sex, urban or rural residency, parent marital status, parent education, and household income.	Students with higher diet quality (high intake of fruit and vegetables, low intake of dietary fat) significantly less likely to fail the literacy assessment than students with poor diet quality (high intake of saturated fat, salt, and "empty calorie foods"). Parental education and income were significantly associated with student performance.

Study	Sample	Dietary measure	Cognitive task	Cognitive domain	Confounders / variables	Findings
Gibson et al. (2013)	Adults (n = 38) aged 25 to 45-years; females only.	Habitual dietary intake and activity assessed using a 7-day food and activity diary. Responses used to estimate total daily energy intake and nutrient intakes.	Verbal recognition memory test (CANTAB)	Verbal memory	Partial correlations were adjusted for age, physical activity, and verbal IQ.	SFA and unsaturated fat intake negatively correlated with scores at immediate recall, and both immediate and delayed recognition tests.
			Visual paired associate learning task (CANTAB)	Visuospatial learning		Total fat, SFA, and trans-fat negatively associated with number of errors.
			Delayed matching to sample task (CANTAB)	Visual memory		No associations with total fat, SFA, unsaturated fat, or trans-fat intake. Authors suggest this may be due to ceiling effects.
Khan et al. (2015b)	Children (n = 150) aged 7 to 10-years.	24-hour food recall interview. Jointly completed by participants and their primary caregiver. Responses used to calculate carbohydrate, protein, and fat intake.	Colour-shape switching paradigm: homogeneous trial sets - all trials required a response based on one dimension (colour or shape) alone	Cognitive control: behavioural inhibition	Confounders: age, sex, SES, IQ, aerobic fitness (VO_{2max} percentile), and BMI for age Z-score. Dependent variables: Accuracy of responding and reaction time.	Total fat, SFA, and cholesterol intake was associated with greater global switch cost* for accuracy. Saturated fat intake associated with increased reaction time for heterogeneous trials.
			Colour-shape switching paradigm: heterogeneous trial sets - trials required selection of the dimension (colour or shape) that dictated response rule, and	Cognitive control: behavioural inhibition, working memory, and cognitive flexibility		Cholesterol intake associated with increased local switch cost** for accuracy and reaction time. *global switch cost: Difference in performance between homogenous and heterogeneous trials.

	Sample	FFQ	Cognitive measure	Assessment	Covariates	Findings
				then respond accurately.		**local switch cost on Difference in performance between sequential trials the required switch and sequential trials that did not require switch.*
Morris et al. (2004)	Adults (n = 2,560) aged 65+ years free from stroke, diabetes, heart attack at baseline.	139-item modified Harvard FFQ completed after baseline cognitive assessment.	Global composite score obtained by averaging scores on the MMSE, East Boston Test of Immediate and Delayed Recall, and Symbol Digit Modalities Test	Global cognitive function. Cognition assessed at Baseline, and 3-year and 6-year follow up.	Covariates: age, sex, race, and education level, smoking status, daily alcohol consumption, hypertension or use of antihypertensive medications, total energy intake, and dietary intake of vitamins.	SFA intake negatively correlated with global cognitive decline over the 6-year period. Individuals with SFA intake in the highest quintile had 68% increase in rate of cognitive decline when compared to individuals in the lowest quintile. Cognitive decline not associated with total fat intake, animal fat intake, vegetable fat intake, or cholesterol intake.
Okereke et al. (2012)	Adults (n = 5,084) aged > 65-years; females only.	131-item semi-quantitative FFQ. Responses used to calculate SFA, MUFA, PUFA, and trans-fat intake.	Telephone Interview for Cognitive Status	Global cognitive function Cognition assessed 5-years after dietary assessment (baseline), and at 2-year and 4-year follow up.	Covariates: age at baseline, education, race, household income, BMI, smoking status, alcohol consumption, diabetes, hypertension, history of antihypertensive or high blood pressure medication, elevated cholesterol, depression, and physical activity	Lower SFA intake and higher MUFA intake positively correlated with favourable global cognitive function trajectory over time. Higher intake of SFA associated with significantly worse global cognitive function trajectory over time. Change in global function for participants in highest quintile of

Study	Sample	Method	Cognitive test	Domain	Covariates	Findings
						SFA intake was equivalent to 5 to 6 added years of aging.
						Change in global function in participants in the highest quintile of MUFA intake was equivalent to 6 to 7 fewer years of aging.
						Lower SFA and higher MUFA intake positively correlated scores over time.
		East Boston Memory Test	Verbal episodic memory			Higher SFA intake associated with significantly worse trajectory of scores over time.
		Category fluency task	Executive function			No effect of fat intake.
Zhang et al. (2005)	Children (n = 3,666) aged 6 to 16-years-old	24-hour food recall interview administered to the child's mother. Responses used to estimate of total energy intake, total fat intake, SFA intake, MUFA	Arithmetic and reading subtests (WRAT-R)	Academic performance	Covariates: ethnicity, maternal education, maternal residence area, rural/urban classification of residence area, maternal marital status, total family income, poverty income ratio, BMI for age Z-score, child's self-reported substance use, and physical activity.	Increased PUFA intake associated with lower odds ratio of poor reading performance.
			Block design subtest (WISC-R)	Nonverbal reasoning		No correlations with total fat, cholesterol, SFA, PUFA, or MUFA intake.
			DS subtests (WISC-R)	Attention and working memory		PUFA intake positively correlated with scores. Replacing SFA with 5% energy from PUFA associated

Study	Sample	Dietary assessment	Cognitive test	Cognitive domain	Analysis / confounders	Findings
		intake, and PUFA intake.				with lower odds ratio for poor score.
						No correlations with total fat, SFA, or MUFA intake.
			Simple reaction time test (NES)	Visuomotor speed	Regressions adjusted for potential confounders:	Cholesterol intake negatively correlated with scores.
Zhang et al. (2006)	Adults (n = 3,960) aged 20 to 59-years (M_age = 36) free from diabetes, stroke, cancer, neurological disorders, or medications for psychiatric or neurologic conditions.	24-hour interview using the Dietary Data Collection (DDC) system.	Symbol-digit substitution test (NES)	Processing speed	Model A- age, sex, education, amount of sleep night before test, self-reported energy level, familiarity with computers, consumption of caffeine or alcohol in 3-hours prior to test in Model A; additionally adjusted for smoking status, alcohol intake, blood pressure, WHR, physical activity, hypertension, glycaemic control, and serum trace elements and vitamins in Model B.	Percentage of energy intake from total fat negatively correlated with performance in model A and B.
						MUFA intake negatively correlated with scores in model A and B.
		Serial digit learning test (NES)	Verbal learning and memory			Cholesterol intake negatively correlated with scores in model A and B.
		Combination of all test scores	Global cognitive function			Cholesterol intake negatively correlated with scores in model A and B.

1.3.3. Dietary Sugar and Cognitive Impairment.

Relatively few studies have examined the relationship between dietary sugar intake and cognition; however, the available research suggests that sugar intake, independent of body weight, is negatively associated with cognitive performance (Table 1.3.). A number of studies in children and adolescents demonstrate that higher sugar intake has a detrimental effect on academic performance, even after controlling for covariates including demographics, BMI, and physical activity. For example, a number of studies in children and adolescents have demonstrated a negative correlation between the intake of sugar-sweetened beverages (SSBs) and performance on standardised tests of writing ability and grammar (Burrows et al., 2017b), reading ability and arithmetic ability (Burrows et al., 2017b; Edwards, Mauch, & Winkelman, 2011a). Similarly, Park and colleagues (2012) found in a sample of 16,188 adolescents aged 12 to 19-years that consumption of one or more SSBs each day was significantly associated with self-reported lower academic grades. Finally, Bleiweiss-Sande et al. (2019) found that scores in a standardised test of English were negatively correlated with higher intake of fruits and sugary snacks in children aged eight to 10-years.

Correlational research has also demonstrated a negative association between sugar intake and cognition across the lifespan, with associations present after controlling for SES, demographic and health factors, and BMI. For example, in a sample of 245 children aged six to seven-years, refined carbohydrate intake was negatively correlated with non-verbal intelligence, measured using Raven's Colourful Progressive Matrices test, which requires children to choose the missing element in a drawing from six possible options (Abargouei et al., 2012). In a sample of 737 middle-aged and older adults (aged 45 to 75-years), Ye et al. (2011) found that cognitive function, assessed using the MMSE, was negatively correlated with a number of measures of dietary sugar intake, including total

sugar intake, added sugar intake, and intake of sucrose, glucose, and fructose. They also found a negative correlation between cognitive function and intake of SSBs, but not 100% fruit juice or sugar-sweetened foods. Similarly, in a sample of 1,209 Malaysian adults aged over 65-years, Chong and colleagues (2019) demonstrated an increased risk of cognitive impairment in those with higher intake of total sugar, free sugar, sucrose, SSBs, cakes and deserts. They also found that, when compared to individuals in the lowest quintile of intake, individuals with total sugar intake and free sugar intake in the highest quintile had significantly worse scores on the MMSE and the Montreal Cognitive Assessment, and poorer short-term visual memory. Finally, free sugar intake in the highest quintile was also associated with poorer short- and long-term verbal memory.

Table 1.3. Summary of experimental details from epidemiological studies that have examined the relationship between dietary sugar intake and performance across a number of cognitive domains. (ApoE ε4 = ε4 allele of the apolipoprotein E (APOE) gene; BMI = Body Mass Index; DSM-IV = Diagnostic and Statistical Manual 4th edition; EF = executive function; FFQ = Food Frequency Questionnaire; GI = Glycaemic Index; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; MoCA Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; SES = Socioeconomic Status; SSB = Sugar-Sweetened Beverage; WAIS-III = Wechsler Adult Intelligence Scale 3rd Edition; WMS-R = Wechsler Memory Scale Revised; YRBSS = Youth Risk Behaviour Surveillance Survey).

Author	Participants (sample size)	Dietary Intake Measure	Test(s) Administered (test battery)	Cognitive Domain Assessed	Covariates or Confounding Variables	Major Findings
Abargouei et al. (2012)	Children (n = 245) aged 6 to 7-years	67-item FFQ containing food items with high GI refined carbohydrate content. Jointly completed by child and primary caregiver.	Raven's Colourful Progressive Matrices test	Non-verbal intelligence	Regressions controlling for: age, gender, birth date, birth order, and breast-feeding pattern in infancy in model 1; parental education and occupation in model 2; BMI in model 3.	Refined carbohydrate intake negatively correlated with test scores in models 1, 2, and 3. Significantly lower test scores in participants with refined carbohydrate intake in the top tertile when compared to participants in bottom tertile in model 1. Non-significant in model 2 and 3.
Burrows et al. (2017b)	Children (n = 2,234); Twins aged 8 to 15-years.	Questionnaire adapted from the Australian Eating Survey. Completed by primary caregiver.	National Assessment Program – Literacy and Numeracy (NAPLAN).	Academic performance	Covariates: sex, birth date, family (due to twins), and parent education level.	SSB intake negatively correlated with scores for reading, writing, grammar, and numeracy. Vegetable intake positively correlated with scores for spelling and writing; trend for correlation with scores on tests of reading and grammar (p = .05) and numeracy (p = .06).

Study	Sample	Diet assessment	Test	Domain	Findings
		Responses used to identify fruit, vegetable, takeaway food, SSB, and breakfast intake.	assessed: reading, writing, grammar, spelling, and numeracy		Fruit intake positively correlated associated with test scores for writing.
Bleiweiss-Sande et al. (2019)	Children (n = 868) aged 8 to 10-years	Responses used to assess frequency and portion size of healthy foods (e.g. fruit, vegetables, water) and unhealthy foods (salty snacks, sweet snacks, SSB).	FLEX FFQ		
			DS-forward	Short-term	No effects
			DS-backward.	Working memory	No effects
			Stroop colour-word task	Attention and behavioural inhibition (EF)	Higher intake of fruits and sweet snacks were associated with lower scores on tests assessing English ability.
			Massachusetts Comprehensive Assessment System (Massachusetts Department of Elementary and Secondary Education).	Academic performance	Intake of unhealthy foods was inversely associated with Numeracy and English scores.
				Scores adjusted for age, sex, race/ethnicity, maternal and paternal education, breakfast consumption on the day of the tests, BMI, and physical activity.	
Chong et al. (2019)	Adults (n = 1,209) aged over 65-years	FFQ and a Dietary History Questionnaire to quantify habitual dietary intake for the previous 7-	MoCA and MMSE	Cognitive Function	Total sugar intake and free sugar intake was negatively correlated with MMSE score.
				Covariates: age, gender, educational years, BMI, daily calorie intake, marital status, smoking status, alcohol consumption status, physical activity, and geriatric depression scale.	Scores on MoCA were lower in participants with total sugar and free sugar intake in the top quintile when compared to participants in the bottom quintile.

Study	Sample	Sugar intake measure	Cognitive test	Cognitive domain	Results
		days. DHQ was used to assess sugar intake and identify details of daily sugar intake.	DS subtest (WAIS-III)	Attention and working memory	Higher intake of total sugar, free sugar, sucrose, SSBs, and cakes and desserts significantly increased the risk of cognitive impairment.
			RAVLT	Verbal memory	No effect.
Edwards et al. (2011a)	Sixth grade students (n = 748)	Questionnaire adapted from the YRBSS	Visual reproduction subtest (WMS)	Visual memory	Free sugar intake in the top quintile had poorer short-term and long-term memory recall than those in the bottom quintile. Total sugar and free sugar intake in the top quintile had poorer immediate recall than those in the bottom quintile. No differences for delayed recall.
Park et al. (2012)	Adolescents (n = 16,188) aged 12 to 19-years	YRBSS	Standardized tests conducted as part of normal school curriculum.	Academic performance	Covariates: regular consumption of breakfast, hours watching television, physical activity, and BMI. Lower intake of SSBs associated with higher scores on mathematics and readings tests.
		Students self-reported grades for the previous school year		Academic performance	Consumption of one or more SSBs per day was significantly associated with lower self-reported grades.
Roberts et al. (2012)	Adults (n = 2,719) aged 70-89-years at baseline.	128-item Health Habits and History Questionnaire	Cognitive assessment conducted 15-	Mild Cognitive Impairment (as per DSM-IV criteria)	Covariates: type 2 diabetes, hypertension, coronary heart disease, history of stroke, ApoE e4 status, depression symptoms, physical activity, and BMI.
		Neurological assessment battery.			Energy intake from carbohydrate in the top quartile associate with a two-fold increased risk of MCI at follow up when compared to intake in the bottom quartile.

Author	Sample	Dietary measurement	Cognitive test	Cognitive domain	Covariates	Findings
		months after measurement of dietary intake.				Sugar intake in the top quartile associated with increased risk of MCI when compared to sugar intake in the bottom quartile.
Ye et al. (2011)	Adults (n = 737) aged 45 to 75-years without diabetes.	246-item semi-quantitative FFQ			Covariates: age, sex, SES, educational attainment, smoking status, alcohol use, physical activity, BMI, blood pressure, and hypertension.	Negatively correlated with total and added sugar intake, and intake of sucrose, glucose, and fructose.
						Negatively correlated w sugar-sweetened beverage, but not 100% fruit juice or sugar-sweetened foods.
			MMSE	Cognitive function		No effect.
			DS-forward and -backward	Attention and working memory		Negatively correlated with total sugar intake and added sugar intake.
			Stroop task	Cognitive flexibility and response inhibition (EFs)		No effect.
			Letter fluency task	Verbal fluency (EF)		No effect.
			Clock drawing and Figure copying tasks	Visuospatial organisation		No effect.
			16 item list-learning task	Verbal memory		Recognition, immediate recall, and delayed recall negatively correlated with total sugar intake.
						Delayed recall negatively correlated with added sugar intake.

1.3.4. Dietary Fat and Sugar in Combination and Cognitive Impairment

Most epidemiological studies that have examined the relationship between dietary intake and cognition have focussed on the so-called Western style high-fat high-sugar diet (Table 1.4.; see Francis & Stevenson, 2013; Yeomans, 2017). Cross-sectional research conducted in children and adolescents demonstrates a negative association between consumption of such a diet and academic performance (see Burrows et al., 2017a). For example, in a sample of 2,222 children aged 6 to 13-years, a dietary pattern characterised by high intake of fried foods and sweet foods was associated with poor academic performance measured using the Inability to Learn subscale from the Scales for Assessing Emotional Disturbance (Fu, Cheng, Tu, & Pan, 2007). Øverby et al. (2013) found in a sample of 475 adolescents aged 13 to 16-years that high intake of discretionary foods (e.g. SSBs, sweets, chocolate, savoury snacks, pizza, and hotdogs) was significantly associated with self-reported difficulties in mathematics, but not in reading and writing, after controlling for gender and body weight. Furthermore, in a sample of 14-year-old Australian adolescents, Nyaradi et al. (2015) demonstrated that consumption of a Western diet, characterised by high intake of take-away food, red and processed meat, SSBs, and fried foods, was negatively correlated with scores on standardised tests of mathematics, reading, and writing. Nyaradi and colleagues also found that specific components of the Western diet correlated with performance on the academic tests; higher intake of confectionary and SSBs was negatively correlated with scores for mathematics and reading, and higher intake of processed meat and fried potato was negatively correlated with scores for reading. These associations remained significant after controlling for total energy intake, family characteristics, BMI, and physical activity.

An association between Western diet and academic performance has also been reported in young adults completing tertiary education. For example, in a sample of 289

students attending medical college in India, Arasegowda and colleagues (2016) found that those who reported daily consumption of fast foods high in SFA and sugar had a lower odds ratio for high performance (score $\geq$ 60%) in exams than those who reported no consumption of such food. Whatnall and colleagues (2019) also demonstrated that a higher percentage of daily energy intake from energy-dense, micronutrient-poor foods was negatively correlated with self-reported grade point average (GPA) in a sample of university students completing undergraduate and postgraduate studies at an Australian university. These investigators further demonstrated a negative correlation between SSB and fried or take-away fast foods and GPA. However, after GPA was adjusted for socio-demographic factors and student characteristics, only the associations between energy-dense, micronutrient-poor foods and SSBs with GPA remained significant.

A negative relationship has been found between consumption of a Western diet and performance on neuropsychological tests across the lifespan. Importantly, the relationship remains significant after controlling for a number of covariates including socioeconomic factors, the presence of chronic disease including diabetes status and hypertension, and BMI. For example, longitudinal research in a sample of 7,044 children participating in a UK-based cohort study found intake of processed foods, high in saturated fat and sugar, at 3-years of age was associated with decreased IQ measured at 8.5-years of age (Northstone, Joinson, Emmett, Ness, & Paus, 2012). Similarly, longitudinal research in a sample of 717 adolescents participating in an Australia-based cohort study found that higher intake of a Western diet at 14-years of age was significantly associated with poorer psychomotor speed, visual learning and memory, and executive function assessed at 17-years of age using the CogState cognitive test battery (Nyaradi et al., 2014).

Cross-sectional research conducted by Francis, Stevenson, and colleagues have demonstrated an inverse relationship between intake of high-fat and high-sugar foods and performance on a number of neuropsychological tests from the Wechsler Memory Scales that are sensitive to hippocampal damage in healthy, lean university students matched for age, sex, BMI, and verbal IQ. This includes slower learning of a list of word pairs across multiple training presentations in a verbal PAL task (Attuquayefio et al., 2016); decreased retention of a list of word pairs in the verbal PAL (Francis & Stevenson, 2011); decreased ability to recall a verbally-presented short story in the LM subtest of the WMS-R (Brannigan et al., 2015; Francis & Stevenson, 2011) and WMS-IV (Francis & Stevenson, 2011); and reduced ability to replicate visual designs after short or longer delays in the Visual Reproduction subtest of the WMS-IV (Francis & Stevenson, 2011). These investigators found no effect of high-fat and high-sugar diets in tasks assessing other cognitive functions such as working memory, attention (Attuquayefio et al., 2016; Brannigan et al., 2015; Francis & Stevenson, 2011), or executive function (Francis & Stevenson, 2011). These findings suggest that the impairments observed with high-fat and high-sugar diet consumption were restricted to hippocampal-dependent learning and memory tasks, rather than a broader impairment in cognitive ability.

Finally, research in middle-aged and older adults also provides evidence of a negative relationship between Western diet intake and cognition function. For example, D'Amico et al. (2020) found in a cross-sectional sample of adults aged 67 to 84-years that consumption of a Western diet was significantly associated with poorer global cognitive function, assessed using the modified MMSE; when examined by gender, this association was significant in male, but not female, participants. Comparable associations between diet and cognitive function have been reported in longitudinal studies. For example, Fortune et al. (2019) found in a sample of middle-aged adults that higher

consumption of fried foods and foods high in fructose were significantly associated with reduced cognitive function, assessed using a battery of standardised neuropsychological tests, at fifteen year follow up. Similarly, Shakersain et al. (2016) found that consumption of a Western-style diet, characterised by frequent intake of processed meats, SFA, trans fats, refined grains, and refined sugar, was associated with significantly greater cognitive decline over a six-year period, as measured by the MMSE, than consumption of a Mediterranean-style diet, characterised by frequent intake of fruits, vegetables, legumes, fish, and whole grains. Shakersain and colleagues further found that cognitive decline was less pronounced in individuals that reported high intake of foods from both the Western-style and Mediterranean- style diets, suggesting that the Mediterranean diet may attenuate the effect of Western diet on cognitive decline.

Table 1.4. Summary of experimental details from epidemiological studies that have examined the relationship between high-fat high-sugar Western diet and performance across a number of cognitive domains. (ApoE ε4 = ε4 allele of the apolipoprotein E (APOE) gene; BMI = Body Mass Index; DS = Digit Span; FFQ = Food Frequency Questionnaire; LM = Logical Memory; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; SFA = Saturated Fatty Acid; WAIS-5 = Wechsler Adult Intelligence Scale 5th Edition; WISC-III = Wechsler Intelligence Scale for Children 3rd Edition; WMS-IV = Wechsler Memory Scale 4th Edition; WRAT-4 = Wide Range Achievement Test 4th Edition).

Author	Participants (sample size)	Dietary Intake Measure	Test(s) Administered (test battery)	Cognitive Domain Assessed	Covariates or Confounding Variables	Major Findings
Arasegowda et al. (2016)	Adolescents and adults (n = 289) aged 17 to 25-years	Questionnaire to examine dietary intake of fast-foods, SSB, and alcohol.	Score on most recent university exam. Participants grouped based on high (score ≥60%) and low (score <60%) performance.	Academic performance		Daily consumption of fast foods high in saturated fats and refined sugars were observed to have lower odds ratio for high performance on university exams than individuals who did not consume fast foods at all.
D'Amico et al. (2020)	Adults (n = 1,268) aged 67 to 84-years.	Western dietary pattern (high intake of processed meats, fried foods, butter, baked foods, sugary foods, SSBs, high-fat dairy, eggs, and salty snacks) 78-item semi-quantitative FFQ.	Modified MMSE (3MS)	Global cognitive function	Covariates: age, education, BMI, diabetes status, daily energy intake, and hypertension.	Consumption of Western dietary pattern significantly associated with poor global cognitive function in male participants, but not female participants.

Study	Participants	Dietary assessment	Cognitive assessment	Outcome	Covariates / Confounders	Findings
Fortune et al. (2019)	Adults (n = 441). and Age at time of assessment was 32.03 ± 5.96 years.	151-item Youth-Adolescent FFQ	Test battery: DS, vocabulary, and digit-symbol coding subtests (WAIS-5); LM subtest (WMS-IV); letter and word reading subtests (WRAT-4); Trail making test parts A & B Age at time of cognitive testing was 49.03 ± 4.86 years.	Cognitive function.	Covariates: education level, salary level, Diabetes status, Hypertension, BMI at time of cognitive testing, and physical activity at baseline.	Higher consumption of fructose and foods fried at home at baseline were significantly inversely associated with cognitive function at follow up 15-years later.
Fu et al. (2007)	Children (n = 2,222) aged 6 to 13-years.	Questionnaire that assessed the intake of 22 general food groups. Jointly completed by participants and primary caregivers.	Scale for Assessing Emotional Disturbance	Academic performance		Negative correlation with frequency of intake of sweet and friend foods. High dietary intake of fried foods and sweets and low intake of dairy and nutrient-dense foods (vegetables, fruit, fish, eggs), was significantly associated with poorer academic performance.
Northstone et al. (2012)	Children (n = 7,044).	FFQ. Completed by the primary caregiver. Dietary intake measured at 3, 4, 7, and 8.5-years of age.	WISC-III Mean age at time of cognitive assessment was 8.5 ± 0.3-years.	Cognitive function / Intelligence Quotient (IQ)	Confounders: WISC-III administrator, number of stressful life events, energy intake for each FFQ, breastfeeding duration, and maternal education, SES during pregnancy, age at birth, and oily fish consumption during pregnancy.	Negative correlation between 'processed' dietary pattern at 3-years and IQ at 8.5-years. One SD increase in processed diet score produced an almost 2-point decrease in IQ score.

Nyaradi et al. (2014)	Adolescents (n = 717).				Confounders: maternal education, family income, the presence of the biological father in the family, and family functioning.	
		212-item Semi-quantitative FFQ.	Detection task (CogState computerized cognitive battery)	Psychomotor speed		Negatively correlated with intake of Western dietary pattern. Processing speed positively correlated with intake of vegetables, and negatively correlated with intake of fried potato.
		Jointly completed by participant and primary caregiver.	Continuous paired association learning task (CogState)	Visual learning and memory		Intake of fried potato negatively correlated with number of errors.
		Dietary intake assessed at 14-years of age, 3-years prior to cognitive assessment.	Groton maze learning test (CogState)	Visual memory and executive function		Intake of a Western dietary pattern negatively correlated with number of errors. Number of errors were positively correlated with intake of fruit, and negatively correlated with intake of fried potato.
		Western dietary pattern (high intake of take-away food, red and processed meat, soft drink, fried and refined food).	Identification task (CogState)	Visual attention		Intake of a Western dietary pattern negatively correlated with visual attention, but not significant after adjustment for confounders.
			One card learning task (CogState)	Memory and attention		Higher intake of a Western dietary pattern negatively correlated with correct responses, but not significant after adjustment for confounders. Number of correct responses negatively correlated with intake of crisps.

Study	Sample	Dietary assessment	Outcome	Analysis / Covariates	Results
Nyaradi et al. (2015)	Adolescents aged 14-years. n = 779 for mathematics scores n = 741 for reading scores n = 470 for writing scores	212-item semi-quantitative FFQ. Jointly completed by participant and primary caregiver. Western dietary pattern (high intakes of take-away food, red and processed meat, soft drink, fried and refined food).	Western Australian Literacy and Numeracy Assessment (WALNA). Academic performance	Regressions adjusting for: total energy intake in model 1; maternal education, maternal race, family income, family functioning and the presence of the biological father in the family in model 2; and BMI and physical activity for model 3.	Negative correlation between Western dietary pattern and scores for mathematics, reading, and writing tests. Difference in score between highest and lowest quartile of Western diet intake was 46 points for mathematics, 59 points for reading, and 57 points for writing. Higher intake of confectionary and SSBs negatively correlated with math and reading scores. Higher intake of processed meats and fried potatoes negatively correlated with reading scores.
Øverby et al. (2013)	Adolescents (n = 475) aged 13 to 16-years.	23-item FFQ. Completed by participant.	Self-reported difficulties for reading and writing difficulties, and mathematics difficulties. School achievement	Scores adjusted for gender and overweight status.	High intake of discretionary foods (SSBs, sweets, chocolate, savoury snacks, pizza and hot dogs) was significantly associated with self-reported learning difficulties in mathematics.
Shakersain et al. (2016)	Adults (n = 2,223) aged over 60-years.	98-item semi-quantitative FFQ. Western dietary pattern (frequent	MMSE Cognitive function assessed at 6-year intervals for younger	Covariates: age, sex, education, civil status, BMI, physical activity, smoking status, vascular and other chronic diseases,	Consumption of a Western dietary pattern associated with significantly greater cognitive decline than consumption of a prudent dietary pattern.

Author	Sample	Dietary assessment	Outcome	Adjustments	Results
		processed meats, SFA, refined grains, and sugar intake). Prudent dietary pattern (frequent fruit, vegetable, legumes, fish, and whole grain intake).	participants (60, 66, 72, and 78-years) and at 3-year intervals for older participants (81, 84, 87, 90, 93, 96, and 99+ years).	dietary supplement use, and *APOE* ε4 status.	Cognitive decline was greatest in individuals with low adherence to prudent diet and high adherence to Western diet; however, the decline was less pronounced in individuals that adhered to high prudent diet and Western diet patterns.
Whatnall et al. (2019)	Adults (n = 278) mean age 26.9 ± 10.5 years	120-item semi-quantitative FFQ. Diet quality determined using the Australian Recommended Food Score	Self-reported grade point average (GPA) from university courses / Academic performance	Scores adjusted for gender, student type, financial support. SSB intake, Aboriginal or Torres Strait Islander (ATSI) descent, hours of paid work, and faculty of study.	Negative correlation between intake of energy dense nutrient poor foods and GPA. Remained significant in adjusted model. Negative correlation between GPA and consumption of SSBs, fried fast foods, and take away fast foods. Only SSB correlation remained significant in adjusted model.

1.3.5. Summary of Epidemiological Research

Epidemiological evidence demonstrates that body weight, composition of adipose tissue, and dietary intake of fat, sugar, or both, are all associated with cognitive impairments that are present across the lifespan. It is important to qualify the inclusion of literature examining the obesity-cognition link. While we do not know whether the link between obesity and cognitive impairment is attributable to the effect of the diet alone and/or the diet-induced changes in physical and metabolic markers of health (e.g. body fat, blood glucose regulation), the observation of greater cognitive impairments in individuals that experience the most common diet-related health disorder globally, when compared to normal weight individuals, is important to examine to appreciate the impact of the modern diet on brain health and function.

Of particular interest, the examination of the available literature provides evidence that the effect of fat is dependent on the quantity and quality of fat consumed, whereas the effect of sugar intake appears to more consistently result in cognitive dysfunction. Much of the evidence suggests that these associations are most apparent in males than females, and also most apparent in elderly populations. However, there is growing evidence from the last 15-years that the relationship between cognition and both bodyweight and diet is occurring earlier in life during childhood, adolescence, and early adulthood. Furthermore, the associations are observed in samples across different continents, and are significant even after adjusting for demographic, SES, and health factors. Notably, the detrimental effect of habitual intake of foods that are high in fat and/or sugar on performance in various cognitive tasks appears to be independent of body weight.

Evaluating the relationship between dietary intake and cognition is complicated by two factors. First, studies have utilised a wide range of assessment tools to examine

cognition, making it difficult to draw comparisons between results reported by different investigators. Second, measurement of dietary intake differs markedly across studies in terms of the assessment tool used to gather food intake data, the time period across which food intake has been assessed, and the method by which the data has been correlated with performance on cognitive tasks (e.g. as a linear or categorical variable; as total intake, percentage of energy intake, frequency of intake). Despite the methodological inconsistencies, there are some common outcomes reported across similar age groups. These include worse academic performance in obese students and in students who consume a high SFA, high-sugar, or Western diet; poorer visuospatial ability, deficits in list-learning and recall, and impaired verbal abilities in younger populations; and impaired global cognitive function and a more rapid cognitive decline in middle-aged and older adults. There is also evidence from experimental research in both children and young adults that hippocampal-dependent forms of cognition are particularly sensitive to obesity and dietary intake. However, despite these similarities, establishing causality between dietary intake and cognitive function is difficult to determine from these studies; it cannot be ruled out that cognitive impairments are a consequence of other factors that are associated with deficits in cognition including diet-induced changes in markers of physical and metabolic health (Farruggia, & Small, 2019; Rasmussen, Thomassen, & Frikke-Schmidt, 2021), or non-diet related health behaviours (e.g. sedentary behaviour; Craig, McNeill, Macdiarmid, Masson, & Holmes, 2010) observed in those with unhealthy dietary habits (Falck, Davis, & Liu-Ambrose, 2017).

1.4. Modern Diet and Cognitive Function: Experimental Research

1.4.1. Human Studies

Only a handful of studies have examined cognitive function in humans after experimental manipulation of dietary intake. This body of research has focused on the effect of short-term dietary manipulations lasting four to seven-days of either fat intake (Edwards et al., 2011b; Holloway et al., 2011) or fat and sugar intake (Attuquayefio, Stevenson, Oaten, and Francis., 2017; Stevenson et al., 2020) on cognition.

Across two studies, Clarke and colleagues have examined the influence of short-term high-fat diet intake on a number of cognitive domains using the Cognitive Drug Research computerized assessment battery (CDR). The CDR assesses frontal lobe-dependent attention and working memory, hippocampal-dependent episodic memory, and self-reported mood and alertness. The first study used a within-subject design to assess the effect of high-fat diet on cognition in 27 sedentary males, aged 27 to 47-years (Edwards et al., 2011b). All participants were first provided a standardized, nutritionally balanced diet for three-days to ensure that pre-manipulation measurements were collected from individuals with comparable nutritional profiles. Participants were then fed a high-fat diet containing 74% energy from fat and 2% energy from carbohydrates for seven-days. The high-fat diet was prescribed by a dietician to ensure the diet accommodated any food intolerances and that the energy content was consistent with the participants usual caloric intake. Cognitive assessment was conducted after the three-day standardized diet and after the seven-day high-fat diet manipulation. Edwards et al. found that seven-days of high-fat diet resulted in reduced performance on tests assessing attention, reaction time, and self-reported calmness. However, there was no effect of the diet on working memory or episodic memory. These results suggested that the diet manipulation impaired frontal-lobe dependent attention and information processing, but had no effect on hippocampal-dependent memory.

The second study examined the effect of a high-fat diet containing 75% energy from fat or a standard diet containing 23% energy from fat on cognition in 16 healthy males aged 22±1-years (Holloway et al., 2011). Participants were first provided with either the high-fat diet or standard diet for five-days, and then switched to the alternate diet for five-days after a two-week washout period. Cognition was assessed daily using alternate, equivalent forms of the CDR. In addition to examining the scores for each cognitive test in the CDR, Holloway et al. calculated a composite score for power of attention and speed of memory retrieval in order to characterize general domains of cognition. The rapid visual information processing (RVIP) task, which is a high cognitive demand task that assesses complex attention and working memory, was also administered daily to allowed for better cognitive discrimination between the participants. Holloway et al. found that five-days of high-fat diet intake resulted in significantly reduced power of attention and speed of memory retrieval, when compared to five-days of standardized diet. Performance on the RVIP task was also reduced with high-fat diet consumption when compared to standard diet. However, there was no effect of diet on performance in the individual cognitive tests that assessed attention, working memory, and episodic memory. These results replicated the impairment in attention and information processing reported by Edwards et al. (2011b), but also extended on these findings by demonstrating that high-fat diet did impair aspects of memory function (i.e. speed of memory retrieval), despite leaving memory formation intact. Notably, the diet-induced changes in cognition were not detectable after the two-week washout period, suggesting that short-term consumption of high-fat diet produced a transient effect on cognition.

Two studies by Francis, Stevenson and colleagues have examined the influence of short-term high-fat and high-sugar diet on cognition in young, healthy university students that reported relatively low intake of saturated fat and sugar. In the first study,

Attuquayefio and colleagues (2017) provided participants a healthy breakfast or one that was high in saturated fat and refined sugar for four consecutive days, and instructed them to eat as they normally would for the remaining meals each day. Participants in the two groups were matched in age, mental well-being, physical exercise, eating attitudes and estimated IQ; however, participants consuming the healthy control breakfast had, on average, higher BMI and waist circumference than participants consuming the experimental breakfast. Cognition was assessed at baseline and after the four-day diet manipulation. Hippocampal-dependent learning and memory was assessed using the LM subtest of the WMS-IV and the Hopkins Verbal Learning Test (HVLT), which measure episodic and verbal memory, respectively. Due to the number of testing sessions, Attuquayefio et al. constructed six additional stories for the LM task to supplement those provided by the WMS-IV. Working memory was assessed using the digit-span (DS) subtest of the WMS-III, and served as a control for general cognitive function and motivation across the experiment. After controlling for total energy intake, Attuquayefio et al. found that four-days of high-fat and high-sugar breakfast consumption significantly reduced participant's ability to learn and later recall a list of words on the HVLT, but did not impact their ability to learn and recall a short story on the LM, nor did it influence working memory on the DS. The impairment in HVLT performance was significant when compared to scores for control group participants on day four and when compared to the performance of participants in the experimental group at baseline. Previous research has demonstrated that list learning tasks provide a more sensitive measure of cognitive impairment than story learning tasks, as such tasks place greater demands on encoding and recall due to being presented in an unstructured format, which contrasts with the organised narrative structure inherent in a story (Silva et al., 2012; Tremont, Miele, Smith, & Westervelt, 2010). Thus, these results suggest that increased consumption of fat and

sugar produced a mild impairment in hippocampal function, while leaving episodic memory and general cognitive functions intact.

The results reported by Attuquayefio et al. (2017) were replicated in a more recent study. Stevenson and colleagues (2020) asked participants to consume their standard diet or to consume one high-fat high-sugar meal each day for seven-days. Participants were matched in age, mental well-being, BMI, WC, physical exercise, eating attitudes and estimated IQ. Cognition was assessed at baseline, after seven-days of diet manipulation, and three-weeks after the dietary manipulation had ceased. Hippocampal-dependent cognition was again assessed using the HVLT, and a DS task was used to control for general cognition and motivation. While there were no differences between groups at baseline, assessment after the seven-day manipulation demonstrated that participants consuming the experimental diet had significantly reduced learning and retention on the HVLT when compared to the control group and when compared to baseline performance; however, participants in the control and experimental diet conditions had comparable working memory on a DS task at both baseline and the seven-day assessment. Notably, the diet-induced changes in HVLT performance were no longer present after the three-week wash-out period, suggesting that the effect of the seven-day high-fat high-sugar diet manipulation was only transient.

1.4.2. Rodent Studies

There is now an extensive body of literature from animal models, particularly in rodents, that provides insight into the effect of fat and sugar consumption on cognition (for reviews, Cordner & Tamashiro, 2015; Leigh & Morris, 2020; Murray & Chen, 2019). The first important insight is that cognition appears to be sensitive to the type and concentration of dietary fat consumed (Winocur & Greenwood, 2005), confirming observations from epidemiological studies in humans. Broadly speaking, fat can be

categorised as saturated or unsaturated fat based on chemical composition and the effects on serum cholesterol levels (Clarke, Frost, Collins, Appleby, & Peto, 1997; Howell, McNamara, Tosca, Smith, & Gaines, 1997). Saturated fat, which is predominantly obtained from meat and dairy food sources, increases circulating levels of low-density lipoprotein (LDL), so-called "bad" cholesterol. Research demonstrates that intake of saturated fat is positively correlated with increased mortality (O'Sullivan, Hafekost, Mitrou, & Lawrence, 2013) and increased incidence of NCCDs including obesity (Corella et al., 2011; Petrus & Arner, 2020; Phillips et al., 2012), type 2 diabetes (Galgani, Uauy, Aguirre, & Díaz, 2008; Rivellese & Lilli, 2003), CVD (Clifton & Keogh, 2017; Mozaffarian, Micha, & Wallace, 2010), and NAFLD (Parks, Yki-Järvinen, & Hawkins, 2017; Rosqvist et al., 2019).. Conversely, unsaturated fats, which are predominantly obtained from marine and vegetable food sources, increases circulating levels of high-density lipoprotein (HDL), so-called "good cholesterol". HDL not only removes circulating LDL (Brites, Martin, Guillas, & Kontush, 2017), but also reduces systemic inflammation (Barter et al., 2004) and helps to build strong cell membranes that are vital for cell integrity (Mineo & Shaul, 2012).

Some of the earliest studies examining the effect of diet on learning and memory did so by manipulating the source of fat in the diet of rodents (e.g. Coscina, Yehuda, Dixon, Kish, & Leprohon-Greenwood, 1986; Greenwood & Winocur, 1990, 1996; Winocur & Greenwood, 1993). These studies not only found that high-fat diet impaired cognition, but also demonstrated that the impairments were more pronounced in rodents fed saturated than unsaturated fat, and differed depending on the concentration of dietary fat. For example, Winocur and Greenwood (1993) fed one-month-old rats a diet of 10% (weight/weight; w/w) or 20% (w/w) saturated fat from lard or unsaturated fat from soybean oil for three-months. Rats were then trained in an operant conditional

discrimination task that required them to respond on one lever when a light stimulus was present and the other lever when the light stimulus was absent. Rats consuming the 20% (w/w) saturated or unsaturated high-fat diet were slower to learn the discrimination than chow-fed control rats. However, of the rats consuming the 10% (w/w) high-fat diet, those consuming saturated fat but not those consuming unsaturated fat were slower to learn than chow-fed controls. These results suggested that consuming saturated fat at any concentration has a detrimental effect on cognition, whereas the detrimental effect of consuming unsaturated fat is conditional on the concentration of fat.

The second insight gained from animal models is that consumption of diets high in fat, sugar, or both fat and sugar, does not produce a global deficit in cognition; rather, the effects of such diets appear to be dependent on task demands and the neural substrates underpinning successful performance. In particular, performance on tasks dependent on the hippocampus appear to be particularly sensitive to high-fat and/or high-sugar diet intake, again replicating observations reported in cross-sectional and experimental research in humans. For example, Stouffer, Warninger, and Michener (2015) provided rats a high-fat diet (60% energy from fat) for eight-weeks and then assessed their ability to form a conditioned cue preference (CCP). Rats were trained to associate one end of a three-chamber apparatus with water access, and the other end with the absence of water access. Half of the rats were trained in a hippocampal-independent version of the task in which the two chambers were distinguished from one another by a single environmental cue (unicoloured walls and floor), and the remaining rats completed a hippocampal-dependent version of the task in which the chambers were distinguished by multiple environmental cues (wall colour, floor material, smell). At test, rats were given free access to all chambers in the apparatus and time spent in the water-paired and non-water-paired compartments was measured. Stouffer et al. found chow-fed control rats showed

a CCP for the water-paired chamber, as indexed by rats spending significantly more time in the water-paired than the non-water-paired compartment, in both versions of the task. However, high-fat rats showed a CCP for the water-paired chamber in the single cue version, but not in the multiple cue version, of the task. These results indicate that eight-weeks of high-fat diet impaired hippocampal-dependent cognition while leaving hippocampal-independent cognition unaffected.

Kanoski, Davidson and colleagues have also demonstrated a selective impairment in hippocampal-dependent cognition on a number of cognitive tasks in rats maintained on a high energy diet (40% energy from fat, 22 % w/w glucose). In one study, rats were maintained on the high energy diet or control chow diet for 90-days prior to training on two non-spatial discrimination learning problems (Kanoski, Zhang, Zheng, & Davidson, 2010). Half of the rats from each diet condition were trained on a discrimination problem and a serial-feature positive discrimination problem, neither of which are dependent on the hippocampus. The remaining rats were trained on a discrimination problem and a serial-feature negative discrimination problem, the latter of which is dependent on the hippocampus (Holland, Lamoureux, Han, & Gallagher, 1999). Kanoski et al. found rats in both diet conditions were equally quick in learning the discrimination and the serial feature positive discrimination problems. However, rats consuming the high energy diet were impaired in their ability to learn the serial feature negative discrimination problem, showing high levels of responding on non-reinforced trials across all training blocks. These results demonstrated that the high energy diet selectively impaired hippocampal-dependent learning but had no influence on hippocampal-independent learning.

In a second study, Kanoski and Davidson (2010) trained rats to solve spatial and nonspatial working memory (WM) and reference memory (RM) problems in an eight-arm radial maze. For the spatial trials, four of the arms of the maze were randomly

allocated as rewarded and the remaining four arms were non-reward; this allocation was retained for all training and testing trials. For nonspatial trials, four removable arm inserts that differed in texture were allocated as rewarded, and another four removable arm inserts were allocated as non-rewarded; these inserts were randomly placed into the maze on each trial, such that the spatial location of the arms provided no information about the presence or absence of a reward. After learning the spatial and nonspatial tasks, rats were fed either a high energy diet or chow diet and tested for retention of the tasks at six time points across a 90-day period. Kanoski and Davidson found that impairments in spatial WM and RM retention emerged after only three-days of high energy diet access, whereas impairment in nonspatial WM and RM retention did not emerge until 30-days of high energy diet access. In each task, the memory retention deficits remained stable for all remaining tests. These results indicate that short-term exposure to high energy diet disrupts hippocampal-dependent spatial memory retention, whereas more extended exposure is required before hippocampal-independent nonspatial memory retention is disrupted.

The early emergence of a selective deficit in hippocampal-dependent cognition has been widely demonstrated using spontaneous object recognition tasks that exploit the innate preference of rodents to explore novel over familiar items (Bevins & Besheer, 2006; Ennaceur & Delacour, 1988). Two of the more commonly used tasks are the perirhinal-dependent object recognition memory task and hippocampal-dependent place recognition memory task, which assess a rodent's ability to discriminate a novel object from a familiar object (i.e. "what" memory) or to discriminate a novel object location from a familiar object location (i.e. "where" memory), respectively. In both tasks, rats are first familiarised to two objects located in an open-field arena and, after a given retention interval, are returned to the arena where either one object has been replaced by a novel

object (object recognition) or one object has been moved to new location in the arena (place recognition).

Research has demonstrated impairments in place recognition memory but intact object recognition memory in rodents consuming: a high-fat diet for two-weeks (Beilharz Kaakoush, Maniam, & Morris, 2016a); a high-sugar diet for five-days (Beilharz, Maniam, & Morris, 2014; Beilharz et al., 2016a) or two-weeks (Abbott, Morris, Westbrook, & Reichelt, 2016; Beilharz et al., 2016a; Beilharz, Maniam, & Morris, 2016b); and a high-fat high-sugar diet for one week (Beilharz et al., 2014, 2016b; Tran & Westbrook, 2015, 2018) or two-weeks (Beilharz, Kaakoush, Maniam, & Morris, 2018; Leigh, Kaakoush, Bertoldo, Westbrook, & Morris, 2020a; Leigh, Kaakoush, Westbrook, & Morris, 2020b). For example, Beilharz et al. (2016a) maintained rats on energy-matched diets that were high in saturated fat (lard), unsaturated fat (sunflower oil), or sugar (10% sucrose solution) for two-weeks before testing object recognition and place recognition memory. While rats in all diet conditions demonstrated comparable performance in the object recognition memory task, rats maintained on high saturated fat or high-sugar diets demonstrated impaired performance on the place recognition memory task compared to chow-fed control rats and rats maintained on a high unsaturated fat diet. These results confirm a selective deficit in hippocampal-dependent cognition, and also demonstrate that this deficit is conditional on consumption of saturated fat but not unsaturated fat.

Much of the literature that has used animal models of dietary manipulation has been restricted to examining diet-induced impairments in hippocampal-dependent spatial cognition. One of the most utilised tasks is the Morris water maze (MWM; Morris, 1984). The MWM consists of a circular pool filled with opaque water that contains a submerged platform in a designated target quadrant. Rats learn to navigate through the pool to the hidden platform by using the local and extra-maze cues; thus, the MWM assesses rodents'

ability to learn and remember the location of the hidden platform. The most common measures of learning include time to reach the hidden platform (escape latency) and distance travelled while navigating to the platform, and memory retention is most commonly assessed using a probe test in which the hidden platform is removed and the percentage of swimming time spent in the target quadrant is measured.

A number of studies report deficits in MWM performance in rodents exposed to high-fat and/or high-sugar diets (e.g., Coscina et al., 1986; Che et al., 2018; Jamshed, Arslan, & Gilani, 2014; Lewis, Singh, & Youssef, 2019; Pathan, Gaikwad, Viswanad, & Ramarao, 2008; Spinelli et al., 2017). For example, Mirzaei and colleagues (2018) demonstrated that compared to chow-fed control rats, rats maintained on a high-fat diet for eight-weeks had significantly increased escape latency and distance travelled during training, and spent significantly less time in the target quadrant at probe test. Similarly, Molteni and colleagues (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Molteni et al., 2004) reported that rats maintained on a diet high in both saturated fat and sugar (40% energy from lard, 40% energy from sucrose) for two-months had significantly increased escape latency during training compared to control rats fed a low-fat diet (13% energy from lard). In both studies, the high-fat high-sugar rats spent equal amounts of time in all four quadrants of the MWM at a probe test conducted three-days after training, whereas control rats spent more time in the target than the other quadrants. Taken together, these studies indicate impairments in both spatial learning and memory function with exposure to high-fat or high-fat high-sugar diets.

However, impaired learning and memory in the MWM has not been consistently reported in the animal literature (e.g. Denver, Gaut, & McLean, 2018; Magnusson et al., 2015; Scichilone, Yarraguntla, Charalambides, Harney, & Butler, 2016; Silva et al., 2005; Wu, Molteni, Ying, & Gomez-Pinilla, 2003). For example, Jurdak, Lichtenstein, and

Kanarek (2008) fed rats a high-sugar diet consisting of chow and 32% sucrose solution or a high-fat diet consisting of chow and a tub of partially hydrogenated fat for five-weeks. Rats consuming the high-sugar diet had increased escape latency during training and reduced time in the target quadrant at probe test when compared to chow-fed control rats and high-fat diet rats, which did not differ from one another. Conversely, Gergerlioglu and colleagues (2016) fed rats a high-sugar diet consisting of semi-purified chow with 100% of carbohydrates provided by sucrose, or a high-fat diet that provided 35% energy from fat (suet). Rats consuming the high-fat diet had increased escape latency on the final day of training and reduced time in the target quadrant during probe test when compared to chow-fed control rats and high-sugar diet rats, which showed comparable performance. Boitard and colleagues (2014) found impaired memory for the platform location in juvenile rats, aged three-weeks at time of diet access, that were exposed to a high-fat (24% w/w) diet for two-months when compared to control rats, but no differences between control rats and high-fat fed adult rats that were aged 12-weeks at time of diet onset. Kendig, Boakes, Rooney, and Corbit, (2013) found that rats provided with access to 10% sucrose solution for two hours per day for four-weeks did not differ from chow-fed control rats in their escape latency across training, but spent significantly less time in the target quadrant on probe tests conducted after three, six, and nine-days of training. Finally, Francis and colleagues (2013) failed to find a significant difference in escape latency across training between rats fed a high-fat and sugar diet for eight-weeks and rats consuming low-fat chow. However, when the platform was re-located to the opposite quadrant, rats consuming the high-fat and sugar diet had longer escape latency across re-training and spent more time in the original target quadrant during probe test. The inconsistent findings across experiments using the MWM may be due to methodological differences between studies. These are discussed below.

1.4.3. Summary of Experimental Research

Evidence from experimental investigations of the relationship between cognition and the consumption of Westernised diets has shown that people fed a diet high in fat or both fat and sugar quickly exhibit impairments in aspects of attention and memory, with relative sparing of more global cognition as measured by working memory capacity. It has also shown that the impairments in cognition following either a high-fat or high-fat high-sugar diet are not permanent; rather, there is emerging evidence that cognitive impairments may be ameliorated when such diets are terminated.

In rodent models, the relationship between diet and cognition appears equivocal. Studies examining the effect of sucrose, either in isolation or in combination with fat, have mostly reported deficits in spatial learning and memory. However, the results of studies examining the impact of dietary fat are more variable, perhaps dependent on the type and concentration of fat consumed, replicating the observations from epidemiological evidence in humans.

The inconsistent findings across experiments of dietary manipulation are most likely a consequence of key differences in experimental design. Such differences include the composition of the diets provided to the rodents: the type and concentration of fat, and the concentration of sucrose; the age of the rats at the start of diet access; different lengths of diet access; and different training protocols for behavioural assessment of cognition. Nevertheless, the experimental studies presented in this section provide compelling evidence that dietary intake of fat, sugar, or both fat and sugar, can impair cognitive function under certain conditions.

While the dietary and metabolic requirements of humans and rodents are similar, it is important to note the differences in their dietary histories. For example, the variety of foods eaten by humans compared with standard chow fed to lab rodents. Such

differences may limit the parallels between studies examining dietary effects in people and rodents. Despite these differences, the research examined here provides converging evidence from studies in humans and rodent models that dietary intake of fat and/or sugar has a particularly adverse effect on hippocampal-dependent cognition, in line with epidemiological evidence of an association between fat/sugar intake and impaired hippocampal-dependent cognition in children and young-adults. Moreover, the evidence from rodents suggests that impairments in hippocampal-dependent cognition emerge rapidly after exposure to such diets.

1.5. Proposed Mechanisms of Modern Diet Impact on Cognition

The specific mechanism or mechanisms by which dietary fat and sugar intake influence cognition are yet to be determined. However, a number of potential mechanisms have been proposed. These include gut microbiome dysbiosis, impairments in glucose regulation and insulin sensitivity, alterations in central nervous system (CNS) insulin sensitivity, neuroinflammation, and impairments in blood-brain barrier (BBB) integrity. A thorough review of these mechanisms is beyond the scope of this thesis, and can be found elsewhere (e.g., Kanoski & Davidson, 2011; Francis & Stevenson, 2013; Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014; Leigh & Morris, 2020).

1.5.1. Gut Microbiome Dysbiosis

Over the past 15-years there has been growing recognition of bidirectional communication between the gut microbiome and the brain, termed the gut-brain axis (Cryan & Dinan 2012; Dinan & Cryan, 2017; Cryan et al., 2019). Research in humans across the life span (e.g., Bajaj et al., 2016; Carlson et al., 2018; Manderino et al., 2017; Renson, Kasselman, Dowd, Waldron, Jones, & Herd, 2020) and in rodents (e.g. Bercik et

al., 2011; Fröhlich et al., 2016; Hoban et al., 2016) demonstrates the substantial influence of the gut microbiome on brain function and cognition. The gut microbiome refers to the collection of microorganisms that reside within the gastrointestinal tract (Thursby & Juge, 2017). The species that reside in the gut are taxonomically identified by genus, family, order, and phyla. The two most common phyla are *Firmicutes* and *Bacteroides* that account for approximately 90% of the microbial community (Arumugam et al., 2011). The ratio between these two phyla is recognised to be a critical determinant of overall health, and alterations in the ratio are associated with several pathological conditions, including obesity (Bervoets et al., 2013; Ley, Turnbaugh, Klein, & Gordon, 2006) and type 2 diabetes (Larsen et al., 2010), as well as neurological (Cryan, O'Riordan, Sandhu, Peterson, & Dinan, 2020) and neurodegenerative diseases (Ambrosini et al., 2019).

The main determinant of gut microbiome composition is dietary intake (Leigh & Morris, 2020; Sandhu, Sherwin, Schellekens, Stanton, Dinan, & Cryan, 2017). Cross-sectional studies in both children and adults have shown that individuals living in geographical regions that differ considerably in their dietary patterns also differ in their gut microbiomes (e.g., De Filippo et al., 2010; Yatsunenko et al., 2012), and that adults from similar geographical regions, but who differ in their intake of plant- and animal-based diets, also differ in their gut microbiomes (e.g. Matijašić et al., 2014; Zimmer et al., 2012). Experimental research in humans (David et al., 2014) and rodents (Carmody et al., 2015; Laffin et al., 2019) has demonstrated that alterations in microbiome composition occur within days of changes in dietary intake. For example, in healthy young adults aged 22 to 33-years, consumption of a diet comprised entirely of animal products or plant products alters the diversity of the microbiome after one-day (David et al., 2014). Similarly, mice fed a chow diet supplemented with 50% ground beef exhibited changes in the microbiome that co-occurred with alterations in learning and memory in a

hippocampal-dependent spatial discrimination task (Li, Dowd, Scurlock, Acosta-Martinez, & Lyte, 2009).

Alterations in the composition of the gut microbiome has been reported in rodents consuming diets that are high in fat (Beilharz et al., 2016a; Magnusson et al., 2015; Saiyasit et al., 2020), sugar (Beilharz et al., 2016a, 2016b, 2018; Li et al., 2019; Magnusson et al., 2015; Noble, Hsu, Jones, Fodor, Goran, & Kanoski, 2017b; Noble et al., 2020), or both fat and sugar (Beilharz et al., 2018; Leigh et al., 2020a, 2020b). For example, intake of a high-fat high-sugar diet decreases *Firmicutes* and increases *Bacteroides* populations in adult rodents (Hildebrandt et al., 2009; Zhang et al., 2012). Importantly, a number of these studies have also demonstrated that the shifts in gut microbiome are associated with cognitive impairment. For example, Beilharz et al. (2016a) observed distinct alterations in the microbiome of rats provided energy-matched diets that were high in saturated fat or high in sugar for two-weeks. The most significant changes in gut microbiome diversity were observed at the level of *Clostridiales* (Phylum: *Firmicutes*), however the changes within this order differed between the rats fed high-fat or high-sugar. Notably, both groups of rats were impaired in hippocampal-dependent place recognition, but the specific microbiota associated with the hippocampal-dependent memory impairment differed depending on the experimental diet. Research from the same group has also demonstrated that two-weeks of probiotic supplementation prior to access to a high-fat high-sugar diet protects against diet-induced alterations in the gut microbiome as well as diet-induced deficits in place recognition memory (Beilharz et al., 2018). These findings therefore not only highlight that the macronutrient profile of a diet produces distinct alterations in the gut microbiome, but also that such alterations are independently correlated with hippocampal-dependent cognition.

The mechanisms by which diet-induced alterations in the gut microbiome mediate cognitive impairment remain unknown (see Martin, Osadchiy, Kalani, & Mayer, 2018; Noble et al., 2017a). One hypothesis is that short-chain fatty acids (SCFAs) produced by the gut microbiome during fermentation of dietary fibre are important for brain health and function (see Dalile, Van Oudenhove, Vervliet, & Verbeke, 2019). Short-term diet interventions in humans have demonstrated significantly decreased production of SCFAs within days of switching from a plant-based diet to a diet high in animal products (David et al., 2014). Similarly, research in rodents has found reduced SCFA production in mice fed a high-sugar diet for two-days (Gill et al., 2018; Laffin et al., 2019), or fed a high-fat diet for two-weeks (Jakobsdottir, Xu, Molin, Ahrne, & Nyman, 2013) and four-weeks (Berger et al., 2014). In light of evidence of a correlation between gut dysbiosis and cognitive impairment after short-term high-fat and/or sugar diet intake (Beilharz et al., 2016a, 2018), the early emergence of decreased SCFA production that accompanies dietary fat and sugar intake is one potential mechanism through which diet impacts cognitive function. However, the gut microbiome also plays a critical role in neuroinflammatory processes (Cryan & Dinan, 2015; Erny et al., 2015), BBB integrity (Braniste et al., 2014), glucose regulation and insulin sensitivity (Ridaura et al., 2013; Vrieze et al., 2012), as well as the transcription of plasticity-related proteins such as brain derived neurotrophic factor (BDNF; Bercik et al., 2011; Stilling, Dinan, & Cryan, 2014). Each of these has been proposed as potential mechanisms underlying diet-induced deficits in cognition. These will be discussed in the following sections.

1.5.2. Glucose Regulation and Insulin Sensitivity

Excessive dietary fat and/or sugar intake are associated with the development of metabolic disorders that are characterised by impaired glucose regulation and reduced insulin sensitivity, such as occurs in diabetes and metabolic syndrome (Fabiani, Naldini,

& Chiavarini, 2019; Kopp, 2019; Rodríguez-Monforte, Sánchez, Barrio, Costa, & Flores-Mateo, 2017). Recent evidence suggests that alterations in glucose regulation and insulin sensitivity may mediate the cognitive impairments observed in individuals consuming such diets (Pal, Mukadam, Petersen, & Cooper, 2018). Epidemiological research provides evidence of a relationship between deficits in cognition and diabetes (Ganguli et al., 2020; Hassing et al., 2004; Marseglia et al., 2019; Mehrabian et al., 2012; Yaffe et al., 2004; Zhang, Jiang, Han, Liu, & Zhou, 2019), as well as cognitive impairment and metabolic syndrome (Assuncao, Sudo, Drummond, de Felice, & Mattos, 2018; Atti et al., 2019; Cavalieri et al., 2010; Dik et al., 2007; Tsai et al., 2016). For example, neuropsychological assessment of adults with Type 2 diabetes mellitus has shown impaired performance in tasks that assess executive function, complex information processing, verbal learning, verbal fluency, and both visual and spatial memory relative to age-matched healthy controls (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Manschot et al., 2006). Furthermore, pharmacological treatment of type 2 diabetes has been associated with improvements in executive function, verbal memory, spatial memory, and visuospatial organisation (Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993; Ryan, Freed, Rood, Cobitz, Waterhouse, & Strachan, 2006); however, this treatment does not completely reverse the deficits in these aspects of cognition (Gold et al., 2007).

Impaired cognitive function has also been linked to alterations in glucose regulation in the absence of metabolic disease (see Smith, Riby, van Eekelen, & Foster, 2011). For example, epidemiological research in young adults has demonstrated that higher fasting blood glucose level is associated with poorer performance on tasks assessing attention, visuospatial memory (Weinstein et al., 2015), and inhibitory control (Hawkins, Gunstad, Calvo, & Spitznagel, 2016). Furthermore, impaired glucose regulation, assessed using a glucose tolerance test, predicted verbal memory, assessed

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using the LM subtest from the WMS-III and a list-learning task (Messier, Awad-Shimoon, Gagnon, Desrochers, Tsiakas, 2011). In older adults, higher blood glucose levels are associated with poorer verbal memory in the Rey Auditory Verbal Learning Test (Kerti, Witte, Winkler, Grittner, Rujescu, & Flöel, 2013) and impaired glucose tolerance is associated with reduced scores on the MMSE, indicating worse global cognitive function (Kalmijn, Feskens, Launer, Stignen, & Kromhout, 1995), and poorer working memory (Ennis, Saelzler, Umpierrez, & Moffat, 2020). Finally, blood glucose levels in older adults also predict greater declines in global cognition function, verbal ability, and spatial ability assessed 16-years later (Seetharaman et al., 2015).

Epidemiological research has also shown that reduced insulin sensitivity is associated with poor cognition. For example, with a number of studies demonstrate poorer verbal fluency in middle-aged (Ekblad et al., 2015, 2017) and older adults (Benedict et al., 2012), poorer declarative memory and executive function in both middle-aged and older adults (Bruehl, Sweat, Hassenstab, Polyakov, & Convit, 2010), and lower scores on the MMSE (Kalmijn et al., 1995). Longitudinal research in older adults has also demonstrated that insulin sensitivity predicts verbal list learning and cognitive function, assessed using the CERAD Plus neuropsychological battery, at four-year follow up (Vanhanen et al., 1998; Willmann et al., 2020). Experimental studies that manipulate peripheral insulin levels have demonstrated alterations in cognition. For example, inducing systemic hyperinsulinemia, while maintaining constant blood glucose concentration with a hyperinsulinemic-euglycemic clamp, reduces reaction times in a visual decision-making task (Rotte et al., 2005) and selective attention in a Stroop task (Kern et al., 2001) in healthy adults, and improves declarative memory in patients with Alzheimer's disease (Craft et al., 1996, 1999). Taken together, the findings from both cross-sectional and experimental research indicate that glucose regulation and insulin

sensitivity, even in the absence of metabolic disease, play a critical role in cognition and that impairments in either are accompanied by cognitive dysfunction.

Experimental research in humans and rodents provides evidence that glucose regulation and insulin sensitivity are associated with diet-induced cognitive impairment. For example, Attuquayefio et al. (2017) showed that the change in blood glucose level across a meal in young healthy adults was significantly greater in participants that consumed a high-fat high-sugar breakfast for four-days than control participants, and that greater increases in blood glucose were associated with a greater decline in verbal memory assessed using the HVLT task. They also found that when blood glucose change was included as a covariate in the statistical analysis of change in HVLT scores between baseline and day four of diet consumption, the difference between the experimental and control conditions became non-significant. Together, these results suggest that a relatively brief exposure to a high-fat high-sugar diet can disrupt blood glucose regulation which may have contributed to the associated impairments in the HVLT task.

Research in rodents provides more direct evidence of a mediating role of glucose regulation and insulin sensitivity in diet-induced cognitive impairments. For example, Greenwood and Winocur (2001) demonstrated that high-fat diet-induced impairments on a variable interval delayed alternation (VIDA) task were improved by acute glucose administration. The VIDA task assesses rat's ability to learn an alternation rule, as well as remember events that occurred on a preceding trial. Rats receive 12 reinforced ("Go") trials alternating with 12 non-reinforced ("No Go") trials that are separated by a variable intertrial interval (ITI) delay; the rats must learn and remember that a successful Go trial is followed by a No-Go trial. Greenwood and Winocur found that rats consuming a 20% high saturated fat diet for three-months were impaired on the VIDA task at both short and long ITI delays relative to chow-fed control. However, intraperitoneal injection of

glucose 30-minutes prior to the VIDA task ameliorated this diet-induced impairment, with glucose-injected rats demonstrating improved performance at both short and long ITIs relative to saline-injected rats. Similarly, Pathan, Gaikwad, Viswanad, and Ramarao (2008) found that rats fed a high-fat diet for five-weeks had significantly increased plasma glucose and plasma insulin concentration along with significantly increased escape latency in a MWM when compared to chow-fed control rats. However, high-fat rats that received intraperitoneal injection of rosiglitazone, an anti-diabetic drug that acts as an insulin sensitizer, for one week prior to behavioural and biochemical assessment had significantly reduced plasma glucose and insulin concentrations when compared to saline injected rats. Moreover, the rosiglitazone-injected rats did not differ from control rats in terms of plasma glucose and plasma insulin concentration, nor in escape latency in the MWM.

Taken together, the results of experimental research involving manipulation of dietary fat and sugar intake provides converging evidence that diet-induced disturbances in glucose regulation and/or insulin sensitivity can mediate cognitive impairments. The specific mechanisms by which this occurs is yet to be clearly elucidated. However, one potential route is through disruption of CNS insulin signalling, which is discussed in detail in the following section.

1.5.3. Central Nervous System Insulin signalling and Sensitivity

Excessive intake of a high-sugar and/or high-fat diet is commonly accompanied by insulin resistance. Although the brain was thought to be insulin insensitive, it is now known that insulin crosses the BBB into the interstitial fluid (ISF) via a saturable receptor-mediated transport system (Begg, 2015). Insulin in the ISF binds to insulin receptors embedded in the cellular membrane of neurons, leading to activation of insulin receptor substrate (IRS) proteins. These IRS proteins stimulate intracellular signalling cascades,

such as phosphoinositide 3-kinase (PI3K)-Akt and MAPK/ERK pathways, that support cognitive function (Blazquez, Velazques, Hurtado-Carneiro, & Ruiz-Albusac, 2014). It is now clear that activation of insulin pathways within the CNS plays important roles in neural circuit formation, neuronal proliferation and survival, synaptic maintenance, dendritic arborization, and learning and memory processes (Banks, Owen, & Erikson, 2012).

Evidence from human and rodent studies supports a role for CNS insulin signalling in cognitive function (reviewed in Ma, Wang, & Li, 2015; Zhao, Chen, Quon, & Alkon, 2004). One example is the enhanced performance on learning and memory tasks by systemic administration of glucose which is now known to be mediated in part by increased delivery of insulin to the CNS (Craft & Watson, 2004). Another example is the improvement in cognition in both healthy adults as well as individuals with neural disease via daily intranasal administration of insulin (see Santiago & Hallschmid, 2019). For example, intranasal insulin for eight-weeks improved declarative memory in normal adults (Benedict et al., 2004, 2007) and in patients with Alzheimer's disease (Reger et al., 2008). However, improved visual-spatial working memory has also been observed in healthy young women and postmenopausal women after a single intranasal dose of insulin (Krug, Benedict, Born, & Hallschmid, 2010).

Diet-induced insulin resistance in the periphery can also develop within the CNS (Mielke et al., 2005). This CNS-specific insulin resistance is characterized by decreased sensitivity of insulin receptor in the BBB. This reduces transportation of insulin across the BBB into the CNS and causes aberrant activation of insulin signalling cascades within neurons (Begg et al., 2013). Experimental research in adults demonstrates the association between body weight and CNS insulin resistance. For example, cross-sectional research in healthy young men has demonstrated a relationship between higher BMI and a lower

plasma insulin to cerebrospinal fluid insulin ratio (Kern et al., 2006). Research using magnetoencephalography (MEG) has also shown reductions in cortical activation in obese adults compared to normal weight adults after hyperinsulinemic-euglycemic clamp (Tschritter et al., 2006). Together, these results are indicative of reduced transport of insulin across the BBB into the ISF. However, reductions in cortical activation in obese adults when compared to normal weight adults have also been reported in MEG studies after acute intranasal delivery of insulin (Guthoff et al., 2011; Stingl et al., 2010). As delivery of insulin to the CNS using intranasal method circumvents the BBB, these results indicate alterations in insulin-mediated neuronal activation.

Experimental research in rodents has provided evidence that dietary fat and sugar intake is associated with disruptions to CNS insulin signalling. For example, Calvo-Ochoa and colleagues (2014) found reduced phosphorylation of IRS and Akt proteins in the hippocampus of rats that received an intraperitoneal insulin injection after seven-days of consuming a diet high in fat (10% w/w lard) and fructose (20% solution) when compared to chow-fed controls. In addition to this altered activation of the PI3k/Akt signalling cascade, rats fed the high energy diet exhibited structural changes in the CA1 region, including reduced dendritic arborisation and spine number, as well as increased phosphorylation of tau protein that is characteristic of Alzheimer's Disease. Pratchayasakul et al. (2011) have demonstrated decreased insulin-mediated long-term depression (LTD) and reduced phosphorylation of IRS and Akt proteins in insulin-incubated hippocampal slices taken from rats fed a high-fat chow (59% energy from lard). Finally, Arnold et al. (2014) found alterations to the PI3k/Akt signalling cascade in the frontal cortex and hippocampus of mice fed a high-fat diet (60% energy from fat) for 17-days. In this study, the frontal cortex and hippocampus of mice were sliced and incubated with insulin. Western blot analysis subsequently showed reduced concentration of

phosphorylated IRS and Akt proteins, as well as reduced activation of signalling targets downstream of Akt, in mice fed the high-fat diet when compared to chow-fed control mice.

Research in rodents has also provided direct evidence that diet-induced alterations in neuronal insulin signaling is associated with cognitive deficits. For example, McNay and colleagues (2010) fed rats a high-fat diet (31.8% energy as fat from butter and corn oil) or standard chow for 20-weeks and then subjected them to a spontaneous alternation task in a four-arm maze in order to assess hippocampal-dependent spatial working memory. Prior to behavior testing, the rats consuming the high-fat diet were separated into two groups based on body weight gain: rats in the top tertile were defined as diet-induced obese (DIO) and the bottom tertile were defined as diet-resistant (DR). When compared to control and DR rats, DIO rats were hyperglycaemic and hyperinsulinemic, and showed significantly reduced spontaneous alternation. There were no differences on these measures between DR and control rats. McNay et al. further demonstrated a dose-dependent improvement in spontaneous alternation with intrahippocampal infusion of insulin in all groups, however the dose-response curve for insulin enhancement was shifted to the right in DIO rats.

In a more recent study, mice were fed a high-fat diet (21% w/w fat) or low-fat control diet (7% w/w fat) for 12-weeks before implantation of mini osmotic pumps that delivered continuous infusion of insulin or saline to the dorsal hippocampus (Gladding, Abbott, Antoniadis, Stuart, & Begg, 2018). After one week of intrahippocampal insulin or saline infusion, spatial memory was assessed using a MWM and a Y-maze spontaneous alternation task. Gladding et al. found that spatial memory was reduced in high-fat mice receiving saline infusion when compared to high-fat mice receiving insulin infusion and control mice; specifically, high-fat mice receiving saline infusion showed reduced time

in the target quadrant across acquisition trials in the MWM and reduced spontaneous alternation in the Y-maze task when compared to all other groups. Critically, mice fed high-fat diet receiving insulin infusion did not differ from low-fat fed mice on either task. Together, the results of McNay et al. (2010) and Gladding et al. demonstrate that diet-induced deficits in hippocampal-dependent spatial memory can be rescued with intrahippocampal insulin administration, supporting a role for aberrant CNS insulin signalling and insulin resistance in diet-induced cognitive impairments.

A number of mechanisms have been proposed to mediate the relationship between CNS insulin signalling and cognition (Biessels & Reagan, 2015; Blázquez et al., 2014; Spinelli, Fusco, & Grassi, 2019). An exhaustive review of such mechanisms is beyond the scope of this thesis, however a few of the proposed mechanisms that are of particular relevance to dietary intake of fat and sugar will be mentioned here. The first mechanism is diet-induced alterations in cerebral energy utilisation. Insulin regulates glucose metabolism, the main source of energy for neurons, within the CNS and periphery. Neurons are high energy-consuming cells, with much of the energy used to generate action potentials and postsynaptic potentials that are critical for learning and memory (Howarth et al., 2012). Basal levels of glucose are maintained by insulin-independent glucose transporters (GLUT)-1 and GLUT-3, which have been found to be decreased in mice maintained on high-fat and sugar diet for 14-weeks (Kothari et al., 2017). However, glucose uptake into neurons during times of high cognitive demand occurs exclusively via PI3k/Akt signalling-mediated translocation of GLUT-4to neuron cell membranes (Grillo, Piroli, Hendry, & Reagan, 2009). Thus, aberrant insulin signalling in the CNS may impair cerebral energy utilisation required for certain cognitive tasks. In support of this proposal, McNay et al. (2010) observed that ISF glucose concentration decreased in control and DR rats across the spontaneous alternation task, but remained stable in DIO

rats. The decrease in ISF glucose concentration observed in cognitively-intact control and DR rats suggests that spontaneous alternation performance was mediated by GLUT-4 induced uptake of glucose. Therefore, the absence of change in ISF glucose concentration in DIO rats may be indicative of reduced GLUT-4 translocation, and thus reduced activation of the PI3k/Akt signalling cascade.

A second potential mechanism is alterations in neuronal activity. Independently of its role in glucose utilisation, insulin regulates the neural circuits involved in cognition through its action on synaptic plasticity, long-term potentiation (LTP), LTD, and neural proliferation (Biessels & Reagan, 2015; Duarte, Moreira, & Oliveira, 2012). Research in rodents has shown that CNS insulin resistance in mice fed a high-fat high-sugar diet for 14-weeks is accompanied by decreased synaptic plasticity in the CA1 hippocampal subregion (Kothari et al., 2017). Similarly, Arnold et al. (2014) reported reduced spontaneous alternation in a T-maze in mice fed high-fat diet, which was accompanied by reduced phosphorylation of IRS and Akt proteins, reduced spinophilin-labelled dendritic spines, and a decrease in post-synaptic PSD-95 protein, which is a scaffolding protein that mediates synaptic plasticity.

A final potential mechanism is neuroinflammation. In vivo and in vitro models of insulin administration decrease proinflammatory responses within the CNS (Adzovic et al., 2015; Canteiro et al., 2019; Mamik et al., 2016; Rajasekar, Nath, Hanif, & Shukla, 2017). Thus, CNS insulin resistance that accompanies intake of fat and sugar may contribute to increased neuroinflammation. In support of this proposal, Gladding et al. (2018) found that mice fed a high-fat diet and infused with saline had significantly increased expression of inflammatory markers in the hippocampus. They also found that expression of these markers was reduced in mice fed the high-fat diet that received intra-hippocampal insulin infusion, with expression levels in this group of mice similar to those

observed in mice fed a low-fat diet. Neuroinflammation as a mediator of diet-induced cognitive deficits is discussed in more detail in the next section of this thesis.

1.5.4. Neuroinflammation

Neuroinflammation is a state of sustained inflammation within the CNS arising from chronic disease and/or dysregulated inflammatory processes (Streit, Mrak, & Griffen, 2004). Neuroinflammation is thought to contribute to several neurodegenerative disorders that are characterised by cognitive impairment. For example, there is a positive correlation between expression of inflammatory markers in the hippocampus and cognitive deficits in patients with Alzheimer's disease (Eikelenboom et al., 2002; Griffin, 2006; Mrak & Griffin, 2001; Shaftel, Griffin, & O'Banion, 2008), mild traumatic brain injury (Girgis, Pace, Sweet & Miller, 2016), and type 2 diabetes (Datusalia & Sharma, 2014; Hwang et al., 2014).

Glial cells are a diverse population of immune cells within the CNS that mediate the neuroinflammatory response (Stephenson, Nutma, van der Valk, & Amor, 2018). Microglia, the resident macrophages in the brain, are the primary glial cell type within the CNS (Stephenson et al., 2018). Microglia play a critical role in initiating the innate inflammatory response (Hanisch & Kettenmann, 2007; Ransohoff & El Khoury, 2016). Microglia produce an array of pro-inflammatory proteins (cytokines) that target and activate other nearby CNS immune cells, such as oligodendrocytes and astrocytes, leading to a cascade of pro-inflammatory cytokine production (Streit et al., 2004). While this cascade is typically under tight physiological control, it is chronically activated in pathological neuroinflammatory states (Ransohoff & El Khoury, 2016).

The brain has traditionally been viewed as immunologically privileged because of the BBB, however substantial evidence now indicates that cytokines released during peripheral inflammation can cross the barrier and activate resident CNS microglia (Banks

& Erikson, 2010; Kelley et al., 2003; Johnson, 2015). For example, peripheral cytokines are theorized to act as molecular signals of sickness that act upon the brain to induce adaptive behaviours that promote and support recovery from illness, such as appetite suppression, resting, and sleeping (Kelley et al., 2003; Konsman, Parnet, & Dantzer, 2002). Research in rodents demonstrates that systemic administration of lipopolysaccharide (LPS), an immune-activating protein located in the cell wall of pathogenic bacteria, increases proinflammatory cytokine Interleukin-1Beta (IL-1β) in the CNS (e.g. Biesmans et al., 2013; Godbout et al., 2015; Ming, Sawicki, & Bekar, 2015), as does a peripheral injection of IL-1β (e.g. Biesmans et al., 2013; Skelly, Henessy, Dansereau, & Cunningham, 2013) or proinflammatory cytokine Tumour Necrosis Factor-Alpha (TNF-α; e.g. Biesmans et al., 2015; Skelley et al., 2015). Such findings demonstrate that neuroinflammatory changes can be a consequence of pathogen-derived proteins or peripheral inflammatory cytokines entering the CNS and activating neuroinflammatory processes.

Peripheral inflammation not only produces neuroinflammation but also cognitive impairments (see Bendorius, Po, Muller, & Jeltsch-David, 2018). In humans, obesity is associated with systemic inflammation as well as increased proinflammatory markers in the brain (e.g. Cazettes, Cohen, Yau, Talbot, & Convit, 2011; Pickup & Crook, 1998; Guillemot-Legris & Muccioli, 2017). Furthermore, a number of studies have shown that peripheral inflammation can induce brain inflammation that contributes to neurodegenerative disease characterised by cognitive impairment (see Cai, 2013 and Estrada & Contreras, 2019). Habitual fat and sugar intake can also result in systemic low-grade inflammation (see Manzel et al., 2014). For example, experimental research in healthy young adults showed that consuming a standard (with sugar) soft drink at all main meals each day for a three-week period significantly increased the concentration of

circulating high sensitivity C-reactive protein (hs-CRP), a blood marker of inflammation (Aberli et al. 2011). Similarly, research in overweight adults found that 10-weeks of consuming standard soft drinks increased the blood concentration of the proinflammatory markers haptoglobin and transferrin, whereas soft drinks containing artificial sweeteners decreased the concentration of these proinflammatory markers (Sørensen, Raben, Stender, & Astrup, 2005). Correlations have been reported between fat intake and peripheral inflammation (Arya et al., 2006; Mozaffarian et al., 2004), but the nature of these correlations depends on the type of dietary fat. Cross-sectional research in elderly men has found that hs-CRP levels are positively correlated with higher plasma levels of SFA and negatively correlated with higher plasma levels of PUFA (Clarke, Shipley, Armitage, Collins, & Harris, 2008). In an experimental dietary intervention in overweight middle-aged adults in the Netherlands, biopsies of abdominal fat pads collected after eight-weeks of a high SFA diet or high MUFA diet were found to contain significantly increased expression of genes implicated in proinflammatory and anti-inflammatory processes, respectively (van Dijk et al., 2009).

Research in rodents has shown that cognitive impairments induced by consumption of diets that are high in fat (e.g. Alghamdi, 2021; Che et al., 2018; Spencer et al., 2017; Thirumangalakudi et al., 2008), sugar (e.g. Beilharz et al., 2016a, 2016b; Gomes et al., 2020; Hsu et al., 2015), or both fat and sugar (e.g., Bondan, Cardoso, Martins, & Otton 2019; Yu et al., 2019) are associated with a neuroinflammatory response in the brain. For example, Almeida-Suhett and colleagues (2017) demonstrated reduced spontaneous alternation in a Y-maze as well as increased hippocampal neuroinflammation, indexed by increased concentration of IL-1β protein, in mice fed a high-fat diet (60% energy from fat) for 16-weeks. Almeida-Suhett et al. also found that the deficits in Y-maze performance were negatively correlated with hippocampal IL-1β

concentration, suggesting a relationship between neuroinflammation and behavioural performance. Similarly, Beilharz et al. (2014) found that the impaired memory in a place recognition task was accompanied by increased hippocampal neuroinflammation, indexed by increased mRNA expression of IL1β and TNF-α, in rats fed chow supplemented with 10% sucrose solution and rats fed a cafeteria diet, comprised of store-bought discretionary foods and supplemented with sucrose solution, for three-weeks. The impaired performance in the place recognition task was also negatively correlated with TNF-α mRNA levels.

Additional evidence of neuroinflammation mediating diet-induced cognitive impairments comes from intervention studies in rodents. Such research has shown that dietary interventions, such as zinc supplementation (de Oliveira et al., 2021), vitamin d supplementation (Hajiluian et al., 2017), and increased intake of omega-3 fatty acids (Labrousse et al., 2012) and dietary fibre (Shi et al., 2020), and pharmacological interventions, such as Formononetin (Fu et al., 2019), Resveratrol (Jeon et al., 2012), Rosuvastatin (Husain et al., 2017), and Ursolic acid (Lu et al., 2011) can reduce neuroinflammation and attenuate cognitive deficits in rodents exposed to high-fat and/or high-sugar diets. For example, Leigh at al. (2020b) co-administered a high-fat high-sugar diet and minocycline, a tetracycline antibiotic, to rats for four-weeks and found no evidence of diet-induced impairment in place recognition memory nor hippocampal gene expression of proinflammatory cytokines when compared to saline-infused experimental diet-alone rats. Leigh et al. also found that introducing minocycline in the fifth week of diet access not only reverses the diet-induced impairment in place recognition memory but also normalizes the increase in proinflammatory gene expression.

Neuroinflammation is associated with altered brain physiology, brain morphology, and synaptic plasticity, which result in aberrant neural signalling. For

example, mice fed a high-fat diet (60% energy from fat) for 21-weeks showed impaired spatial memory in a Stone T-maze, which requires animals to learn a sequence of left and right turns to escape from a maze (Pistell et al., 2010). These mice were also found to have increased neuroinflammation, indicated by increased expression of TNF-α and Interleukin-6 (IL—6), and decreased expression of BDNF, which plays a critical role in neural growth and survival. Hao, Dey, Yu, and Stranahan (2016) have also demonstrated impaired hippocampal-dependent spatial memory that was associated with neuroinflammation, altered neuronal morphology, and disrupted synaptic plasticity within the hippocampus of mice fed a high-fat diet (60% energy from fat) for five-months when compared to mice maintained on a low-fat diet (10% energy from fat). Specifically, high-fat diet mice had reduced alternation in a Y-maze, increased expression of proinflammatory cytokine IL-1β, decreased LTP at signalling inputs to the dentate gyrus, decreased expression of synaptic scaffolding proteins, reduced dendritic spine density, and evidence of synaptic phagocytosis by microglia. Notably, the cognitive impairment, disrupted neuronal morphology, and reduced synaptic plasticity were normalised in mice fed the high-fat diet for three-months and then reversed to the low-fat diet for 2-months, despite these mice showing similar levels of adiposity as mice fed the high-fat diet for five-months. These findings suggest that dietary fat intake, in the absence of obesity, influence neuroinflammation and neural function. Similar findings have been reported using shorter diet exposures. For example, mice fed a high-fat (18.4%) diet for eight-weeks showed impaired memory for the location of the platform in the MWM, increased neuroinflammation, indicated by increased expression of IL-1β and TNF-α, decreased expression of BDNF, and decreased Synapsin-1, a vesicle-associated protein that regulates the release of neurotransmitters at the synapse (Che et al., 2018). Together, the evidence from these studies suggests that disrupted neuronal morphology and synaptic

function may be mechanisms through which diet-induced neuroinflammation impairs cognition.

1.5.5. Blood-Brain Barrier Integrity

The BBB is a semi-permeable membrane that regulates the movement of molecules, ions, hormones, and cells from the blood to the CNS. The BBB is comprised of brain endothelial cells, pericytes, basal lamina, and astrocyte end-feet that are held together by tight junctions comprised of claudins, occludin, and tight junction proteins (Daneman & Prat, 2015). The BBB is critical for regulating CNS homeostasis; disrupted integrity of the BBB alters the permeability of the membrane, leading to entry of immune cells and peripheral molecules into the CNS and, as a result, disrupted homeostasis (see Abbott, Patabendige, Dolman, Yusof, & Begley, 2010 and Daneman, 2012). A number of studies have demonstrated that obesity is associated with alterations in BBB integrity (see Buie, Watson, Smith, & Sims-Robinson, 2019; Rhea et al., 2017). For example, longitudinal research in middle-aged females demonstrated that participants whose BMI placed them in the overweight or obese category at baseline had reduced BBB integrity, indexed by a high cerebrospinal fluid-to-serum albumin ratio, across a 24-year follow up period when compared to those who fell in the normal BMI category (Gustafson et al., 2007). Furthermore, altered integrity of the BBB has been observed in a number of neurological diseases and neurodegenerative disorders (see Zlokovic, 2008, 2010).

In rodents, dietary fat and sugar intake has been demonstrated to disrupt BBB integrity and permeability (e.g. Davidson et al., 2012, 2013; Rutkowsky et al., 2018). For example, Kanoski et al. (2010) demonstrated a selective impairment in hippocampal-dependent cognition that was associated with reduced BBB integrity in rats fed a high-fat and sugar diet for 90-days. In this study, high-fat high-sugar diet rats were impaired in a discrimination task that was hippocampal-dependent but not in one that was

hippocampal-independent. These rats were also found to have decreased expression of proteins that comprise BBB tight junctions and higher sodium fluorescence, a tracer that is typically excluded from the CNS by the BBB, in the hippocampus. Notably, sodium fluorescence was not found in the prefrontal cortex or striatum, indicating that the increased permeability of the BBB selectively affected the hippocampus and its associated cognitive processes. Similarly, Hargrave, Davidson, Zheng, and Jenzig (2016) reported disrupted BBB integrity in the hippocampus, evidenced by increased sodium fluorescence, but not in other brain regions in rats prone to weight gain but not in rats resistant to weight gain. However, the increased fluorescence was only observed in rats consuming a high-fat high-sugar diet for 90-days, but not in rats consuming the diet for 10 or 40-days. Hargrave et al. further reported that the disruption in BBB integrity was associated with a shift in the behavioural response used for spontaneous alternation in a Y-maze from a hippocampal-dependent place strategy to a hippocampal-independent response strategy. Together, this evidence suggests that high energy diets gradually affect BBB integrity, selectively impairing hippocampal function.

It is presently unknown how diet-induced alterations in BBB integrity promote deficits in hippocampal-dependent learning and memory. One hypothesis is that increased permeability of the BBB allows toxins, such as those generated by gut microbes, and other harmful molecules, such as peripheral proinflammatory cytokines, to enter the CNS (Kanoski & Davidson, 2011; Hsu & Kanoski, 2014). Notably, however, changes in BBB integrity appear to develop with long diet exposure, but cognitive impairments have been observed after only a few days of diet. This does not preclude disruption in BBB integrity as a contributing factor to cognitive impairment; rather, it suggests that BBB dysfunction may contribute to the maintenance, rather than the onset, of impairments.

1.5.6. Summary of Proposed Mechanisms

The evidence reviewed above suggests a number of mechanisms may be responsible for the cognitive impairments that accompany high-fat and/or high-sugar diets. It is unlikely that these mechanisms operate independently; rather, it is most likely that the disruptions are a result of a cascade effect that begins in the periphery. Figure 1.2. provides a schematic that outlines the pathway through which the various mechanisms are connected. The most likely start of this cascade is gut dysbiosis, which is observed within days of dietary change, followed by disruption of glucose regulation and insulin sensitivity and activation of systemic inflammation, both of which can be detected within as little as two-weeks of diet access. This is followed by disrupted BBB integrity, CNS insulin resistance, and neuroinflammation. Of note is the converging evidence that the proposed mechanisms occur in both healthy individuals consuming high-fat and/or high-sugar diets, as well as those with NCCDs; this suggests that dietary intake of fat and sugar can produce cognitive impairment in the absence of obesity or the development of metabolic disease. Finally, the evidence reviewed suggests that the hippocampus may be particularly sensitive to high-fat and/or high-sugar diet intake. In particular, diet-induced impairments are frequently observed in the hippocampal-dependent forms of cognition, but not cognition dependent on other brain regions. Furthermore, there is evidence that certain diet-induced changes in these mediators of cognitive impairment may be observed first in the hippocampus before spreading more widely to the general CNS; this sensitivity is possibly a result of the disrupted BBB-integrity that is observed early in dietary access, leaving the hippocampus region susceptible to alterations in biological homeostasis before other brain regions.

Diet
HF, HS, HFHS

Gut Dysbiosis

↑ Adiposity

↓ Glucose
Regulation
& Insulin
Sensitivity

↑ Peripheral
Inflammation

↓ BBB Integrity

CNS Insulin
Resistance

↑ Neuroinflammation

Cognitive Impairment
Altered Neuron Morphology
& Synaptic Plasticity
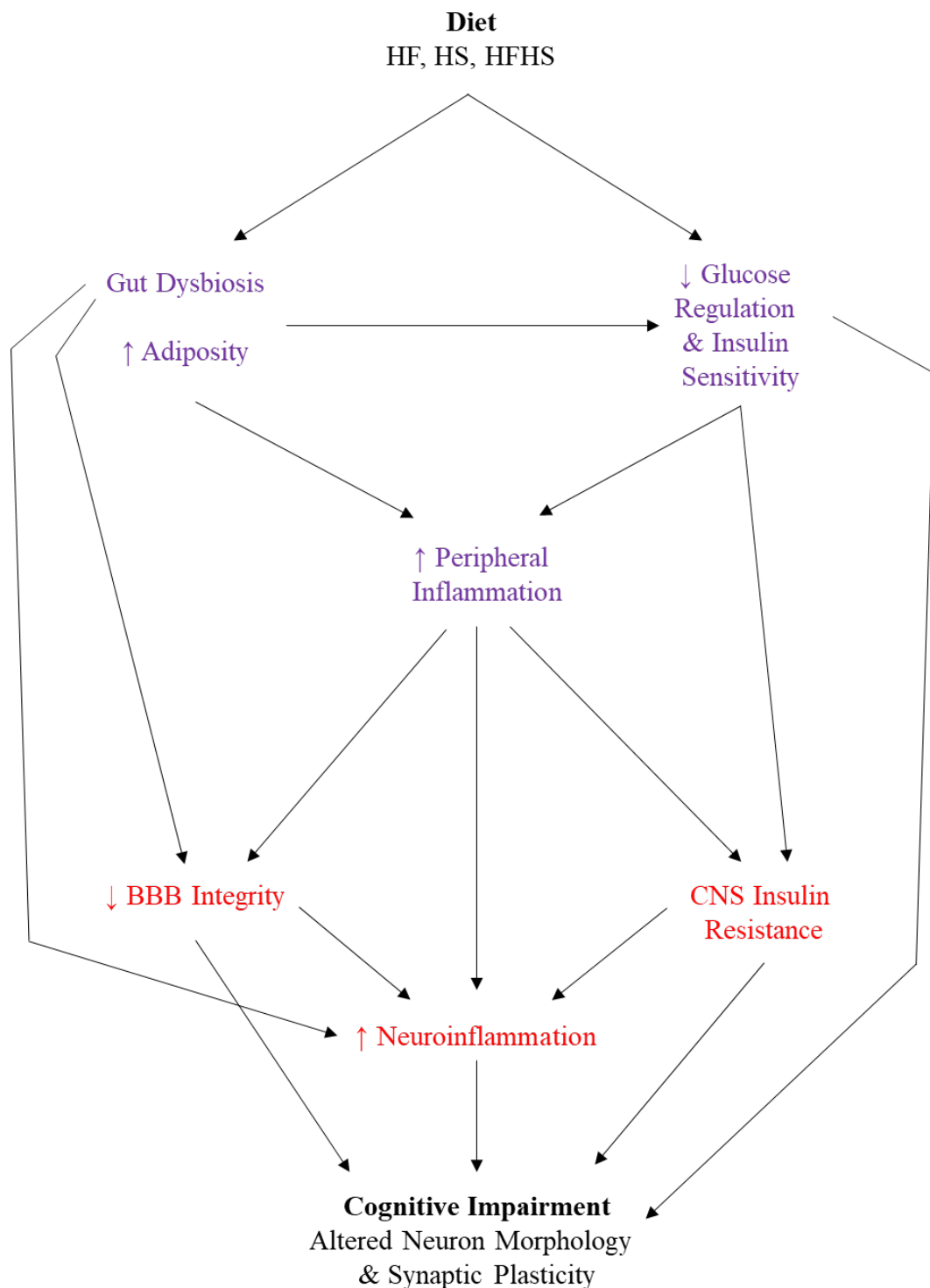
Figure 1.2. Potential mechanisms underlying diet-induced cognitive impairments. Purple represents potential mechanisms that occur within the periphery. Red represents mechanisms that occur within the central nervous system. (BBB = Blood Brain Barrier; CNS = Central Nervous System; HF = high-fat diet; HFHS = high-fat high-sugar diet; HS = high-sugar diet).

1.6. The Present Thesis

The research reviewed above provides convergent evidence to support the hypothesis that the hippocampus is particularly sensitive to the effects of dietary fat and sugar intake. While the hippocampus has been shown to support a number of cognitive functions (reviewed in Lisman et al., 2017; Olson, Moses, Riggs, & Ryan, 2012), it plays a critical role in processing spatial (e.g. Collin, Milivojevic, & Doeller, 2017; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Miller et al., 2018) and contextual information (Chaaya, Battle, & Johnson, 2018; Cullen, Ferrara, Pullins, & Helmstetter, 2017; Daumas, Halley, Francés, & Lassalle, 2005; Yassa & Reagh, 2013). Experimental research in rodents demonstrates that learning and memory for spatial and contextual information is mediated by a subset of neurons within the hippocampal dentate gyrus (DG) and cornu Ammonis (CA) subregions known as place cells (Anderson & Jeffery, 2003; O'Keefe & Dostrovsky, 1971; Moser, Kropff, & Moser, 2008). These cells encode the geometric (e.g., distance, length) and non-geometric (e.g. colour, shape, smell) features of a given space, or environment, in a unique pattern of activity, termed a hippocampal engram; this engram acts as a cognitive representation of a specific environment that can be utilised in associative learning and memory processes (e.g. Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004; Ramirez et al., 2013; reviewed in Bulkin, Law, & Smith, 2016 and Rudy, 2015).

Many of the studies that have used rodents to examine the relationship between high-fat and/or high-sugar diet consumption and hippocampal-dependent cognition have done so using tasks that assess spatial learning and memory. This research has provided considerable evidence of diet-induced impairments in spatial cognition. For example, several studies have reported diet-induced deficits in the use of spatial cues to navigate to the hidden platform in the Morris (e.g., Che et al., 2018, Pathan et al., 2008; Spinelli

et al., 2017) and radial arm water mazes (e.g., Alzoubi, Khabour, Salah, & Abu Rashid, 2013a; Alzoubi, Khabour, Salah, & Hasan, 2013b; Alzoubi, Mayyasm Mahafzah, & Khabour, 2018), or to avoid arms that have been visited and depleted of food in the radial arm maze (e.g. Kanoski & Davidson, 2010); other studies have found deficits in short-term place, but not object recognition memory (e.g., Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b, 2018; Leigh et al., 2020a, 2020b; Tran & Westbrook, 2015), and to remember previously visited arms in spontaneous alternation tasks in Y- (Hargrave et al., 2016; Park et al., 2018) and T-mazes (Arnold et al., 2014). These deficits have been reported after as little a few days of high-fat and/or high-sugar diet consumption (Beilharz et al., 2014; Kanoski & Davidson, 2010; Tran & Westbrook, 2015), and suggest that dietary intake may rapidly influence the neural substrates in the hippocampus that underpin spatial learning and memory.

However, a number of studies have failed to find such dietary effects on these spatial memory tasks (e.g. Ayabe, Ohya, Kondo, & Ano, 2018; Jurdak et al., 2008; Pratchayasakul et al., 2015; Ross, Darling, & Parent, 2013; Scichilone et al., 2016; Silva et al., 2005; Valladolid et al., 2013; Zhao, Stafstrom, Fu, Hu, & Holmes, 2004). The failure to replicate these findings may be a consequence of experimental differences between the studies; for example, the age of the rodents, the dietary manipulation used, or the behavioral procedures used to assess spatial cognition. Nevertheless, the inconsistent evidence of diet-induced impairments suggests that the deficit in spatial learning and memory may be fragile, or only observed under certain experimental conditions.

Fewer studies have examined the influence of dietary fat and sugar intake on context-dependent cognition. Context is an essential component of learning and memory. Firstly, context serves as a potent retrieval cue of information stored in

memory. For example, some of the earliest experimental research in humans reliably demonstrated that information learned in one context is better retrieved when the individual is tested in that context than in a different one (e.g. Farnsworth, 1934; Jensen, Harris, & Anderson, 1971; Pessin, 1932; reviewed in Bulkin et al., 2016). Secondly, context serves as an occasion setting cue that indicates the relationship between a conditioned stimulus (CS) and an unconditioned stimulus (US). Under these circumstances, the context serves as a disambiguating cue that allows for retrieval of the appropriate CS-US association for a given context, and reduces interference from other associations that have been learned in different contexts (Fraser & Holland, 2019).

The hippocampus is thought to play a critical role in context learning and memory due to its capacity for configural processing, which allows the hippocampus to arrange the unique geometric and non-geometric cues that comprise an experienced context into a unified representation (Rudy & O'Reilly, 1999, 2001). These unified, or configural, representations are believed to mediate the retrieval of context-appropriate information from memory and support the occasion setting property of contexts. In the absence of hippocampal function, the individual cues are encoded by cortical regions as independent, or elemental, representations. While these can support formation of context-dependent information, they do not support disambiguation between contexts that are comprised of similar features and can result in an inability to disambiguate similar contexts and thus retrieval of context-inappropriate information.

Rodent studies provide evidence that high-fat diet intake impairs hippocampal-dependent configural processing. For example, Stouffer et al. (2015) demonstrated that rats exposed to a high-fat diet (60% energy from fat) for eight-weeks showed a preference for a water-paired compartment over a non-water-paired compartment in a conditioned cue preference task when the compartments were distinguished by a single environmental

cue; however, did not show a preference for the water-paired chamber when the compartments were distinguished by multiple environmental cues. These results indicated that the high-fat diet impaired performance on hippocampal-dependent, but not hippocampal-independent, versions of the task. Similarly, Sobesky and colleagues found that rats exposed to a high-fat diet (60% energy from fat) for 12-weeks were impaired relative to chow-fed control rats in a context pre-exposure fear conditioning task, which has been shown to be critically dependent on hippocampal configural processing (see Fanselow, 2010); however, rats exposed to a 42% energy from fat diet were not significantly different from control rats. As observed with the literature that has used spatial memory tasks, these findings suggest that diet-induced impairments in hippocampal-dependent configural processing may be fragile and only observed under certain experimental conditions, such as the type of diet used or the behavioural task used to assess cognition.

Experimental research in humans (Attuquayefio et al., 2017; Holloway et al., 2011; Stevenson et al., 2020) and in rodents (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b, 2018; Kanoski & Davidson, 2010; Tran & Westbrook, 2015) have demonstrated that deficits in hippocampal-dependent cognition are observable after only brief dietary manipulations lasting days to two-weeks. Thus, the main aim of the present thesis was to extend the present body of literature on short-term high-fat and/or high-sugar diet-induced cognitive impairment. The first aim was to determine whether the discrepant findings from studies that have used spatial learning and memory tasks to examine the relationship between short-term dietary interventions and hippocampal-dependent cognition was a consequence of differences in experimental design. To achieve this, the published literature was subjected to a meta-analysis. It specifically assessed the contribution of diets high in fat, sugar, or both, to impairments of spatial learning and

memory, and, asked whether inconsistent findings in the literature were due to differences in the composition of the diet and/or the behavioural task used to assess its effects. The second was to examine the influence of dietary fat and sugar intake on hippocampal-dependent configural processing of context information. This was done using two Pavlovian fear conditioning paradigms that have been demonstrated to be dependent on intact hippocampal function; the first was a context fear generalisation test, which requires animals to use configural representations of context to discriminate between two contexts comprised of similar features, and the second was a context pre-exposure fear conditioning task, which requires animals to form a configural representation of context in order to form a context fear memory. Given that the previous studies examining configural processing of context have used high-fat diet manipulations, we were particularly interested in examining the effect of high-sugar diets. As such, the context generalisation test was focussed on high-sugar diet exposed rats and the context pre-exposure fear conditioning test was focussed on rats exposed to high-sugar, or fat, or both fat and sugar.

Chapter 2: The effect of high-fat, high-sugar, and combined high-fat high-sugar diets on spatial learning and memory in rodents: A meta-analysis.

2.1. Introduction

The modern diet contains many foods and drinks that are rich in saturated fat and sugar (Kearney, 2010; Khatibzadeh et al., 2016; Ritchie & Roser, 2017; Vasileska & Rechkoska, 2012; reviewed in Cordain et al., 2005; Popkin et al., 2012). It has long been recognized that excessive intake of this diet is associated with increased body weight, even obesity, some forms of cancer, as well as metabolic and cardiovascular diseases (Carrera-Bastos, Fontes-Villalba, O'Keefe, Lindeberg, & Cordain, 2011; Cordain et al., 2005; Mente, de Koning, Shannon, & Anand, 2009). More recent epidemiological evidence has indicated that this diet is also associated with deficits in cognition (reviewed in Kanoski & Davidson, 2011, and Yeomans, 2017). For example, longitudinal studies of middle-aged (Eskelinen et al., 2008) and older adults (Gustaw-Rothenberg, 2009; Morris et al., 2004; Okereke et al., 2012; Naqvi et al., 2011; Roberts et al., 2012) showed that consumption of diets high in saturated fat and refined carbohydrates was negatively correlated with overall cognitive "well-being" (e.g., memory, executive function, psychomotor speed) in later life and positively correlated with neurological disorders such as Alzheimer's disease (see Pugazhenthi, Qin, & Reddy, 2017).

Hippocampal-dependent forms of cognition seem to be particularly susceptible to the detrimental effects of diets that are high in saturated fat and/or refined sugar. A cross-sectional study of young adults (Francis & Stevenson, 2011) found that self-reported intake of so-called "fast" foods predicted scores on subtests of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) that are sensitive to left hippocampal damage, specifically, the verbal paired associates and LM subtests. However, intake of such foods failed to predict scores on the hippocampal-independent, digit span (DS) subtest of the

WMS-R. Similarly, cross-sectional research in healthy young women found that habitual intake of saturated fat predicted lower scores on the CANTAB eclipse (v3) suite of cognitive tests (Cambridge Cognition Ltd., Cambridge, UK) that are sensitive to hippocampal damage, such as verbal recognition memory, delayed-matching-to sample, and paired associate learning (Gibson et al., 2013). Finally, there is even evidence that cognitive deficits can be detected after relative short exposures to such diets. Attuquayefio et al. (2017) found a statistically significant pre- to post decline in scores on the Hopkins Verbal Learning Task Revised in healthy adults who consumed a breakfast high in saturated fat and refined sugar for four-days, but not in a control group of adults that consumed a low-fat, low sugar diet of similar palatability.

Rodent models have confirmed that diets high in saturated fat, sugar, or both fat and sugar are associated with deficits in tasks that require the hippocampus and surrounding cortices (see Table 2.1.). Several studies have reported such dietary effects in the use of spatial cues to navigate to the hidden platform in the Morris (e.g., Che et al., 2018) and radial arm water mazes (e.g., Alzoubi et al., 2013a, 2013b, 2018), or to avoid arms that have been visited and depleted of food in the radial arm maze (e.g. Kanoski & Davidson, 2010). Other studies have found deficits in short-term place, but not object, recognition memory (e.g., Abbott et al., 2016; Beilharz et al, 2014; Tran & Westbrook, 2015), and in spontaneous alternation tasks in Y- (Hargrave et al., 2015; Park et al., 2018) and T-mazes (Arnold et al., 2014). Deficits in these tasks have been observed in rodents fed such diets across time periods that have ranged from months (e.g., Molteni et al., 2002) to weeks (Abbott et al., 2016; Hargrave et al., 2015), and even days (Beilharz et al., 2014; Kanoski & Davidson, 2010; Murray et al., 2009; Tran & Westbrook, 2015), indicating that deficits can occur rapidly, well in advance of diet-induced increases in body weight.

Although diet-induced deficits in cognition are relatively well-documented, there have also been failures to detect such effects. For example, rats fed a high-fat high-sugar diet for four-weeks (Ross et al., 2013) or mice fed a high-fat diet for seven-weeks (Ayabe et al., 2018) did not differ significantly from chow-fed controls in the place recognition memory task at four-hour (or longer) retention intervals. Further, several investigators (Jurdak et al., 2008; Pratchayasakul et al., 2015; Scichilone et al., 2016; Silva et al., 2005; Zhao at al.,2004) failed to detect differences in spatial memory in the Morris water maze between rats fed a high-fat diet for four to eight-weeks and chow-fed control. Finally, older (eight-week-old) mice placed on a high-fat diet for eight-weeks failed to show a deficit in place recognition memory at a one-hour retention interval, whereas younger (five-week-old) placed on that diet for that length of time did show a deficit in place recognition memory (Valladolid et al., 2013).

A major difficulty in interpreting the discrepant findings is due to the procedural variation across studies, especially in the dietary manipulations and the behavioural tasks used to assess the effects of these manipulations. One of the most notable differences between studies is diet composition. For example, lard is typically used to increase the amount of fat in the diet (Che et al., 2018; Kang et al., 2014; Wei, Yao, Zhao, Jiang, & Ge, 2018), but saturated fatty acids (Moreira et al., 2014; Murray et al., 2009; Spinelli et al., 2017), hydrogenated vegetable oil (Jurdak et al., 2008), and suet (Gergerlioglu et al., 2016) have also been used. The total content of fat has also varied between studies, ranging from 18 g/kg (Che et al., 2018) to approximately 47.5 g/kg of lard (Scichilone et al., 2016; Zhao et al., 2004). Sugar content also varies across studies, ranging from sucrose concentrations of 10% (Abbott et al., 2016; Kendig et al., 2013) to 32% (Jurdak et al., 2008). Finally, other studies have altered the sugar content of the solid foods in the diet (Gergerlioglu et al., 2016; Magnusson et al., 2015). A second notable difference is

the task used to assess cognitive ability. These tasks include the various types of mazes and recognition memory paradigms. Moreover, there are between-study differences in the parameters used in each of these tasks. For example, studies using the Morris water maze differed in the number of acquisition trials, the duration of the interval between trials as well as that between the final acquisition trial and the first test trial (where the hidden platform is absent or moved to a new location).

The several failures to replicate reports of diet-induced deficits in hippocampal-dependent forms of learning and memory raise the possibility that such deficits are relative fragile. Alternatively, such deficits may be more readily induced by certain dietary manipulations and/or the tasks and protocols used to assess their effects. While this topic has been extensively reviewed (see Beilharz et al., 2015; Cordner & Tamashiro, 2015; Kanoski & Davidson, 2011; Yeomans, 2017), as far as we are aware, an analysis of the circumstances which do or do not produce diet-induced deficits in cognition has not been conducted. We aimed to provide such an analysis by subjecting some of the published literature on diet-induced deficits in cognition to a meta-analysis. More specifically, we sought, first, to assess the contribution of diets high in saturated fat, refined sugar, or both, to impairments of spatial learning and memory, and, second, to examine whether inconsistent findings in the literature were due to differences in the composition of the diet and/or the behavioural task used to assess its effects. We used two criteria for inclusion in analysis. First, we only included studies in which rodents were provided with the diet for a maximum of eight-weeks. We did so on the assumption that such relatively short dietary manipulations would be more likely to allow us to detect any differential effects of the diet composition and/or behavioural task used for assessment of hippocampal-dependent learning and memory. Inspection of the literature indicated that eight-weeks of dietary exposure was both short enough to reveal differences and long

enough to provide a sufficient sample for analysis. We note that some studies included in the meta-analysis report disturbances in metabolic parameters, such as hyperglycaemia, insulin resistance, and body weight gain (see Table 2.1. and Discussion), but did not incorporate these disturbances into the analyses due to the lack of statistical power arising from the large variability in the parameters measured and reported across studies. The second inclusion criterion was studies that used rodents older than four-weeks. We did so in order to ensure that the animals were weaned, which typically occurs between postnatal day 21 to 28 (Sengupta, 2011, 2013), and to avoid any interaction effects of dietary interventions on developmental processes, such as hippocampal maturation, which occurs at approximately postnatal day 21 (Fan, Sun, & Liu, 2018; Radic et al., 2017; Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013).

Table 2.1. Body weight and metabolic parameters of experimental and control animals provided a high-fat, high-sugar, or high-fat high-sugar diet (* = unless otherwise stated; BGL = Blood Glucose Level; CD = Control Diet; ELISA = Enzyme Linked Immunosorbent Assay; Expt = Experimental; GTT = Glucose Tolerance Test; HbA1c = Haemoglobin A1c; HDL = High Density Lipoprotein; HF = High-Fat Diet; HFHS = High-Fat High-Sugar Diet; HFruc = High Fructose Diet; HOMA = Homeostatic Model Assessment; HS = High-Sugar Diet; ITT = Insulin Tolerance Test; LDL = Low Density Lipoprotein; MWM = Morris Water Maze; PR = Place Recognition; QUICKI = Quantitative Insulin Sensitivity Check; RAM = Radial arm maze; RAWM = Radial Arm Water Maze; RI = Retention Interval; SA = Spontaneous Alternation; TC = Total Cholesterol; TGLs = Triglycerides).

Study	Species & Strain [Sex; Age when multiple age groups used]	Expt Diet (length when multiple groups)	Spatial Task	Diet-induced Deficit	Body Weight (BW)	Blood* Glucose Level (BGL)	Plasma* Insulin Level	HOMA Index	Plasma* TGLs	Others
Abbott et al. (2016) Expt 1	Sprague Dawley rats [Male & Female]	HS	PR	Yes	No effect	-	-	-	-	-
			Object-in-Place	No (Female); Yes (Male)						
Alzoubi et al. (2013a) Expt 1	Wistar rats [Male]	HF (labelled Western diet)	RAWM (6-arm)	Yes	Sig effect (P<.05)	-	-	-	-	-

Study	Subject	Diet	Task	Impairment				
Alzoubi et al. (2013b) Expt 1	Wistar rats [Male]	HF (labelled high-fat cholesterol diet)	RAWM (6-arm)	Yes	Sig effect (P<.05)	-	-	-	-
Alzoubi et al. (2018)	Wistar rats [Male]	HF	RAWM (6-arm)	Yes	-	-	-	-	-
Arnold et al. (2014)	C57BL/6J mice [Male]	Extreme HF	T-Maze SA	Yes	Sig effect (P<.01)	Sig effect (P<.001)	-	-	-
Arnold et al. (2014)	C57BL/6J mice [Male]	Moderate HF	T-Maze SA	Yes	Sig effect (P<.05)	Sig effect on BGL and GTT (Ps<.05)	-	-	-
Ayabe et al. (2018)	C57BL/6J mice [Male]	HF	PR	No	Sig effect [week 3+] (Ps<.01)	-	-	Sig effect (P<.01)	-
Beilharz et al. (2014) Expt 1	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose solution	PR	Yes (all tests)	Sig effect [day 16+] (Ps<.05)	-	-	-	-

Study	Species	Diet	Test							
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	HS	PR	Yes (all tests)	No effect	-	[ELISA] no effect	-	No effect	[ELISA] no effect on plasma leptin
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose solution	PR	Yes (all tests)	Sig effect [day 15+] (Ps<.05);	[ELISA] sig effect (P<.05)	-	-	Sig effect (P< .05)	[ELISA] sig effect plasma leptin (P<.05)
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria Diet	PR	Yes (all tests)	Sig effect [day 15+] (Ps<.05);	-	[ELISA] no effect	-	Sig effect (P<.05)	[ELISA] sig effect plasma leptin (P<.05)
Beilharz et al. (2018)	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose solution	PR	Yes (all tests)	Sig effect (P<.001)	No effect	-	-	-	[ELISA] sig effect plasma leptin (P<.05)
Boitard et al. (2014)	Wistar rats [Male]	HF	MWM	No	Sig effect (P<.05)	Sig effect (P<.05)	No effect	-	No effect	No effect on plasma cholesterol ; sig effect plasma leptin (P<.05)

Study	Animal	Diet	Task						
Che et al. (2018)	SAMP8 mice [Male]	HF	MWM	Yes	-				
Denver et al. (2018)	C57BL/6J mice [Male]	HF (10-days)	MWM	No	Sig effect [day 4+] (Ps<.05)	-	-	-	-
Denver et al. (2018)	C57BL/6J mice [Male]	HF (26-days)	MWM	No	Sig effect [day 24+] (Ps<.05)	-	-	-	-
Denver et al. (2018)	C57BL/6J mice [Male]	HF (8-weeks)	MWM	No	Sig effect [week 2+] (Ps<.05)	-	-	-	-
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	HF	MWM	Yes	No effect	No effect	-	-	-
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	HS	MWM	No	No effect	No effect	-	-	-

Study	Animal model	Diet	Task							
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	Ketogenic Diet	Y-maze SA	No	No effect	No effect	No effect	-	-	-
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	High-fat, high-dextrose diet	Y-maze SA	Yes (10-day test, P<.05); No (40-day test)	No effect	No effect	No effect	-	-	-
Jamshed et al. (2014) Expt 1	Sprague Dawley rats [Male & Female]	HF (labelled cholesterol chocolate butterfat diet)	MWM	Yes	-	-	-	-	Sig effect week 6 (P<.01)	Sig effect on TC, LDL & HDL:LDL ratio in week 6 (Ps<.01)
Jurdak et al. (2008)	Long–Evans rats [Male]	HF	MWM	No	Sig effect (P<.05)	Overnight Fasted. No effect on BGL or GTT response	-	-	No effect	No effect on TC, HDL, or non-HDL.

Study	Animal	Diet	Task							
Jurdak et al. (2008)	Long–Evans rats [Male]	HS	MWM	No (24-hr RI); Yes (10-day RI)	Sig effect (P<.05)	Overnight Fasted. No effect on BGL, Sig effect on GGT response (P<.01)	-	-	Sig effect (P<.05)	No effect on TC, HDL, or non-HDL.
Kanoski & Davidson (2010)	Sprague Dawley rats [Male]	HFHS (labelled *High Energy Diet*)	RAM (8-arm)	Yes	Sig effect [day 14+] (Ps<.05)	-	-	-	-	-
Kendig et al. (2013)	Hooded Wistar rats [Male & Female]	HS	MWM	Yes (Probe tests 1-3); No (28-day RI)	No effect	Sig effect [day 29+] (main effect, P<.05) but not day 14	-	-	-	-
Liang et al. (2015)	Sprague Dawley rats [Male]	HF	MWM	Yes	-	-	-	-	-	-

Magnusson et al. (2015)	C57BL/6J mice [Male]	HF	MWM	No						
			MWM Reversal Task	Yes	Sig effect [week 4+] (Ps<.05).	-	-	-	-	-
			PR	No						
			MWM	No						
Magnusson et al. (2015	C57BL/6J mice [Male]	HS	MWM Reversal Task	Yes	No effect	-	-	-	-	-
			PR	No						
Mirzaei et al. (2018)	Wistar rats [Male]	HF	MWM	Yes	-	-	-	-	-	-

Molteni et al. (2004)	Fisher 344 rats [Female]	Powdered HFHS	MWM	Yes	-	-	-	-	-	Sig effect on TC, non-HDL, and HDL (Ps<.05)
Moreira et al. (2014)	Swiss Albino Mice [Male]	HF (labelled hypercho-lestermic diet)	PR	Yes	No effect on plasma glucose	-	-	-	-	Sig effect on TC, non-HDL, and HDL (Ps<.05)
Park et al. (2018)	ICR mice [Male]	HF	Y-Maze SA	Yes	Sig effect [week 5+] (Ps<.05)	-	-	-	-	-
Pathan et al. (2008)	SD rats [Male]	HF	MWM	Yes	Sig effect (P<.05)	[ELISA] sig effect (P<.001)	[ELISA] sig effect (P<.001)	-	[ELISA] sig effect on blood trigs (P<.001)	[ELISA] sig effect on blood TC (P<.001)
Pratchayasakul et al. (2015)	Wistar rats [Female; 4-weeks-old]	HF	MWM	No	No effect	12-hours Fasted. No effect on plasma glucose or GTT response	12-hours Fasted. [ELISA] no effect	no effect	12-hours Fasted. No effect	12-hours Fasted. No effect on TC, LDL, or HDL.

Study	Strain	Diet	Test							
Pratchayasakul et al. (2015)	Wistar rats [Female; 8-weeks-old]	HF	MWM	No	Sig effect (P<.05)	12-hours Fasted. No effect on plasma glucose or GTT response	12-hours Fasted. [ELISA] sig effect (P<.05)	Sig effect (P<.05)	12-hours Fasted. No effect	12-hours Fasted. Sig effect on TC & LDL (Ps<.01) but not HDL
Ross et al. (2013)	Sprague Dawley rats [Male]	HFHS	PR	No	Sig effect (P<.05)	-	-	-	-	-
Scichilone et al. (2016)	Sprague Dawley rats [Male]	Ketogenic Diet	MWM	No	No effect	Sig effect week 2 (P<.01), but not-weeks 4 or 8	-	-	-	-
Silva et al. (2005)	Wistar rats [Male]	Ketogenic Diet	MWM	No	-	-	-	-	-	-
Spencer et al. (2017)	F344xbn F1 rats [Male; 3-months-old]	HF	MWM	No	Sig effect (P<.05)	Non-fasted. No effect	Non-fasted. [ELISA] no effect	-	-	-

Study	Animal [strain]	Diet	Task						
Spencer et al. (2017)	F344xbn F1 rats [Male; 24-months-old]	HF	MWM	No	Sig effect (P<.05)	Non-fasted. No effect [ELISA]	Non-fasted. [ELISA] no effect	-	-	-
Spinelli et al. (2017)	C57BL/6J mice [Male]	HF	MWM	Yes	-	-	[ELISA] sig effect (P<.05)	Non-fasted. Sig effect (P<.01)	-	-
Takechi et al (2017)	C57BL6/J mice [Male]	High Fat Fructose Diet	MWM	No	Sig effect (P<.001)	Sig effect on BGL and HbA1c level (Ps<.01)	[ELISA] sig effect (P<.05)	-	-	-
Thirumangalakudi et al. (2008)	C57BL/6 mice	HF	RAWM (8-arm)	Yes	-	-	-	-	-	-
Tran & Westbrook (2015) Expt 1	Sprague Dawley rats [Male]	HFHS Diet	PR	Yes (all tests)	Sig effect overall (P<.001) but not at first test (day 6-7)	-	-	-	-	-

Study	Subjects	Diet	Task						
Tran & Westbrook (2018) Expt 1	Sprague Dawley rats [Male]	HFHS Diet	PR	Yes	-	-	-	-	-
Valladolid-Acebes et al. (2011)	C57BL/6J mice [Male]	HF	RAM (8-arm)	Yes	Sig effect [week 2+] (Ps<.001)	6-hours Fasted no effect	6-hours Fasted sig effect (P<.001)	-	6-hours Fasted. No effect on plasma leptin	6-hours Fasted. No effect on plasma leptin
Valladolid-Acebes et al. (2013) Expt 1	C57BL/6J mice [Male]	HF	PR	Yes	Sig effect (P<.001)	No effect	No effect	-	-	Sig effect plasma leptin (P<.001)
Valladolid-Acebes et al. (2013) Expt 3	C57BL/6J mice [Male]	HF	PR	No	Sig effect (P<.001)	Sig effect (P<.05)	No effect	-	-	Sig effect plasma leptin (P<.001)
Wei et al. (2018)	C57BL/6J mice [Male]	HF	MWM	Yes	Sig effect [week 2+] (Ps<.05)	-	-	-	-	-

Study	Animal	Diet	Task	Effect	BW				
Woodie & Blythe (2018)	Sprague Dawley rats [Male]	HF	MWM	No	Sig effect (BW and % BW change; Ps<.05);	4-6 hours Fasted. No effect vs CD; sig effect vs HFruc (P<.05).	-	4-6 hours Fasted. No effect on QUICKI	4-6 hours Fasted. No effect on QUICKI
			MWM Reversal Task	No			-		
Woodie & Blythe (2018)	Sprague Dawley rats [Male]	High Fructose (HFruc) Diet	MWM	No	No effect (BW and % BW change)	4-6 hours Fasted. No effect	4-6 hours Fasted. [ELISA] no effect vs CD; sig effect vs HF (P<.05).	-	4-6 hours Fasted. No effect on QUICKI
			MWM Reversal Task	No		4-6 hours Fasted. No effect		-	4-6 hours Fasted. No effect
Wu et al. (2003) Expt 1	Sprague Dawley rats [Male]	Powdered HFHS Diet	MWM	No	-	-	-	-	-
Xu & Reichelt (2018)	Sprague Dawley rats [Male]	HS	PR	Yes	No effect	-	-	-	-

Xu et al. (2018)	C57BL/6J mice [Male]	HF	MWM	Yes	Sig effect [week 2+] (Ps<.05)	Sig effect on BGL and GTT response (Ps<.01)	4-hour Fasted. Sig effect on ITT response (Ps<.01)	-	Sig effect on serum trigs (P<.05)	Sig effect on serum TC, LDL, & HDL (Ps<.01)

2.2. Method

2.2.1. Eligibility Criteria

The meta-analysis was limited to published, peer-reviewed research that fed rats or mice diets high in either fat or sugar, or high in both fat and sugar. To be included in the analysis, the animals were required to be at least four-weeks of age at the start of diet administration and be on the diet for no longer than eight-weeks (or two-months). For studies that used transgenic rodent or murine models, the only data included for analysis were from control and diet intervention wild type animals. For studies that included a drug manipulation, the only data included for analysis was taken from control and diet intervention animals that received saline administration. Studies that used a maternal diet manipulation were excluded. All the included studies used a hippocampal-dependent task, specifically, the Morris water maze (Compton, Griffith, McDaniel, Foster, and Davis, 1997), radial arm maze and radial arm water maze (Floresco, Seamans, & Phillips, 1997), place and object-in-place recognition memory tasks (Barker & Warburton, 2011), and spontaneous alternation task (Lalonde, 2002; Stevens & Cowey, 1973). Some studies have used other hippocampal-dependent tasks (e.g., context fear conditioning; Sobesky et al., 2014), but these studies did not meet the other inclusion criteria. A number of studies have investigated the effects of diet on occasion-setting/conditioned inhibition processes (e.g., hippocampal-dependent feature negative discrimination) but these either did not meet the inclusion criterion of diet exposure duration (Kanoski, Meisel, Mullins, & Davidson, 2007; Kanoski et al., 2010), or were excluded for splitting animals into diet-resistant and diet-prone obesity groups (Davidson, Monnot, Neal, Martin, Horton, & Zheng, 2012).

2.2.2. Database Search

We used Pubmed and Proquest central databases (Appendix A) and limited the search to papers published on or before June 30th 2018.

2.2.3. Screening for Inclusion

The process of selecting papers for inclusion in the meta-analysis is shown in Figure 2.1. Papers were first screened for eligibility using information provided in the title and abstract. Full texts of papers that passed the eligibility test were then screened by two reviewers to confirm that they had in fact met the requirements for inclusion in the meta-analysis. In instances where there was disagreement, a third party would have been asked to decide whether an article reached the eligibility criteria, but there was no such disagreement.

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│  991 total articles │────────────┐
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           │              ┌──────────────────┐
           │              │  194 duplicates  │
           ▼              │     removed      │
┌─────────────────────┐   └──────────────────┘
│ 797 articles assessed│
│ for eligibility by   │────────────┐
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           │              │ 717 articles     │
           │              │ excluded based   │
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           │              │ 39 articles meet │
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│ 41 articles included │
│  in meta-analysis    │
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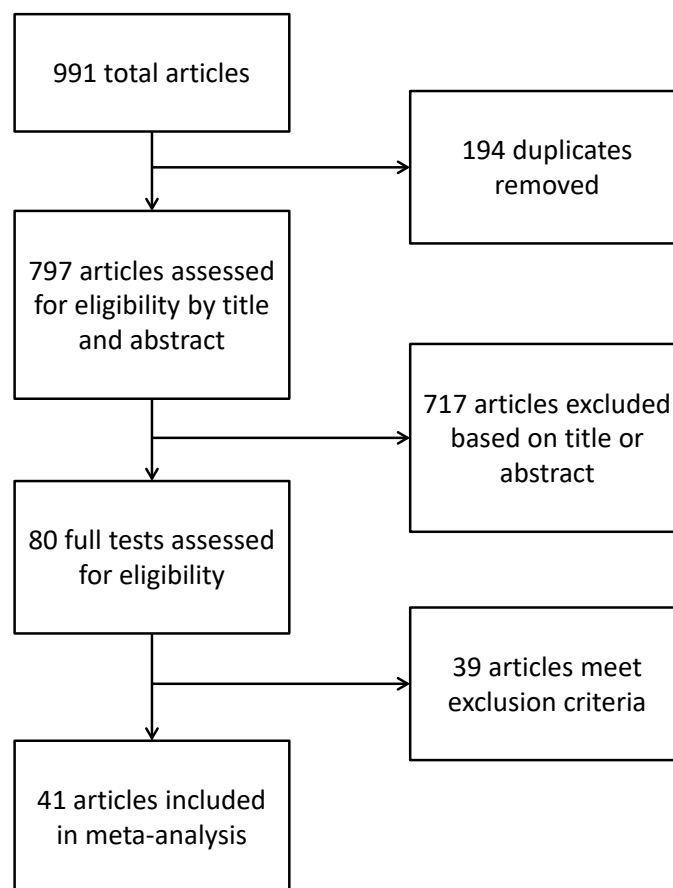
Figure 2.1. Flow chart showing the process of selecting articles for inclusion in the meta-analyses.

2.2.4. Data Collection

The two reviewers independently extracted data from studies that met the eligibility criteria and recorded information about the animals, diet manipulation, behavioural assays, outcomes measured, and results. For studies where subject body weights were provided, growth charts from Charles River Laboratories were used to confirm animals were at least four-weeks of age based on weights provided. For studies where there was no statistically significant difference between control and diet animals but insufficient statistical details were provided in the published methods and supplementary material, the corresponding author was contacted twice to provide these details. If details were not provided, a nominal F- or t-value of 1 was used for the meta-analysis. Excluding these results would have contributed to any publication biases towards papers reporting statistically significant results. When the number of animals used for statistical analysis was provided as a range rather a single value, the lowest, most conservative numerical value of the range was used for analysis of effect size. When a study had multiple test points but did not report a main effect, the data from each individual test point was included. For studies that compared multiple diet manipulations to a single control group, the values for the single control group were used in each of the diet manipulation meta-analyses.

2.2.5. Data Analysis

Data were analysed using Comprehensive Meta-Analysis version 3 (CMA v3; Biostat Inc, New Jersey, USA). The studies were organized by (1) type of diet (high-fat, high-sugar, and high-fat high-sugar) and (2) type of behavioural task (Morris water maze, place recognition, radial arm or water maze, and spontaneous alternation). The standardized mean difference (SMD), calculated as Hedge's g (Hedge, 1981) and

weighted by sample size, was used to measure the effects of diet and task. A random effects model was selected due to differences across the studies in calories, percentage of fats and sugars, and behavioural tests. Therefore, statistics measuring heterogeneity are not reported. We did not run a subgroups meta-analysis because the division into subgroups by three diet conditions and four task types had a high degree of variance in the number of experiments (or datasets) included in each subgroup. Additionally, the datasets in one subgroup were not all strictly independent from those in another subgroup; some datasets included across subgroups used the same control group for comparison (e.g., for studies that compared multiple diet manipulations to a single control group, the values for the single control group were used in each of the diet manipulation meta-analyses). Regardless, we were not so much concerned with an omnibus test result from a subgroups meta-analysis but rather with the magnitude of the effect size in each subgroup. Therefore, we ran separate meta-analyses with a Bonferroni correction to control for the use of the same data set across two analyses (by diet and by task), an alpha of $\alpha = 0.025$ was considered significant.

2.3. Results

2.3.1. Study Selection

The initial search yielded 991 articles. After the removal of duplicates, 797 articles were screened based on the title and abstract, and 717 were excluded. Of the remaining 80 articles reviewed in full text, a further 39 were excluded as they did not meet inclusion criteria. Of these articles, 14 had a diet manipulation longer than the eight-weeks prior to behavioural testing, nine did not include a spatial learning and memory behavioural task, seven started diet manipulations in animals younger than four-weeks, two had transgenic subjects but no wild type control, two involved drug manipulations but lacked a vehicle control, two did not make statistical comparisons between groups, one had no appropriate

control diet condition, one assessed the effect of maternal diet on offspring, and one was a review article.

2.3.2. Study Characteristics

Across the 41 articles that met eligibility criteria (with some articles comprising of multiple eligible experiments or datasets), there were a total of 32 experiments that investigated the effect of a high-fat diet (Table 2.2.), nine experiments investigated the effect of a high-sugar diet (Table 2.3.), and eleven experiments investigated the effect of a diet high in both fat and sugar (Table 2.4.). The effect of diet on spatial learning and memory was assessed via the use of: extra-maze cues to navigate in the Morris water maze, radial arm maze, or radial arm water maze; spontaneous alternation in a T- or Y-maze; or via the use of novel object location in recognition memory tasks. Twenty-two experiments used the Morris water maze (Table 2.5.), 13 used the place recognition task (Table 2.6.), six used the radial arm or radial arm water maze (Table 2.7.), and four used spontaneous alternation (Table 2.8.).

2.3.2.1. High-Fat Diet

A total of 674 - 706 rats and mice (control $n = 335\text{-}351$; high-fat diet $n = 339\text{-}355$) were used to assess the effect of high-fat diet intake. Of the 32 studies, 13 used C57BL/6J mice (Arnold et al., 2014; Ayabe et al., 2018; Denver et al., 2018; Magnusson et al., 2015; Silva et al., 2005; Spinelli et al., 2017; Thirumangalakudi et al., 2008; Valladolid-Acebes et al., 2011, 2013; Wei et al., 2018; Xu et al., 2018), eight used Wistar rats (Alzoubi et al., 2013a, 2013b, 2018; Boitard et al., 2014; Gergerlioglu et al., 2016; Mirzaei et al., 2018; Pratchayasakul et al., 2015; Silva et al., 2005), and six used Sprague-Dawley rats (Hargrave et al., 2015; Jamshed et al., 2014; Liang et al., 2015; Pathan et al., 2008; Scichilone et al., 2016; Woodie & Blythe, 2018). The remaining studies used Swiss Albino mice (Moreira et al., 2014), ICR mice (Park et al., 2018), SAMP-8 mice (Che et

al., 2018), F344xBN F1 rats (Spencer et al., 2018), and Long-Evans rats (Jurdak et al., 2008). All the animals were males, except for Jamshed et al. (2009) who used males and females, and Pratchayasakul et al. (2015) who used only females.

A total of 53 dependent variables were extracted from the 32 experiments (some studies conducted multiple tests within a single experiment) for inclusion in the analysis. Experimental animals were provided *ad libitum* access to a formulated high-fat diet obtained from a local manufacturer, except for Jamshed et al. (2014) who used a diet consisting of store-bought foods, and Jurdak et al. (2008) and Wei et al. (2018) who used control chow mixed with partially-hydrogenated fat or lard, respectively.

2.3.2.2. High-Sugar Diet

A total of 241 rats and mice (control $n = 117$; high-sugar diet $n = 124$) were used to assess the effect of a high-sugar diet intake. Of the nine experiments, four used Sprague-Dawley rats (Abbott et al., 2016; Beilharz et al., 2014; Kendig et al., 2013; Xu & Reichelt, 2018), one used C57BL/6J mice (Magnusson et al., 2015), one used Wistar rats (Gergerlioglu et al., 2016), one used hooded Wistar rats (Kendig et al., 2013), and one used Long Evans rats (Jurdak et al., 2008). All experiments used male subjects, with the exception of Abbott et al. (2016) and Kendig et al. (2013) who used male and female rats.

A total of 18 dependent variables were extracted from the nine experiments for inclusion in the analysis. Experimental animals were provided 10% sucrose solution *ad libitum* (Beilharz et al., 2014; Jurdak et al., 2008) or in a 2-hour daily access period (Abbott et al., 2016; Kendig et al., 2013; Xu & Reichelt, 2018), 32% sucrose solution *ad libitum* (Jurdak et al., 2008), or a semi-purified rodent chow with a high-sugar content (Gergerlioglu et al., 2016; Magnusson et al., 2015; Woodie & Blythe, 2018).

2.3.2.3. High-Fat High-Sugar Diet

A total of 303 rats and mice (control n = 155; high-fat high-sugar diet n = 148) were used to assess the effect of a high-fat high-sugar diet. Of the 11 experiments, nine used Sprague-Dawley rats (Beilharz et al., 2014, 2018; Hargrave et al., 2015; Kanoski & Davidson, 2010; Ross et al., 2013; Tran & Westbrook, 2015, 2018; Wu et al., 2003), one used C57BL/6J mice (Takechi et al., 2015), and one used F344 rats (Molteni et al., 2004). All experiments used male subjects, with the exception of Molteni et al (2004) who used female rats.

A total of 13 dependent variables were extracted from 11 experiments for inclusion in the analysis. Experimental animals were provided *ad libitum* access to a formulated high-fat high-sugar diet in pelleted (Hargrave et al., 2015; Takechi et al., 2017) or powdered (Kanoski & Davidson, 2010; Molteni et al., 2004; Wu et al., 2003) form, a diet consisting of chow supplemented with store-bought foods (Beilharz et al., 2014, 2018; Tran et al., 2015, 2018), or chow supplemented with lard and a bottle of 32% sucrose solution (Ross et al., 2013).

2.3.2.4. Morris Water Maze

A total of 531-544 (control n = 258-266; experimental diet n = 273-278) animals were used to assess the effect of dietary intake on spatial memory using the Morris water maze. Of the 22 experiments, five examined the effect of a high-sugar diet (Gergerlioglu et al., 2016; Jurdak et al., 2008; Kendig et al., 2013; Magnusson et al., 2015; Woodie & Blythe, 2018), 18 examined the effect of high-fat diet (Boitard et al., 2014; Che et al., 2018; Denver et al., 2018; Gergerlioglu et al., 2016; Jamshed et al., 2014; Jurdak et al., 2008; Liang et al., 2015; Magnusson et al., 2015; Mirzaei et al., 2018; Pathan et al., 2008; Pratchayasakul et al., 2015; Scichilone et al., 2016; Silva et al., 2005; Spencer et al., 2017; Spinelli et al., 2017; Wei et al., 2018; Woodie & Blythe, 2018; Xu et al., 2018), and three

examined the effect of high-fat high-sugar diet (Molteni et al., 2004; Takechi et al., 2017; Wu et al., 2003). All experiments used male subjects, except for Jamshed et al. (2014) and Kendig et al. (2013) who used males and female rats, and Molteni et al. (2004) and Pratchayasakul et al. (2015) who used female rats.

Thirty-nine dependent variables were extracted from the 22 experiments for inclusion in the analysis. All of the experiments used time in target quadrant as their dependent variable of spatial memory, except for those reported by Boitard et al. (2014), which used number of target crossings, Magnusson et al. (2015), which used proximity from platform location, and, finally, by Jamshed et al. (2014), Pathan et al. (2008), and Wei et al. (2018) which all used escape latency.

2.3.2.5. Place Recognition

A total of 391-394 (control $n = 189$-190; experimental diet $n = 202$-204) animals were used to assess the effect of dietary intake on spatial memory using the place recognition task. Of the 13 experiments, four examined the effect of a high-sugar diet provided *ad libitum* (Beilharz et al., 2014; Magnusson et al., 2015) or 2-hour restricted access (Abbott et al., 2016; Xu & Reichelt, 2018), five examined the effect of high-fat diet (Ayabe et al., 2018; Magnusson et al., 2015; Moreira et al., 2014; Valladolid-Acebes et al., 2011, 2013), and five examined a high-fat high-sugar diet (Beilharz et al., 2014, 2018; Ross et al., 2013; Tran & Westbrook, 2015, 2018). All experiments used male rats and mice, with the exception of Abbott et al. (2016) who used male and female rats.

Twenty-one dependent variables were extracted from the 13 experiments for inclusion in the analysis. All of the experiments assessed spatial memory using a score to quantify the difference in time spent exploring the object in a novel location compared with the time spend exploring the object in a familiar location. The exact formula for calculating the memory score sometimes differed between studies (e.g., novelty

proportion vs discrimination ratio), but more time spent exploring the novel location was always taken to index better recognition memory.

2.3.2.6. Radial Arm or Radial Arm Water Maze

A total of 147-153 (control $n = 72$-75; experimental diet $n = 75$-78) animals were used to assess the effect of dietary intake on spatial memory using either the RAM or RAWM task. Of the six experiments, five examined the effect of high-fat diet intake (Alzoubi et al., 2013a, 2013b, 2018; Thirumangalakudi et al., 2008; Valladolid-Acebes et al., 2011) and one examined the effect of high-fat high-sugar diet intake (Kanoski & Davidson, 2010). All experiments used male subjects.

Thirteen dependent variables were extracted from the six experiments for inclusion in the analysis. All experiments assessed spatial memory by measuring the total number of working memory errors, defined as re-entry into an arm that previously contained a reward or platform, and reference memory errors, defined as entry or re-entry an arm that has never contained a reward or platform; two experiments evaluated working memory errors only (Thirumangalakudi et al., 2008; Valladolid-Acebes et al., 2011).

2.3.2.7. Spontaneous Alternation

A total of 76 (control $n = 43$; experimental diet $n = 33$) animals were used to assess the effect of diet on spatial memory using spontaneous alternation in either a T- (Arnold et al., 2014) or Y-maze (Hargrave et al., 2015; Park et al., 2018). All four experiments examined the effect of a high-fat diet (Arnold et al., 2014; Hargrave et al., 2015; Park et al., 2018), and one additionally examined the effect of high-fat high-sugar diet (Hargrave et al., 2015). All experiments used male subjects.

A total of seven dependent variables were extracted from the four experiments for inclusion in the analysis. One experiment assessed spatial memory by measuring the

percentage of sequential arm entries (Hargrave et al., 2015), and the remaining three examined the number of entries into a new arm in the T- or Y-maze.

2.3.3. Meta-analysis Output

The forest plots and individual statistics for the diets high in fat, sugar, and both fat and sugar are shown in Figures 2.2-2.4, respectively. There was a significant overall negative effect of consuming a diet high in fat ($k = 53$, $g = -0.595$, 95% CI [-0.715 – -0.474], $p < .001$), refined sugar ($k = 18$, $g = -0.552$, 95% CI [-0.750 – -0.355], $p < .001$), or both fat and refined sugar ($k = 13$, $g = -0.654$, 95% CI [-0.882 – -0.426], $p < .001$), on hippocampal-dependent spatial learning and memory. Each diet had a medium effect size.

The forest plots and individual statistics for the Morris water maze, place recognition task, radial arm mazes, and spontaneous alternation tasks are shown in Figures 2.5-2.8, respectively. There was a significant overall negative effect of consuming a diet high in fat, sugar, or high in both fat and sugar, on performance in the Morris water maze ($k = 43$, $g = -0.375$, 95% CI [-0.511 – -0.239], $p < .001$), place recognition task ($k = 21$, $g = -0.759$, 95% CI [-.939 – -0.578], $p < .001$), radial arm or radial arm water maze ($k = 13$, $g = -0.932$, 95% CI [-1.153 – -0.710], $p < .001$), and spontaneous alternation ($k = 7$, $g = -0.557$, 95% CI [-0.894 – -0.219], $p < .01$). The effect of diet on behavioural performance was a medium effect size for all tasks except for the radial arm maze where the effect size was large.

Table 2.2. Composition and energy density of experimental and control diets provided to animals to examine the effect of high-fat diet (HF) consumption on hippocampal-dependent learning and memory. (* = where provided; kcal = kilocalories; Unsat = unsaturated; w/w = weight / weight).

Author & Expt	Species & Strain [sex]	Experimental diet [Energy Density*]	Experimental Diet Label	Fat Content	Protein	Control Diet [Energy Density*]
Alzoubi et al. (2013a) Expt 1	Wistar rats [Male]	Formulated diet (Sahil-Huran Animal Food Company, Jordan)	Western Diet	25% (w/w) total fat including 11% (w/w) Unsat fat	18% (w/w)	Standard diet (Sahil-Huran Animal Food Company)
Alzoubi et al. (2013b) Expt 1	Wistar rats [Male]	Formulated diet (Sahil-Huran Animal Food Company, Jordan)	High Fat Cholesterol Diet	25% (w/w) total fat including 11% (w/w) Unsat fat	18% (w/w)	Standard diet (Sahil-Huran Animal Food Company)
Alzoubi et al. (2018)	Wistar rats [Male]	Formulated diet (Unknown supplier)	HF	25% (w/w) total fat including 11% (w/w) Unsat fat	18% (w/w)	Standard diet (Sahil-Huran Animal Food Company)
Arnold et al. (2014)	C57BL/6J mice [Male]	Research Diets #D12492 [5.21 kcal/g]	Extreme HF	60% kcal	20% kcal	Research Diets Low-Fat Rodent Diet #D12450B [3.82 kcal/g]
Arnold et al. (2014)	C57BL/6J mice [Male]	Research Diets #D12451 [4.7 kcal/g]	Moderate HF	45% kcal	20% kcal	Research Diets Low-Fat Rodent Diet #D12450B [3.82 kcal/g]

Study	Animal [Sex]	Diet source	Diet type	Fat content		Control diet
Ayabe et al. (2018)	C57BL/6J mice [Male]	Research Diets #D12492 [5.21 kcal/g]	HF	60% kcal (30% w/w Lard)	20% kcal	Research Diets Low-Fat Rodent Diet #D12450J [3.85 kcal/g]
Boitard et al. (2014)	Wistar rats [Male]	Research Diets #D12451 [4.7 kcal/g]	HF	24% (w/w)	-	Standard chow A04 SAFE (Augy, France) [2.9 kcal/g]
Che et al. (2018)	SAMP8 mice [Male]	OpenSource diets #D12492	HF	18.4% (w/w) Lard + 4.6% (w/w) Corn Oil	14%	OpenSource Diets Low Fat Chow #D12450
Denver et al. (2018)	C57BL/6J mice [Male]	Special Diet Services (Witham, UK)	HF	45% (w/w) fat	-	Standard chow (Harlan UK Ltd)
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	Formulated Diet (Nukleon Ltd., Ankara, Turkey)	HF	35% kcal from suet	-	Standard rat chow
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	Research Diets #D06040601 [6.1 kcal/g]	Ketogenic Diet	80% kcal	15%	Standard chow (Harlan Teklad) [3.3 kcal/g]
Jamshed et al. (2014) Expt 1	Sprague Dawley rats [Male & Female]	Diets made from store bought ingredients by authors	cholesterol-chocolate-butterfat (CCB) diet	5% (w/w) Butter-fat & 2% (w/w) Cholesterol	-	Standard chow

Reference	Animal	Diet	Type	% kcal		Control
Jurdak et al. (2008)	Long–Evans rats [Male]	Purina chow [3.6 kcal/g] with partially-hydrogenated fat (traditional Crisco) [9.0 kcal/g]	HF	9.0 kcal/g	-	Purina Chow [3.6 kcal/g]
Liang et al. (2015)	Sprague Dawley rats [Male]	Formulated Diet (Anlimo Technology, China)	HF	40% kcal	-	Standard chow (Anlimo Technology)
Magnusson et al. (2015)	C57BL/6J mice [Male]	Harlan Laboratories #TD.88137 [4.5 kcal/g]	HF	42% kcal	17.3% Kcal	PicoLab Rodent Diet #20 (LabDiet) [4.07 kcal/g]
Mirzaei et al. (2018)	Wistar rats [Male]	Royal Laboratory #D12492 [5.21 kcal/g]	HF	60% kcal	20% kcal protein	Standard chow
Moreira et al. (2014)	Swiss Albino Mice [Male]	Chow is produced at the Universidade Estadual de Campinas, Campinas, SP, Brazil	Hypercholestermic Diet	20% (w/w) Saturated fat + 1.25% (w/w) Cholesterol	-	Nuvilab-CR1 non-purified diet
Pathan et al. (2008)	SD rats [Male]	High Fat Pellet Diet (Pranaw Agro Industries, New Delhi)	HF	58% total kcal	25%	Standard chow diet (Pranaw Agro Industries) [64 kcal/day]
Pratchayasakul et al. (2015)	Wistar rats [Male]	Diet containing fat, mostly from lard [5.35 kcal/g]	HF	59.28% kcal (Lard)	26.45%	C.P. Company #CP 082 Standard laboratory diet

Reference	Strain	Diet	Type	Fat content	Value	Control diet
Park et al. (2018)	ICR mice [Male]	AIN-76A [3.77 kcal/g] + 40% beef Tallow No. 101556	HF	40% (w/w; Beef Tallow)	-	Dyets Inc. Standard Chow AIN-76A No. 100000 [3.77 kcal/g]
Scichilone et al. (2016)	Sprague Dawley rats [Male]	Bio-Serv #F5155 supplemented with 14% protein	Ketogenic Diet	73.5% (w/w)	14%	Standard chow
Silva et al. (2005)	Wistar rats [Male]	-	Ketogenic Diet	69% (w/w)	24%	Nuvilab-CR1 non-purified diet
Spencer et al. (2017)	F344xBN F1 rats [Male]	Teklands Diets #TD.06414 [5.1 kcal/g]	HF	60.3% kcal	18%	Teklad Diets Standard chow #TD. 8640 [3.0 kcal/g]
Spinelli et al (2017)	C57BL/6J mice [Male]	Diets obtained from Mucedola (Italy)	HF	60% kcal (saturated fatty acids)	-	Standard chow
Thirumangalakudi et al. (2008)	C57BL/6 mice	Tekland Diets	HF	21% fat, 1.25% cholesterol	-	-
Valladolid-Acebes et al. (2011)	C57BL/6J mice [Male]	Research Diets #D12451 [4.73 kcal/g]	HF	45% kcal (20% w/w lard)	20 kcal%	Research Diets Low-Fat Rodent Diet #D12450B [3.85 kcal/g]

Valladolid-Acebes et al. (2013) Expt 1	C57BL/6J mice [Male]	Research Diets #D12451. [4.73 kcal/g]	HF	45% kcal (20% w/w lard)	20% kcal	Standard chow
Valladolid-Acebes et al. (2013) Expt 3	C57BL/6J mice [Male]	Research Diets #D12451. [4.73 kcal/g]	HF	45% kcal (20% w/w lard)	20% kcal	Standard chow
Wei et al. (2018)	C57BL/6J mice [Male]	74% control diet and 10% lard compound (Shanghai Pu Lu Teng Biological Technology)	HF	5.28% (w/w) in CD + 10% (w/w) Lard	5% (w/w)	Regular Diet
Woodie & Blythe (2018)	Sprague Dawley rats [Male]	Research Diets #D08060104	HF	60% kcal	-	Harlan-Teklad Rat Chow #LM-485
Xu et al. (2018)	C57BL/6J mice [Male]	Research Diets #D12492 [5.21 kcal/g]	HF	60% kcal	-	Standard diet

Table 2.3. Composition and energy density of experimental and control diets provided to animals to examine the effect of high-sugar diet (HS) consumption on hippocampal-dependent learning and memory. (* = where provided; kcal = kilocalories; w/w = weight / weight).

Author & Expt	Species & Strain [sex]	Experimental diet [Energy Density*]	Experimental Diet Label	Refined Sugar Content	Protein	Control Diet [Energy Density*]
Abbott et al. (2016) Expt 1	Sprague Dawley rats [Male & Female]	Control diet [3.53 kcal/g] + 10% Sucrose solution [0.4 kcal/g]	HS	0.4 kcal/g sucrose solution	-	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Control diet [3.53 kcal/g] + 10% Sucrose solution [0.4 kcal/g]	HS	0.4 kcal/g sucrose solution	-	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	Formulated Diet (Nukleon Ltd., Ankara, Turkey)	HS	100% kcal of carbohydrate from sucrose	-	Standard rat chow
Jurdak et al. (2008)	Long–Evans rats [Male]	Purina Chow [3.6 kcal/g] with sucrose solution [1.28 kcal/g]	HS	1.28 kcal/g sugar solution	-	Purina Chow [3.6 kcal/g]
Kendig et al. (2013)	Hooded Wistar rats [Male & Female]	Control diet [3.4 kcal/g] with 10% sucrose solution [0.4 kcal/g]	HS	0.4 kcal/g sugar solution	-	Specialty Feeds Standard Chow [3.4 kcal/g]

Magnusson et al. (2015)	C57BL/6J mice [Male]	Harlan Laboratories # TD.98090 [4 kcal/g]	HS	66% (w/w) sucrose	17.7% kcal	PicoLab Rodent Diet #20 [4.07 kcal/g]
Xu & Reichelt (2018)	Sprague Dawley rats [Male]	Control diet [2.63 kcal/g] with 10% sucrose solution [0.4kcal/g]	HS	0.4kcal/g sucrose solution	-	Standard rat chow [2.63 kcal/g]
Woodie & Blythe (2018)	Sprague-Dawley rats [Male]	Research Diets #D05111802	High Fructose Diet	55% kcal/g	-	Standard chow

Table 2.4. Composition and energy density of experimental and control diets provided to animals to examine the effect of high-fat high-sugar (HFHS) diet consumption on hippocampal-dependent learning and memory. (* = where provided; kcal = kilocalories; w/w = weight / weight).

Author & Expt	Species & Strain [sex]	Experimental diet [Energy Density*]	Experimental Diet Label	Fat Content	Refined Sugar Content	Protein	Control Diet [Energy Density*]
Beilharz et al. (2014) Expt 1	Sprague Dawley rats [Male]	Cafeteria diet consisting of store-bought "junk foods" & 10% sucrose solution [0.4 kcal/g]	Cafeteria Diet with Sucrose solution	45% (w/w)	0.4 kcal/g sucrose solution; Unknown from solid diet	5%	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria diet consisting of store-bought "junk foods" & 10% sucrose solution [0.4 kcal/g]	Cafeteria Diet with Sucrose solution	45% (w/w)	0.4 kcal/g sucrose solution; Unknown from solid diet	5%	
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria diet consisting of store-bought "junk foods"	Cafeteria Diet	45% (w/w)	Unknown	5%	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]

Study	Animal	Diet	Diet type	Fat	Sugar	%	Control diet
Beilharz et al. (2018)	Sprague Dawley rats [Male]	Cafeteria diet consisting of store-bought "junk foods" & 10% sucrose solution [0.4 kcal/g]	Cafeteria Diet with Sucrose	45% (w/w)	0.4 kcal/g sucrose solution; Unknown from solid diet	5%	Standard chow
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	Harlan #TD.10768 [4.5kcal/g]	High-fat, high-dextrose "Western" diet	38% kcal	20% kcal Dextrose	24%	Harlan Teklad Standard chow [3.3 kcal/g]
Kanoski & Davidson (2010)	Sprague Dawley rats [Male]	Harlan Teklad Powdered Diet #TD.04489 [4.55 kcal/g]	High Energy Diet	170g/kg lard	220.5g/kg glucose	-	Purina LabDiet #5001 [3.0 kcal/g]
Molteni et al. (2004)	Fisher 344 rats [Female]	Powdered HFS diet (Purina Mills Inc., Test Diets Inc.)	HFHS	39% kcal (primarily lard)	40% kcal from sucrose	-	Powdered low-fat, complex carbohydrate diet (Purina Mills Inc., Test Diets Inc.)

Reference	Animal [Sex]	Diet description	Diet name	Fat	Sugar		Control diet
Ross et al. (2013)	Sprague Dawley rats [Male]	Control diet, a petri dish containing animal lard [9.0 kcal/g], and a bottle of 32% sucrose solution [1.13 kcal/g]	HFHS	Free access to lard (9.0 kcal/g)	32% sucrose solution; Unknown from solid diet	-	Purina LabDiet #5001 [3.0 kcal/g]
Takechi et al. (2017)	C57BL6/J mice [Male]	Specialty Feeds #SF14-088	High Fat Fructose Diet	30% (w/w) lard, 0.5% (w/w) cholesterol	15% (w/w) fructose	-	Specialty Feeds Low-Fat chow #AIN-93M
Tran & Westbrook (2015) Expt 1	Sprague Dawley rats [Male]	Cafeteria diet made of store-bought "junk foods"	HFHS Diet	40% (w/w; primarily lard)	40% (w/w) sucrose	5%	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]
Tran & Westbrook (2018) Expt 1	Sprague Dawley rats [Male]	Cafeteria diet made of store-bought "junk foods"	HFHS Diet	40% (w/w; primarily lard)	40% (w/w) sucrose	5%	Gordon's Premium Rat and Mouse Breeder diet (Australia) [3.53 kcal/g]

| Wu et al. (2003) Expt 1 | Sprague Dawley rats [Male] | Powdered HFS diet (Purina Mills Inc., Test Diets Inc.) | HFHS Diet | 39% kcal (primarily lard) | 40% kcal from sucrose | - | Powdered low-fat, complex carbohydrate diet (Test Diets Inc.) |

Table 2.5. Experimental details and behavioural outcomes for studies examining the effect of dietary manipulation on hippocampal-dependent learning and memory in the Morris water maze. (*Approximate age based on growth charts; When multiple groups of diet manipulation lengths have been used: [+] = separate experimental groups; When multiple tests have been used: [^] = ongoing test without training between test sessions; # = isolated test involving training and testing; CD = Control Diet; HF = High-Fat Diet; HFFruc = High-Fat High-Fructose Diet; HFHS = High-Fat High-Sugar Diet; HS = High-Sugar Diet; KD = Ketogenic Diet).

Author & Expt	Species & Strain [sex]	Experimental Diet	Age* at Diet Onset	Diet Duration	Dependent Variable [Retention Interval]	Behavioural Outcomes
Boitard et al. (2014)	Wistar rats [Male]	HF	12-weeks	2-months	Number Target Crossings [2-hr][^]	Rats consuming HF had an equivalent number of target crossings as control rats at both 2-hr and 4-day retention intervals.
					Number Target Crossings [4-days][^]	
Che et al. (2018)	SAMP8 mice [Male]	HF	10-months-old	8-weeks	Time in target quadrant [24-hr]	HF mice spent significantly less time in the target quadrant than control mice.
Denver et al. (2018)	C57BL/6J mice [Male]	HF	7-14-weeks	10-days[+]	Time in target quadrant [24-hr]	Rats consuming the HF did not significantly differ from rats consuming control diet, however the time in target quadrant for both groups did not significantly differ from chance.
				26-days[+]		
				8-weeks[+]		

Study	Rat strain [Sex]	Diet	Age	Diet duration	Outcome measure [time-point]	Result
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	HF	10–12-weeks	3-weeks	Time in target quadrant [24-hr]	Rats consuming HF spent significantly less time in the target quadrant than rats consuming control diet.
Gergerlioglu et al. (2016) Expt 1	Wistar rats [Male]	HS	10–12-weeks	3-weeks	Time in target quadrant [24-hr]	Rats consuming HS and CD spent equivalent time in the target quadrant during probe test.
Jamshed et al. (2014) Expt 1	Sprague Dawley rats [Male & Female]	HF (*labelled cholesterol-chocolate-butterfat diet by authors*)	6+-weeks* *(180-200 grams)*	6-weeks	Escape Latency [24-hr]	Rats consuming the CCB diet took significantly longer to reach the escape platform than rats consuming control diet.
Jurdak et al. (2008)	Long–Evans rats [Male]	HF	6-weeks	5-weeks	Time in target quadrant [10-day]^ ; Time in target quadrant [24-hr]^	No effect of HF on time spent in the target quadrant at 24-hrs or 10-days post-training.
Jurdak et al. (2008)	Long–Evans rats [Male]	HS	6-weeks	5-weeks	Time in target quadrant [24-hrs] ; Time in target quadrant [10-days]	Rats consuming HS spent equivalent time in the target quadrant as control rats when tested 24-hrs after training, but significantly less time in the target quadrant than control rats when tested 10-days after training.

Author	Strain [Sex]	Diet	Duration	Duration	Measure	Results
Kendig et al. (2013)	Hooded Wistar rats [Male & Female]	HS	4-weeks	4-weeks	Time in target quadrant (Probe tests 1-3) [24-hrs]^	During the first three probe trials, rats consuming HS spent significantly less time in the target quadrant than control rats.
			8-weeks	4-weeks	Time in target quadrant [28-day]^	Rats consuming HS spent less time in the target quadrant than control rats, however this difference was not significant.
Liang et al. (2015)	Sprague Dawley rats [Male]	HF	6-weeks	6-weeks	Time in target quadrant [24-hr]	Rats consuming a HF spent significantly less time in the target quadrant than control rats.
					Proximity from Platform (Probe 1) [1-hr]#	Rats consuming HF had greater proximity from platform location than control rats, however this difference was not significant.
					Proximity from Platform (Probe 2) [1-hr]#	Rats consuming HF had greater proximity from platform location than control rats, however this difference was not significant.
Magnusson et al. (2015)	C57BL/6J mice [Male]	HF	8-weeks	5-weeks	Proximity from Platform (Probe 3) [1-hr]#	Rats consuming HF had greater proximity from platform location than control rats, however this difference was not significant.
					Proximity from Platform (Probe 4) [1-hr]#	Rats consuming HF had a smaller proximity from platform location than rats consuming chow, however this was not significant.

	Magnusson et al. (2015)	C57BL/6J mice [Male]	HS	8-weeks	Reversal Task [1-hr]	Proximity from new platform location did not differ between HF and CD rats, however HF had significantly smaller proximity to old platform location than CD rats.
					Proximity from Platform (Probe 1) [1-hr]#	Rats consuming HF had greater proximity from platform location than control rats, however this was not significant.
					Proximity from Platform (Probe 2) [1-hr]#	No effect of diet on proximity from platform, with rats in both groups having a similar distance.
				5-weeks	Proximity from Platform (Probe 3) [1-hr]#	Rats consuming HF had a smaller proximity from platform location than rats consuming chow, however this was not significant.
					Proximity from Platform (Probe 4) [1-hr]#	Rats consuming HF had a smaller proximity from platform location than rats consuming chow, however this was not significant.
					Reversal Task [1-hr]	Proximity from new platform location did not differ between HS and CD rats, however HS had significantly smaller proximity to old platform location than CD rats.

Reference	Rat strain [Sex]	Diet			Measure	Outcome
Mirzaei et al. (2018)	Wistar rats [Male]	HF	8-weeks	8-weeks	Time in target quadrant [24-hrs]	Rats consuming HF spent significantly less time in the target quadrant than rats consuming chow.
Molteni et al. (2004)	Fisher 344 rats [Female]	Powdered HFHS	8-weeks	2-months	Time in target quadrant [3-days]	Rats consuming HFHS spent equal time in the MWM quadrants at test. Time in target quadrant was significantly lower in HF than control rats.
Pathan et al. (2008)	SD rats [Male]	HF	5+-weeks* (150-190 grams)	5-weeks	Escape Latency [24-hr]	Decrease in escape latency across the 5-days of training was significantly greater in rats consuming the control diet than rats consuming HF.
Pratchayasakul et al. (2015)	Wistar rats [Female]	HF	8+-weeks* (200-220 grams)	4-weeks+	Time in target quadrant [24-hr]	No effect of diet on time in target quadrant.
Pratchayasakul et al. (2015)	Wistar rats [Female]	HF	8+-weeks* (200-220 grams)	8-weeks+	Time in target quadrant [24-hr]	No effect of diet on time in target quadrant.
Scichilone et al. (2016)	Sprague Dawley rats [Male]	Ketogenic Diet	4-weeks	8-weeks	Time in target quadrant [2-hr]	Rats consuming KD spent less time in the target quadrant than control rats, however this was not significant.
Silva et al. (2005)	Wistar rats [Male]	Ketogenic Diet	30-days-old	40-days	Time in target quadrant [24-hr]	Rats consuming KD spent less time in the target quadrant than control rats, however this was not significant.

Spencer et al (2017)	F344xBN F1 rats [Male]	HF	3-months[+]	4-days	Time in target quadrant [4-days]	There was no effect of diet on time spent in the target quadrant.
			24-months[+]		Time in target quadrant [4-days]	There was no effect of diet on time spent in the target quadrant.
Spinelli et al. (2017)	C57BL/6J mice [Male]	HF	30 to 35-days	6-weeks	Time in target quadrant [24-hrs]	Mice consuming HF spent significantly less time in the target quadrant than control mice.
Takechi et al. (2017)	C57BL6/J mice [Male]	High Fat Fructose (HFFruc) Diet	6-weeks	4-weeks	Escape latency [24-hour]	Mice consuming HFFruc had a slower latency to platform than mice consuming CD, however this was not statistically significant.
Wei et al. (2018)	C57BL/6J mice [Male]	HF	12 to 14-months	8-weeks	Time in target quadrant [24-hr]	HF mice spent less time in the target quadrant than mice consuming the control diet.
					Time in target quadrant [24-hr]	There was no effect of diet on the time spent in the target quadrant during probe test.
Woodie & Blythe (2018)	Sprague Dawley rats [Male]	HF	6-weeks	8-weeks	Reversal Task Time in target quadrant [24-hr]	There was no effect of diet on time spent in new target quadrant.

Study	Strain [Sex]	Diet	Age	Diet Duration	Task / Measure	Findings
Woodie & Blythe (2018)	Sprague Dawley rats [Male]	High Fructose Diet	6-weeks	8-weeks	Time in target quadrant [24-hr] Reversal Task Time in target quadrant [24-hr]	There was no effect of diet on the time spent in the target quadrant during probe test. There was no effect of diet on time spent in new target quadrant.
Wu et al. (2003) Expt 1	Sprague Dawley rats [Male]	Powdered HFHS Diet	6+-weeks* (200-240 grams)	4-weeks	Time in target quadrant [4-hrs]	HFHS fed rats spent equivalent time in the target quadrant as control rats.
Xu et al. (2018)	C57BL/6J mice [Male]	HF	4 Weeks	8-weeks	Time in target quadrant [24-hr]	HF spent significantly less time in the target quadrant than mice consuming the control diet.

Table 2.6. Experimental details and behavioural outcomes for studies examining the effect of dietary manipulation on hippocampal-dependent learning and memory in the place recognition task. (*Approximate age based on growth charts; When multiple tests have been used; When multiple groups of diet manipulation lengths have been used: + = separate experimental groups; ^ = ongoing test without training between test sessions; # = isolated test involving training and testing; HF = high-fat diet; HS = high-sugar diet; HFHS = high-fat high-sugar diet; CD = control diet).

Author & Expt	Species & Strain (sex)	Experiment Diet	Age* at Diet Onset	Diet Duration	Behavioural Task [Retention Interval]	Behavioural Outcomes
Abbott et al. (2016) Expt 1	Sprague Dawley rats [Male & Female]	HS	4-weeks	2-weeks	Place Recognition [5-min]	Male and female HS rats spent a significantly smaller proportion of time exploring the novel object location than control rats.
				3-weeks	Object-in-Place Recognition [5-min]	Male HS rats spent a significantly smaller proportion of time exploring the novel object locations than male control mice. No effect of HS on object location exploration in females.
Ayabe et al. (2018)	C57BL/6J mice [Male]	HF	6 Weeks	7 Weeks	Place Recognition [4-hr]	HF rats spent a smaller proportion of time exploring the novel object location then control rats, however this was not significant.
Beilharz et al. (2014) Expt 1	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose solution	8+-weeks* (363-463 grams)	5-6-days	Place Recognition [5-min]#	Main effect of diet, such that rats consuming cafeteria diet with sucrose solution spent a significantly smaller
				11 to 12-days	Place Recognition [5-min]#	solution spent a significantly smaller

Study	Animal [Sex]	Diet	Age / Weight	Testing days	Task	Findings
				20 to 21-days	Place Recognition [5-min]#	proportion of time exploring the novel object location than control rats.
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	HS	7+-weeks* (302–366 grams)	5 to 6-days, 11 to 12-days, & 20 to 21-days	Place Recognition [5-min]#	Main effect of diet, such that rats consuming the HS, cafeteria diet, or the cafeteria diet with sucrose solution spent a significantly smaller proportion of time exploring the novel object location than control rats.
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose solution	7+-weeks* (302–366 grams)	5 to 6-days, 11 to 12-days, & 20 to 21-days	Place Recognition [5-min]#	
Beilharz et al. (2014) Expt 2	Sprague Dawley rats [Male]	Cafeteria Diet	7+-weeks* (302–366 grams)	5 to 6-days, 11 to 12-days, & 20 to 21-days	Place Recognition [5-min]#	object location than control rats.
Beilharz et al. (2018)	Sprague Dawley rats [Male]	Cafeteria Diet with Sucrose	5+-weeks* (200 grams)	10 to 11-days	Place Recognition [5-min]#	Rats consuming cafeteria diet with sucrose solution spent a significantly smaller proportion of time exploring the novel object location than control rats.
				17 to 18-days	Place Recognition [5-min]#	
Magnusson et al. (2015)	C57BL/6J mice [Male]	HF	8-weeks	2-weeks	Place Recognition [1-hr]^	There was no significant effect of diet on proportion of time spent exploring the object in the novel object location,

Study	Animal	Diet	Age/Duration	Diet Duration	Test	Findings
Magnusson et al. (2015)	C57BL/6J mice [Male]	HS	8-weeks	2-weeks	Place Recognition [24-hr]^	however exploration did not occur above chance for either diet condition.
					Place Recognition [1-hr]^	There was no significant effect of diet on proportion of time spent exploring the object in the novel object location, however exploration did not occur above chance for either diet condition.
Moreira et al. (2014)	Swiss Albino Mice [Male]	Hypercholester-nic Diet	3-months-old	8-weeks	Place Recognition [90-min]	Mice consuming a hypercholesterolemic diet spent a significantly smaller proportion of time exploring the novel object location than control mice.
Ross et al. (2013)	Sprague Dawley rats [Male]	HFHS	7-8-weeks	4-weeks	Place Recognition [24-hrs]	There was no effect of diet on the proportion of time spent exploring the novel object location.
Tran & Westbrook (2015) Expt 1	Sprague Dawley rats [Male]	HFHS Diet	5+-weeks* (200-300 grams)	1 week	Place Recognition [5-min]#	Main effect of diet, such that rats consuming HFHS diet spent a significantly smaller proportion of time exploring the novel object location than control rats.
				2-weeks	Place Recognition [5-min]#	
				3-weeks	Place Recognition [5-min]#	

Study	Species [Sex]	Diet	Duration	Task	Results
Tran & Westbrook (2018) Expt 1	Sprague Dawley rats [Male]	HFHS Diet	5+-weeks* (200-300 grams)	Place Recognition [5-min]	Rats consuming HFHS diet spent a significantly smaller proportion of time exploring the novel object location than control rats.
Valladolid-Acebes et al. (2013) Expt 1	C57BL/6J mice [Male]	HF	5-weeks	1 week	Place Recognition [1-hr]^	Mice consuming HF spent a significantly smaller proportion of time exploring the novel object location than control mice tested 1-hr and 24-hrs following training.
			8-weeks	Place Recognition [24-hr]^	
Valladolid-Acebes et al. (2013) Expt 3	C57BL/6J mice [Male]	HF	8-weeks	Place Recognition [1-hr]^	There was no effect of diet on proportion of time spent exploring the novel object location when tested 1-hr following training, and a smaller proportion of time exploring the novel object location at 24-hr test, however this difference was not significant.
			8-weeks	Place Recognition [24-hr]^	
Xu & Reichelt (2018)	Sprague Dawley rats [Male]	HS	4-weeks	3-weeks	Place Recognition [5-min]	HS rats spent a significantly smaller proportion of time exploring the novel object location than control rats.

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Table 2.7. Experimental details and behavioural outcomes for studies examining the effect of dietary manipulation on hippocampal-dependent learning and memory in the radial arm maze or radial arm water maze. (*Approximate age based on growth charts; When multiple tests have been used: ^ = ongoing test without training between test sessions; HF = high-fat diet; HFHS = high-fat high-sugar diet; WM errors = working memory errors; RM errors = reference memory errors).

Author & Expt	Species & Strain [sex]	Experimental Diet	Age* at Diet Onset	Diet Duration	Maze Type & Dependent Variable [Retention Interval]		Behavioural Outcomes
Alzoubi et al. (2013a) Expt 1	Wistar rats [Male]	HF (labelled western diet)	6-7-weeks	6-weeks	6-arm water maze WM & RM errors [30-min]^		Rats consuming HF made significantly more incorrect arm entries than rats consuming control diet when tested 30-min, 5-hrs, and 24-hrs post-training.
					6-arm water maze WM & RM errors [5-hr]^		
					6-arm water maze WM & RM errors [24-hr]^		
Alzoubi et al. (2013b) Expt 1	Wistar rats [Male]	HF (labelled high-fat cholesterol diet)	6-7-weeks	6-weeks	6-arm water maze WM & RM errors [30-min]^		Rats consuming HF made significantly more incorrect arm entries than rats consuming control diet when tested 30-min, 5-hrs, and 24-hrs post-training.
					6-arm water maze WM & RM errors [5-hr]^		
					6-arm water maze WM & RM errors [24-hr]^		

Study	Animal [Sex]	Diet	Age	Duration	Test	Findings
Alzoubi et al. (2018)	Wistar rats [Male]	HF	4+-weeks* (160–200 grams)	4-weeks	6-arm water maze WM & RM errors [5-hr]^	Rats consuming HF made significantly more incorrect arm entries than rats consuming control diet when tested 5-hrs and 24-hrs post-training.
					6-arm water maze WM & RM errors [24-hr]^	
Kanoski & Davidson (2010)	Sprague Dawley rats [Male]	HFHS (labelled high energy diet)	8 to 9-weeks	6 tests starting at 3-days	8-arm radial maze WM & RM errors	HFHS rats made significantly more incorrect arm entries than control rats.
Thirumangalakudi et al. (2008)	C57BL/6 mice	HF	4-months-old	2-months	8-arm water maze WM Errors [24-hrs]	HF mice made significantly more entries into an arm that previously contained a platform than control mice consuming control diet.
					8-arm water maze WM & RM errors [24-hrs]	HF mice made significantly more incorrect arm entries than mice consuming the control diet.
					8-arm radial maze WM errors [24-hrs]	HF mice made significantly more entries into a previously baited arm than mice consuming control diet.
Valladolid-Acebes et al. (2011)	C57BL/6J mice [Male]	HF	4-weeks-old	8-weeks	8-arm radial maze WM & RM errors [24-hrs]	HF mice made significantly more incorrect arm entries than mice consuming the control diet.

Table 2.8. Experimental details and behavioural outcomes for studies examining the effect of dietary manipulation on hippocampal-dependent learning and memory in the spontaneous alternation task. (*Approximate age based on growth charts; When multiple groups of diet manipulation lengths have been used: + = separate experimental groups; HF = high-fat diet; HFHS = high-fat high-sugar diet; KD = ketogenic diet; # = number; % = percentage).

Author & Expt	Species & Strain [sex]	Experimental Diet	Age* at Diet Onset	Diet Duration	Maze Type & Dependent Variable	Behavioural Outcomes
Arnold et al. (2014)	C57BL/6J mice [Male]	Extreme HF	8-weeks	17-days	T-Maze # of new arm entries	Control mice showed significantly greater spontaneous alternation than HF mice.
Arnold et al. (2014)	C57BL/6J mice [Male]	Moderate HF	8-weeks	8-weeks	T-Maze # of new arm entries	Control mice showed significantly greater spontaneous alternation than HF mice.
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	Ketogenic Diet	7+-weeks* (275-300 grams)	10-days+	Y-maze % sequential arm entries	No effect of KD on % of sequential arm entries.
				40-days+		KD rats had a higher % of sequential arm entries than control rats, but this was not significant.

Study	Species [Sex]	Diet	Age/Weight	Duration	Task	Result
Hargrave et al. (2015) Expt 1	Sprague Dawley rats [Male]	High-fat high-dextrose "Western" diet	7+-weeks* *(275-300 grams)*	10-days+	Y-maze % sequential arm entries	HFHS diet rats had a significantly lower % of sequential arm entries than control rats.
				40-days+		No effect of HFHS diet on % of sequential arm entries.
Park et al. (2018)	ICR mice [Male]	HF	10-months-old	8-weeks	Y-Maze # of new arm entries	HF mice had significantly reduced spontaneous alternation than control mice.

Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alzoubi et al (2013a)	24 hr test	6-am WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Alzoubi et al (2013a)	30 min test	6-am WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Alzoubi et al (2013a)	5 hr test	6-am WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Alzoubi et al (2013b)	24 hr test	6-am WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Alzoubi et al (2013b)	30 min test	6-am WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Alzoubi et al (2013b)	5 hr test	6-am WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Alzoubi et al (2018)	24 hr test	6-am WM	HF	-0.728	0.367	0.135	-1.448	-0.007	-1.980	0.048
Alzoubi et al (2018)	5 hr test	6-am WM	HF	-0.728	0.367	0.135	-1.448	-0.007	-1.980	0.048
Arnold et al (2014)	Ext HFD	SA T-maze	Extreme HF	-1.120	0.624	0.389	-2.342	0.103	-1.795	0.073
Arnold et al (2014)	Mod HFD	SA T-maze	Moderate HF	-0.961	0.454	0.206	-1.841	-0.061	-2.005	0.036
Ayabe et al (2018)	Blank	Place Recognition	HF	-0.296	0.475	0.225	-1.167	0.694	-0.488	0.618
Boland et al (2014)	2 hr test	MWM - Number target crossings	HF	-0.571	0.389	0.151	-1.334	0.191	-1.469	0.142
Boland et al (2014)	4 hr test	MWM - Number target crossings	HF	-0.190	0.382	0.146	-0.939	0.558	-0.498	0.618
Che et al (2018)	Blank	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Denver et al (2018)	10 day diet	MWM	HF	-0.197	0.395	0.156	-0.972	0.577	-0.499	0.618
Denver et al (2018)	26 day diet	MWM	HF	0.197	0.395	0.156	-0.577	0.972	0.499	0.618
Gergerlioglu et al (2016)	8 week diet	MWM	HF	-1.567	0.596	0.343	-3.106	-0.809	-3.341	0.001
Hargrave et al (2015)	Expt 1	SA Y-maze	Ketogenic Diet	0.214	0.430	0.185	-0.628	1.056	0.498	0.618
Hargrave et al (2015)	Expt 1 - 10 days	SA Y-maze	Ketogenic Diet	0.214	0.430	0.185	-0.628	1.056	0.498	0.618
Jamshed et al (2014)	Expt 1 - 40 days	MWM escape latency	HF	-1.529	0.578	0.334	-2.661	-0.396	-2.645	0.008
Juntak et al (2008)	Expt 1	MWM	HF	-0.037	0.428	0.183	-0.876	0.803	-0.086	0.932
Juntak et al (2008)	10 day probe	MWM	HF	-0.201	0.429	0.184	-1.043	0.640	-0.469	0.639
Liang et al (2015)	24 hr probe	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Magnusson et al (2015)	Blank	Place Recognition	HF	-1.759	0.643	0.413	-3.019	-0.500	-2.738	0.006
Magnusson et al (2015)	1 hr	MWM/Dist from plat	HF	0.515	0.543	0.295	-0.550	1.590	0.948	0.343
Magnusson et al (2015)	24 hr	MWM/Dist from plat	HF	0.486	0.542	0.294	-0.577	1.548	0.896	0.370
Magnusson et al (2015)	Probe 1	MWM/Dist from plat	HF	-0.723	0.553	0.306	-1.807	0.361	-1.308	0.191
Magnusson et al (2015)	Probe 2	MWM/Dist from plat	HF	0.383	0.539	0.290	-0.673	1.439	0.711	0.477
Magnusson et al (2015)	Probe 3	MWM/Dist from plat	HF	-0.209	0.535	0.286	-1.256	0.839	-0.390	0.696
Magnusson et al (2015)	Probe 4	MWM/Dist from plat	HF	-1.269	0.473	0.224	-2.196	-0.342	-2.682	0.007
Magnusson et al (2015)	Reversal	MWM/Dist from old plat	HF	-1.690	0.504	0.254	-2.667	-0.692	-3.333	0.001
Mizael et al (2018)	Blank	MWM	HF	-1.429	0.445	0.198	-2.301	-0.557	-3.212	0.001
Moreira et al (2014)	Blank	Place Recognition	HF	-0.286	0.575	0.330	-1.412	0.841	-0.497	0.619
Pathan et al (2008)	Blank	SA Y-maze	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Pak et al (2018)	Blank	MWM/escape latency	HF	-0.286	0.575	0.330	-1.412	0.841	-0.497	0.619
Pratchayasakul et al (2015)	Blank	MWM	HF	-0.172	0.345	0.119	-0.849	0.504	-0.499	0.618
Pratchayasakul et al (2015)	8 weeks	MWM	HF	-0.234	0.469	0.220	-1.154	0.686	-0.499	0.618
Scichione et al (2016)	4 weeks	MWM	HF	0.376	0.398	0.158	-0.403	1.156	0.946	0.344
Silva et al (2016)	Blank	MWM	HF	-1.967	0.596	0.343	-3.106	-0.809	-3.341	0.001
Spencer et al (2017)	Blank	MWM	HF	-1.187	0.595	0.343	-2.335	-0.040	-2.028	0.043
Spinelli et al (2017)	3 & 24 month old	MWM	HF	-1.187	0.595	0.343	-2.335	-0.040	-2.028	0.043
Thirumangalakud et al (2008)	Blank	8-am WM	HF	-1.417	0.362	0.131	-2.127	-0.706	-3.909	0.000
Thirumangalakud et al (2008)	Total errors	8-am WM	HF	-1.159	0.350	0.122	-1.845	-0.474	-3.314	0.001
Valladolid-Acebes et al (2011)	WM errors	8-am Radial Maze	HF	-1.495	0.449	0.202	-2.375	-0.614	-3.326	0.001
Valladolid-Acebes et al (2011)	Expt 1 - WM error	Place Recognition	HF	-0.197	0.396	0.157	-0.973	0.578	-0.499	0.618
Valladolid-Acebes et al (2013)	Expt 3 - 5 wks - 1 hr	Place Recognition	HF	-1.495	0.449	0.202	-2.375	-0.614	-3.326	0.001
Valladolid-Acebes et al (2013)	Expt 3 - 5 wks - 24 hr	Place Recognition	HF	-0.197	0.396	0.157	-0.973	0.578	-0.499	0.618
Valladolid-Acebes et al (2013)	Expt 3 - 8 wks - 1 hr	Place Recognition	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Wei et al (2018)	Blank	MWM	HF	0.269	0.422	0.178	-0.557	1.095	0.639	0.523
Woode & Blythe (2018)	Blank	MWM	HF	0.210	0.421	0.177	-0.614	1.035	0.500	0.617
Woode & Blythe (2018)	MWM Reversal	MWM Reversal	HF	-1.407	0.534	0.285	-2.454	-0.360	-2.634	0.008
Xu et al (2018)	Blank	MWM	HF	-0.595	0.061	0.004	-0.715	-0.474	-9.672	0.000

Figure 2.2. Forest plots and meta-analysis results of experiments using a high-fat diet.

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Study name	Subgroup within study	Comparison	Outcome	Statistics for each study							Hedges's g and 95%CI
				Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Abbott et al (2016)	Expt1	Object-in-Place Recognition	HS	-1.010	0.305	0.093	-1.608	-0.412	-3.309	0.001	
Abbott et al (2016)	Expt-1	Place Recognition	HS	-1.010	0.305	0.093	-1.608	-0.412	-3.309	0.001	
Beilharz et al (2014)	Expt2	Place Recognition	HS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045	
Gergerlioglu et al (2016)	Expt1	MWM	HS	-0.236	0.475	0.225	-1.167	0.694	-0.498	0.618	
Jurdak et al (2008)	10 day probe	MWM	HS	-1.106	0.463	0.214	-2.013	-0.200	-2.391	0.017	
Jurdak et al (2008)	24 hr probe	MWM	HS	0.057	0.428	0.184	-0.782	0.897	0.134	0.893	
Kendig et al (2013)	24 hr (Ave probes 1-3)	MWM	HS	-0.746	0.321	0.103	-1.375	-0.117	-2.325	0.020	
Kendig et al (2013)	28 day probe	MWM	HS	-0.521	0.315	0.099	-1.139	0.097	-1.652	0.099	
Magnusson et al (2015)	1 hr	Place Recognition	HS	-0.086	0.533	0.284	-1.131	0.959	-0.161	0.872	
Magnusson et al (2015)	24 hr	Place Recognition	HS	-0.261	0.536	0.287	-1.310	0.789	-0.487	0.626	
Magnusson et al (2015)	Probe 1	MWM Dist from plat	HS	-1.240	0.590	0.348	-2.396	-0.084	-2.102	0.036	
Magnusson et al (2015)	Probe 2	MWM Dist from plat	HS	0.048	0.533	0.284	-0.997	1.093	0.090	0.928	
Magnusson et al (2015)	Probe 3	MWM Dist from plat	HS	0.830	0.559	0.313	-0.266	1.926	1.485	0.138	
Magnusson et al (2015)	Probe 4	MWM Dist from plat	HS	0.758	0.555	0.308	-0.330	1.846	1.366	0.172	
Magnusson et al (2015)	Reversal Probe	MWM Dist from old location	HS	-1.562	0.621	0.386	-2.780	-0.345	-2.516	0.012	
Woodie & Blythe (2018)	Blank	MWM	HS	0.063	0.420	0.176	-0.759	0.886	0.151	0.880	
Woodie & Blythe (2018)	Reversal Task	MWM Reversal	HFruc	-0.404	0.424	0.180	-1.235	0.427	-0.953	0.341	
Woodie & Blythe (2018)	Blank		HFruc	-0.957	0.440	0.194	-1.820	-0.094	-2.174	0.030	
Xu & Reichelt (2018)	Blank	Place Recognition	HS	-0.552	0.101	0.010	-0.750	-0.355	-5.480	0.000	

Diet Group Performs Worse Diet Group Performs Better

Figure 2.3. Forest plots and meta-analysis results of experiments using a high-sugar diet.

Study name	Subgroup within study	Comparison	Outcome	Statistics for each study						
				Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Beilharz et al (2014)	Expt1	Place Recognition	HFHS	-1.527	0.544	0.296	-2.594	-0.460	-2.805	0.005
Beilharz et al (2014)	Expt2	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Beilharz et al (2018)	Test1	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Beilharz et al (2018)	Test2	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Hargrave et al (2015)	Expt1 - 10 days	SAY-maze	HFHS	-0.900	0.451	0.204	-1.784	-0.015	-1.994	0.046
Hargrave et al (2015)	Expt1 - 40 days	SAY-maze	HFHS	0.021	0.428	0.183	-0.818	0.861	0.050	0.960
Kanoski & Davidson (2010)	6 testsaverage	8-arm Radial Maze	HFHS	-1.407	0.534	0.285	-2.454	-0.360	-2.634	0.008
Molteni et al (2004)	Blank	MWM Probe	HFHS	-1.187	0.585	0.343	-2.335	-0.040	-2.028	0.043
Ross et al (2013)	Blank	Place Recognition	HFHS	-0.193	0.271	0.074	-0.724	0.339	-0.710	0.478
Takechi et al (2017)	Blank	MWM Probe	HFHFruc	-0.308	0.431	0.186	-1.153	0.537	-0.715	0.475
Tran & Westbrook (2015)	Expt1	Place Recognition	HFHS	-1.034	0.368	0.135	-1.755	-0.313	-2.809	0.005
Tran & Westbrook (2018)	Expt1	Place Recognition	HFHS	-1.230	0.432	0.187	-2.077	-0.383	-2.845	0.004
Wu et al (2003)	Expt1	MWM Probe	HFHS	-0.015	0.310	0.096	-0.623	0.592	-0.050	0.960
				-0.654	0.116	0.014	-0.882	-0.426	-5.626	0.000

Figure 2.4. Forest plots and meta-analysis results of experiments using a high-fat high-sugar diet.

Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bolard et al (2014)	2 hr test	MWM - number target crossings	HF	-0.571	0.389	0.151	-1.334	0.191	-1.469	0.142
Bolard et al (2014)	4 hr test	MWM - number target crossings	HF	-0.190	0.382	0.146	-0.939	0.558	-0.499	0.618
Che et al (2018)	Blank	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Denver et al (2018)	10 day diet	MWM	HF	-0.197	0.395	0.156	-0.972	0.577	-0.499	0.618
Denver et al (2018)	26 day diet	MWM	HF	0.197	0.395	0.156	-0.577	0.972	0.499	0.618
Denver et al (2018)	8 week diet	MWM	HF	0.197	0.395	0.156	-0.577	0.972	0.499	0.618
Gergerlioglu et al (2016)	Expt1	MWM	HF	-1.957	0.586	0.343	-3.106	-0.809	-3.341	0.001
Jamshed et al (2014)	Expt1	MWM escape latency	HF	-1.529	0.578	0.334	-2.661	-0.396	-2.645	0.008
Jurdak et al (2008)	10 day probe	MWM	HF	-0.037	0.428	0.183	-0.876	0.803	-0.086	0.932
Jurdak et al (2008)	24 hr probe	MWM	HF	-0.201	0.429	0.184	-1.043	0.640	-0.469	0.639
Liang et al (2015)	Blank	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Magnusson et al (2015)	Probe 1	MWM Dist from plat	HF	-0.763	0.555	0.308	-1.851	0.325	-1.374	0.169
Magnusson et al (2015)	Probe 1.	MWM Dist from plat	HS	-1.240	0.590	0.348	-2.396	-0.084	-2.102	0.036
Magnusson et al (2015)	Probe 2	MWM Dist from plat	HF	-0.723	0.553	0.306	-1.807	0.361	-1.308	0.191
Magnusson et al (2015)	Probe 2.	MWM Dist from plat	HS	0.048	0.533	0.284	-0.997	1.093	0.090	0.928
Magnusson et al (2015)	Probe 3	MWM Dist from plat	HF	0.486	0.542	0.294	-0.577	1.548	0.896	0.370
Magnusson et al (2015)	Probe 3.	MWM Dist from plat	HS	0.748	0.554	0.307	-0.338	1.835	1.349	0.177
Magnusson et al (2015)	Probe 4	MWM Dist from plat	HF	0.515	0.543	0.295	-0.550	1.580	0.948	0.343
Magnusson et al (2015)	Probe 4.	MWM Dist from plat	HS	0.758	0.555	0.308	-0.330	1.846	1.366	0.172
Magnusson et al (2015)	Reversal	MWM Dist from old plat	HS	-1.759	0.643	0.413	-3.019	-0.500	-2.738	0.006
Magnusson et al (2015)	Reversal Probe.	MWM Dist from old location	HS	-1.562	0.621	0.386	-2.780	-0.345	-2.516	0.012
Mirzaei et al (2018)	Blank	MWM	HS	-1.680	0.504	0.254	-2.667	-0.692	-3.333	0.001
Pathan et al (2008)	Blank	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Pratchayasakul et al (2015)	4 weeks	MWM escape latency	HF	-0.286	0.575	0.330	-1.412	0.841	-0.497	0.619
Pratchayasakul et al (2015)	8 weeks	MWM	HF	-0.286	0.575	0.330	-1.412	0.841	-0.497	0.619
Scichilone et al (2016)	Blank	MWM	HF	-0.172	0.345	0.119	-0.849	0.504	-0.499	0.618
Silva et al (2016)	Blank	MWM	HF	-0.234	0.469	0.220	-1.154	0.686	-0.498	0.618
Spencer et al (2017)	3 & 24 month old	MWM	HF	0.376	0.398	0.158	-0.403	1.156	0.946	0.344
Spinelli et al (2017)	Blank	MWM	HF	-1.957	0.586	0.343	-3.106	-0.809	-3.341	0.001
Wei et al (2018)	Blank	MWM	HF	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Woodie & Blythe (2018)	MWM.	MWM	HFruc	0.269	0.422	0.178	-0.557	1.095	0.639	0.523
Woodie & Blythe (2018)	MWM	MWM	HFruc	0.628	0.430	0.185	-0.216	1.471	1.458	0.145
Woodie & Blythe (2018)	Reversal Task	MWM Reversal	HF	0.210	0.421	0.177	-0.614	1.035	0.500	0.617
Woodie & Blythe (2018)	Reversal Task.	MWM Reversal	HFruc	-0.020	0.419	0.176	-0.842	0.802	-0.047	0.963
Xu et al (2018)	Blank	MWM	HF	-1.407	0.534	0.285	-2.454	-0.360	-2.634	0.008
Molteni et al (2004)	Blank	MWM	HFHS	-1.187	0.585	0.343	-2.335	-0.040	-2.028	0.043
Wu et al (2003)	Expt1	MWM	HFHS	-0.155	0.310	0.096	-0.763	0.453	-0.499	0.618
Kendig et al (2013)	24 hr (Ave probes 1-3)	MWM	HS	-0.746	0.321	0.103	-1.375	-0.117	-2.325	0.020
Kendig et al (2013)	28 day probe	MWM	HS	-0.521	0.315	0.099	-1.139	0.097	-1.652	0.099
				-0.375	0.073	0.005	-0.518	-0.231	-5.128	0.000

Hedges's g and 95% CI

Diet Group Performs Worse   Diet Group Performs Better

Figure 2.5. Forest plots and meta-analysis results of experiments using a Morris water maze.

| Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ayabe et al (2018)	Blank	Place Recognition	HF	-0.236	0.475	0.225	-1.167	0.694	-0.498	0.618
Magnusson et al (2015)	1 hr	Place Recognition	HF	-0.209	0.535	0.286	-1.256	0.839	-0.390	0.696
Magnusson et al (2015)	1-hr	Place Recognition	HS	-0.086	0.533	0.284	-1.131	0.959	-0.161	0.872
Magnusson et al (2015)	24 hr	Place Recognition	HF	0.383	0.539	0.290	-0.673	1.439	0.711	0.477
Magnusson et al (2015)	24-hr	Place Recognition	HS	-0.261	0.536	0.287	-1.310	0.789	-0.487	0.626
Moreira et al (2014)	Blank	Place Recognition	HF	-1.269	0.473	0.224	-2.196	-0.342	-2.682	0.007
Valladolid-Acebes et al (2013)	Expt3 - 5 wks - 1 hr	Place Recognition	HF	-1.495	0.449	0.202	-2.375	-0.614	-3.326	0.001
Valladolid-Acebes et al (2013)	Expt3 - 5 wks - 24 hr	Place Recognition	HF	-1.495	0.449	0.202	-2.375	-0.614	-3.326	0.001
Valladolid-Acebes et al (2013)	Expt3 - 8 wks - 1 hr	Place Recognition	HF	-0.197	0.396	0.157	-0.973	0.578	-0.499	0.618
Valladolid-Acebes et al (2013)	Expt3 - 8 wks - 24 hr	Place Recognition	HF	-0.197	0.396	0.157	-0.973	0.578	-0.499	0.618
Beilharz et al (2014)	Expt1	Place Recognition	HFHS	-1.527	0.544	0.296	-2.594	-0.460	-2.805	0.005
Beilharz et al (2014)	Expt2	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Beilharz et al (2014)	Expt2	Place Recognition	HS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Beilharz et al (2018)	Test1	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Beilharz et al (2018)	Test2	Place Recognition	HFHS	-1.014	0.506	0.256	-2.005	-0.023	-2.005	0.045
Ross et al (2013)	Blank	Place Recognition	HFHS	-0.193	0.271	0.074	-0.724	0.339	-0.710	0.478
Tran & Westbrook (2015)	Expt1	Place Recognition	HFHS	-1.034	0.368	0.135	-1.755	-0.313	-2.809	0.005
Tran & Westbrook (2018)	Expt1	Place Recognition	HFHS	-1.230	0.432	0.187	-2.077	-0.383	-2.845	0.004
Abbott et al (2016)	Expt1	Object-in-Place Recognition	HS	-1.010	0.305	0.093	-1.608	-0.412	-3.309	0.001
Abbott et al (2016)	Expt-1	Place Recognition	HS	-1.010	0.305	0.093	-1.608	-0.412	-3.309	0.001
Xu & Reichelt (2018)	Blank	Place Recognition	HS	-0.957	0.440	0.194	-1.820	-0.094	-2.174	0.030
				-0.759	0.092	0.009	-0.939	-0.578	-8.223	0.000

Figure 2.6. Forest plots and meta-analysis results of experiments using a place recognition task.

Figure 2.7. Forest plots and meta-analysis results of experiments using a radial arm or radial arm water maze.

Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Azoubi et al (2013a)	24 hr test	6-arm WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Azoubi et al (2013a)	30 min test	6-arm WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Azoubi et al (2013a)	5 hr test	6-arm WM	HF	-0.754	0.381	0.145	-1.500	-0.008	-1.982	0.047
Azoubi et al (2013b)	24 hr test	6-arm WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Azoubi et al (2013b)	30 min test	6-arm WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Azoubi et al (2013b)	5 hr test	6-arm WM	HF	-0.817	0.411	0.169	-1.624	-0.011	-1.987	0.047
Azoubi et al (2018)	24 hr test	6-arm WM	HF	-0.728	0.367	0.135	-1.448	-0.007	-1.980	0.048
Azoubi et al (2018)	5 hr test	6-arm WM	HF	-0.728	0.367	0.135	-1.448	-0.007	-1.980	0.048
Thirumangalakudi et al (2008)	Total errors	8-arm WM	HF	-1.187	0.585	0.343	-2.335	-0.040	-2.028	0.043
Thirumangalakudi et al (2008)	WM errors	8-arm WM	HF	-1.187	0.585	0.343	-2.335	-0.040	-2.028	0.043
Valladolid-Acebes et al (2011)	Expt1 - Total errors	8-arm Radial Maze	HF	-1.417	0.362	0.131	-2.127	-0.706	-3.909	0.000
Valladolid-Acebes et al (2011)	Expt1 - WM error	8-arm Radial Maze	HF	-1.159	0.350	0.122	-1.845	-0.474	-3.314	0.001
Valladolid-Acebes et al (2011)	Expt1 - WM error	8-arm Radial Maze	HF	-1.407	0.534	0.285	-2.454	-0.360	-2.634	0.008
Kanoski & Davidson (2010)	6 test average	8-arm Radial Maze	HFHS	-0.932	0.113	0.013	-1.153	-0.710	-8.247	0.000

Figure 2.8. Forest plots and meta-analysis results of experiments using a spontaneous alternation task.

Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Arnold et al (2014)	ExtHFD	SAT-maze	Extreme HF	-1.120	0.624	0.389	-2.342	0.103	-1.795	0.073
Arnold et al (2014)	Mod HFD	SAT-maze	Moderate HF	-0.951	0.454	0.206	-1.841	-0.061	-2.095	0.036
Hargrave et al (2015)	Expt1 - 10 days	SAY-maze	HFHS	-0.900	0.451	0.204	-1.784	-0.015	-1.994	0.046
Hargrave et al (2015)	Expt1 - 40 days	SAY-maze	HFHS	0.214	0.430	0.185	-0.628	1.056	0.498	0.618
Hargrave et al (2015)	Expt1 - 10 days	SAY-maze	Ketogenic Diet	0.214	0.430	0.185	-0.628	1.056	0.498	0.618
Hargrave et al (2015)	Expt1 - 40 days	SAY-maze	Ketogenic Diet	0.214	0.430	0.185	-0.628	1.056	0.498	0.618
Park et al (2018)	Blank	SAY-maze	HF	-1.429	0.445	0.198	-2.301	-0.557	-3.212	0.001
				-0.465	0.172	0.030	-0.803	-0.127	-2.698	0.007

2.4. Discussion

There is considerable evidence that rodents fed a diet high in fat, sugar, or both fat and sugar exhibit impairments in tasks assessing hippocampal-dependent forms of learning and memory (Kanoski et al., 2010; Yeomans, 2017). However, there have been failures to detect such impairments (e.g., Ayabe et al., 2018; Ross et al., 2013, Jurdak et al., 2009). One source of the inconsistent results is the type of diet used, while a second source is the type of task used to assess the effects of the diet. Therefore, we subjected this evidence to a meta-analysis in order to provide a quantitative assessment of the protocols under which dietary manipulations adversely affect hippocampal-dependent forms of cognition. We had two aims: The first was to assess the contribution of diets high in saturated fat, refined sugar, or both, to impairments of spatial learning and memory. The second aim was to examine the tasks used to determine whether they differed in their sensitivity to the dietary manipulations.

2.4.1. Summary of Results

The meta-analysis revealed that all three diet manipulations produce a significant impairment in spatial learning and memory tasks, relative to a control diet that is usually starch based and low in saturated fats and refined sugars. While direct statistical comparisons between the diet manipulation categories were not permitted, the size of the Hedge's *g* for the three manipulations suggests that the largest effect size was found for studies that used a diet high in both fat and sugar, followed closely by studies using a high-fat diet, and, finally, a high-sugar diet. Nonetheless, all three dietary manipulations were observed to have a medium effect size, which suggests that differences in dietary composition are unlikely to be the single or primary factor responsible for the inconsistent findings in the literature.

A second source of variability in the findings reported is the behavioural task used to assess dietary effects on learning and memory. As noted in the Introduction, tasks assessing hippocampal forms of cognition, specifically, spatial learning and memory, appear to be especially sensitive to dietary manipulations. The role of the hippocampus in successful performance on the tasks selected for inclusion in the meta-analysis has been well documented: the Morris water maze (e.g., Compton et al., 1997), place recognition (e.g., Barker & Warburton, 2011), radial arm and radial arm water maze (e.g., Floresco et al., 1997), spontaneous alternation (e.g., Lalonde, 2002). When the performance of animals consuming a diet high in saturated fat, refined sugar, or both, on these tasks were considered separately, the meta-analysis revealed a significant diet-induced impairment in spatial learning and memory for each task group. Again, direct statistical comparisons between the behavioural tasks was not permitted. However, the largest impairment was seen on the radial arm and radial water maze tasks, where there was a large effect size, followed by the place recognition task, the spontaneous alternation task, and the Morris water maze task, each of which had a medium effect size. It should be noted that nearly half of the experiments included in the meta-analysis for the radial arm maze and radial water maze tasks were extracted from two papers (Alzoubi et al., 2013a and 2013b), which may have biased the results. However, the weighted effect sizes of the six dependent measures extracted from these two papers were among the smaller effect sizes in the analysis, suggesting that the large SMD observed for this task group does not exclusively rely on their inclusion in the analysis.

The role of the hippocampus in successful performance on spatial learning and memory tasks is well established (Barker & Warburton, 2011; Compton et al., 1997; Floresco et al., 1997; Lalonde, 2002), but studies differed in the procedures used in these tasks. Moreover, variations in how these tasks are implemented may affect the degree to

which the hippocampus is recruited. For example, studies that used the Morris water maze differed in terms of the number of training days, the number of training trials per day, the inter-trial and inter-training day intervals, and the retention interval before test. Similarly, there were differences across studies in the place recognition task, such as the number of objects used, the length of familiarization time, the retention interval before test, and the arena where the task was conducted. Procedural variations in these tasks, particularly in the amount of training, length of retention interval, and maze set-up (affecting the amount of extra-maze spatial information that can be extracted), have been argued to affect the involvement of brain regions outside the hippocampus (e.g., Tran & Westbrook, 2017; Vorhees & Williams, 2006, 2014; see Tran & Westbrook, 2018 for discussion in relation to object recognition memory). Thus, such variations may have affected the difficulty of the task; increasing or decreasing the reliance on a functioning hippocampus for successful performance. Moreover, the effects of diet on learning and memory can be highly specific, impairing some, but not other, similar tasks (e.g., Tran & Westbrook, 2015). Therefore, the inconsistencies in the literature on the observed relationship between diet and cognition are likely a consequence of procedural difference in the assessment measure rather than the content of dietary manipulation.

2.4.2. Rodent Species as a Variable for Diet-Induced Cognitive Impairment

Rats and mice, as well as different strains within these species, can perform differently on hippocampal-dependent behavioural tasks (e.g. Cressant, Besson, Suarez, Corimer, & Granon, 2007; Ennaceur, Michalikova, Bradford, & Ahmed, 2005; Genzel et al., 2017; Stranahan, 2011; reviewed in Hok et al., 2016; Keeley, Bye, Trow, & McDonald, 2015). Such differences are thought to be due to variations in metabolism (Chang, Graham, Yakubu, Lin, Peters, & Hill, 1990), hippocampal neurogenesis (Merritt & Rhodes, 2015), gene expression (Malki et al., 2015), brain volume (Keeley et al., 2015),

and place cell activity (Ji, Mou, Cheng, Yu, & Kee, 2018; see Manahan-Vaughan, 2019). These differences in turn could interact with dietary manipulations to affect performance on hippocampal-dependent tasks (Bollheimer, 2007; Stöckli et al., 2017; West, Boozer, Moody, & Atkinson, 1992; West, Waguespack, & McCollister, 1995). However, we found little if any evidence for such effects based on the study descriptives.

Of the 41 articles that were included in the present meta-analysis, 16 experiments were extracted from 14 articles examining dietary manipulations in mice and 29 experiments were extracted from 27 articles examining dietary manipulations in rats. Impairment in hippocampal-dependent learning and memory was observed in 10 experiments (approximately 63%) using mice (Arnold et al., 2014; Che et al., 2018; Moreira et al., 2014; Park et al., 2018; Spinelli et al., 2017; Thirumangalakudi et al., 2008; Valladolid-Acebes et al., 2011; Valladolid-Acebes et al., 2013, Experiment 1; Wei et al., 2018; Xu et al., 2018) and 16 experiments (approximately 55%) using rats (Abbott et al., 2016; Alzoubi et al., 2013a, 2013b, 2018; Beilharz et al., 2014; Kanoski & Davidson, 2010; Liang et al., 2015; Mirzaei et al., 2018; Molteni et al., 2004; Pathan et al., 2008; Tran & Westbrook, 2015, 2018; Xu & Reichelt, 2018); no deficits were observed in five experiments using mice (Ayabe et al., 2018; Denver et al., 2018; Magnusson et al., 2015; Takechi et al., 2017) and nine experiments using rats (Boitard et al., 2014; Jamshed et al., 2014; Pratchayasakul et al., 2015; Ross et al., 2013; Scichilone et al., 2016; Silva et al., 2005; Spencer et al., 2017; Woodie & Blythe, 2018, Wu et al., 2018). Mixed results were reported in one study using mice, in which a deficit was detected on a place recognition task after a 24-hour retention period but not a 1-hour retention period (Valladolid-Acebes et al., 2013, Experiment 3). Mixed results were also reported in four experiments using rats: one study reported a deficit on time in target quadrant on the Morris water maze in rats consuming high-fat but not high-sugar diet (Gergerlioglu et al., 2016); one reported

a deficit on the Y-maze after 10-days of a high-fat high-sugar diet, but no deficit after 40-days of the diet, nor after 10 or 40-days of a high-fat diet (Hargrave et al., 2015); one reported a deficit measuring time spent in target quadrant on the Morris water maze task in rats consuming high-sugar diet at a 10-day retention interval but not a 24-hr retention interval but not in rats consuming high-fat diet at either retention interval (Jurdak et al., 2008), and one reported impaired learning in the Morris water maze task but no difference in the time spent in the target quadrant at probe test (Kendig et al., 2013). Thus, diet-induced impairments on hippocampal-dependent spatial learning and memory do not appear to be specific to rodent species.

2.4.3. Sex as a Variable for Diet-Induced Cognitive Impairment

Sex differences in hippocampal-dependent spatial learning and memory are well documented in both humans and rodents (reviewed in Keeley et al., 2015; Koss & Frick, 2017; Yagi & Galea, 2018), with the bulk of the evidence suggesting a male advantage in spatial navigation (Astur, Purton, Zaniewski, Cimadevilla, & Markus, 2016; Moffat, Hampson, & Hatzipantelis, 1998; Piber, Nowacki, Mueller, Wingenfeld, & Otto, 2018), and a female advantage in place recognition (Voyer, Postma, Brake, & Impertao-McGinley, 2007; Voyer, Voyer, & Saint-Aubin, 2017). Such differences have been suggested to be due to sex hormones (reviewed in Brake & Lacasse, 2018; Ervin & Choleris, 2019; Hammes & Levin, 2019), such as the differential role of estradiol on hippocampal synaptic plasticity in males and females (Bäumler, Strickland, & Privitera, 2019; Jain, Huang, & Woolley, 2019; Wang et al., 2018). Males have typically been used to examine dietary effects on hippocampal-dependent tasks. When females have been included, the experimental designs often lack direct comparison between the sexes (e.g. use of female subjects only, or collapsing across male and female data points for analysis). Of the 41 articles included in the present meta-analysis, five articles used female subjects

across six experiments (Abbott et al., 2016; Jamshed et al., 2014; Kendig et al., 2013; Molteni et al., 2004; Pratchayasakul et al., 2015), with deficits observed in object location memory (Abbott et al., 2016) and in learning (Kendig et al., 2013) and remembering the platform location (Jamshed et al., 2014; Molteni et al., 2004) in the Morris water maze task. Two of these studies collapsed male and female data for analysis (Jamshed et al., 2014; Kendig et al., 2013), and another two studies used only female subjects (Molteni et al., 2004; Pratchayasakul et al., 2015). Of the included studies, only Abbott et al. (2016) specifically compared the influence of a high-sugar diet on the performance of male and female rats in place recognition and object-in-place memory tasks. They reported that both males and females were impaired in the place recognition task and males but not females were impaired on object-in-place memory, perhaps indicating that female rats have better memory for object-in-place configurations than male rats (e.g. Cost, Williams-Yee, Fustok, & Dohanich, 2012).

2.4.4. Age as a Variable for Diet-Induced Cognitive Impairment

Adolescents may be more susceptible than adults to the effects of dietary manipulations on hippocampal-dependent learning and memory (reviewed in Noble & Kanoski, 2016) and hippocampal morphology and function in general (Del Olmo & Gayo, 2018). The transition from adolescence to adulthood occurs at approximately postnatal day 63 (9-weeks) in rats (Sengupta, 2011, 2013) and postnatal day 70 (10-weeks) in mice (Dutta & Sengupta, 2016). Using these ages as a cut-off, we extracted 27 experiments from 24 articles that manipulated the diet during adolescence (i.e. when aged less than 9-weeks in rats and less than 10-weeks in mice), and nine experiments extracted from nine articles that provided dietary manipulations to subjects in adulthood. The remaining eight articles combined both adolescents and adults in their control and dietary manipulation conditions (Beilharz et al., 2014, 2018; Denver et al., 2018; Hargrave et al.,

2015; Kanoski & Davidson, 2010; Kendig et al., 2013; Tran & Westbrook 2015, 2018).

Deficits in hippocampal-dependent spatial learning and memory was observed in 15

experiments (56%) using adolescent animals (Abbott et al., 2016; Alzoubi et al., 2013a,

2013b, 2018; Arnold et al., 2014; Jamshed et al., 2014; Liang et al., 2015; Mirzaei et al.,

2018; Molteni et al., 2004; Pathan et al., 2008; Spinelli et al., 2017; Valladolid-Acebes et

al., 2011; Valladolid-Acebes et al., 2013, Experiment 1; Xu et al., 2018; Xu & Reichelt

2018) and in five experiments (56%) using adults (Che et al., 2018; Moreira et al., 2014;

Park et al., 2018; Thirumangalakudi et al., 2008). Nine experiments failed to detect

impairments in adolescents (Ayabe et al., 2018; Magnusson et al., 2015; Ross et al., 2013;

Scichilone et al., 2016; Silva et al., 2005; Takechi et al., 2017; Woodie & Blythe, 2018;

Wu et al., 2018) and three failed to detect impairments in adults (Boitard et al., 2014;

Pratchayasakul et al., 2015; Spencer et al., 2017). Mixed results were reported in three

experiments using adolescents (Abbott et al., 2016; Jurdak et al., 2008; Valladolid et al.,

2013, Experiment 3) and one experiment using adults (Gergerlioglu et al., 2016). Thus,

the findings from the articles included in the present analysis suggests that the use of

adolescent or adult subjects is not a critical factor in determining the impact of dietary

manipulations on hippocampal-dependent spatial learning and memory. Nevertheless,

future meta-analyses may wish to consider age at the start of the dietary manipulation as

a moderator of diet-induced hippocampal impairment.

2.4.5. Body Weight, Metabolic Changes, and Dietary-Induced Cognitive Impairments

Our meta-analyses focused on the composition of the diet and the task used to

assess the effects of the diet on cognition. However, we now consider the evidence from

the included studies regarding the effects of the diet on body weight and metabolic

changes (see Table 2.1). Of the 32 experiments using a high-fat diet: nine experiments

did not provide information regarding body weight, 18 reported a significant difference in body weight between control and experimental animals at the time of behavioural testing (Alzoubi et al., 2013a, 2013b; Arnold et al., 2014; Ayabe et al., 2018; Boitard et al., 2014; Denver et al., 2018; Jurdak et al., 2008; Magnusson et al., 2015; Park et al., 2018; Pathan et al., 2008; Spencer et al., 2017; Valladolid-Acebes et al., 2011, 2013; Wei et al., 2018; Woodie & Blythe, 2018; Xu et al., 2018); four reported no significant difference in body weight (Gergerlioglu et al., 2016; Magnusson et al., 2015; Moreira et al., 2014; Scichilone et al., 2016); and one reported a significant difference in body weight for rats consuming the diet from eight-weeks of age, but not for rats consuming the diet from four-weeks (Pratchayasakul et al., 2015). Of the experiments reporting a significant difference in body weight between control and experimental animals: three reported a deficit on the RAM or RAWM (Alzoubi et al., 2013a, 2013b; Valladolid-Acebes et al., 2011); three reported a deficit on the MWM (Pathan et al., 2008; Wei et al., 2018; Xu et al., 2018); two reported a deficit on the reversal stage of the MWM despite intact performance during the probe test for the original platform location (Magnusson et al., 2015; Woodie & Blythe, 2018); three reported deficits in spontaneous alternation (Arnold et al., 2014, Extreme HF & Moderate HF; Park et al., 2018); and one reported a deficit in place recognition (Valladolid-Acebes et al., 2013, Experiment 1). The remaining experiments that reported body weight differences failed to detect an effect of diet manipulation on the MWM (Boitard et al., 2014; Denver et al., 2018; Jurdak et al., 2008; Magnusson et al., 2015; Pratchayasakul et al., 2015; Spencer et al., 2017; Woodie & Blythe, 2018), in place recognition (Ayabe et al., 2018; Valladolid-Acebes et al., 2013, Experiment 3), or in spontaneous alternation (Hargrave et al., 2015). Of the studies reporting no significant difference in body weight: one reported a deficit on the MWM (Gergerlioglu et al., 2016) and one reported a deficit in Place recognition (Moreira et al.,

2014); the remaining two studies reported no behavioural deficit on the MWM (Scichilone et al., 2016) or in place recognition (Magnusson et al., 2015).

Of the nine experiments using a high-sugar diet, only one experiment (Jurdak et al., 2008) reported a significant difference in body weight between control and experimental animals at the time of behavioural testing and a dietary-induced deficit in MWM. The remaining eight experiments reported no significant difference in body weight (Abbott et al., 2016; Beilharz et al., 2014; Gergerlioglu et al., 2016; Magnusson et al., 2015). Of these reporting no difference in body weight: four experiments reported a deficit in place recognition (Abbott et al., 2016; Beilharz et al., 2014; Xu & Reichelt, 2018), and one reported a deficit in the MWM (Kendig et al., 2013). The remaining experiments reported no deficit in place recognition (Magnusson et al., 2015) or the MWM (Gergerlioglu et al., 2016; Magnusson et al., 2015).

Of the 11 studies using a HFSD: four reported a significant difference in body weight between control and experimental animals at the time of behavioural testing (Beilharz et al., 2018; Kanoski & Davidson, 2010; Ross et al., 2013; Takechi et al., 2017); one reported no significant difference in body weight (Woodie & Blythe, 2018); one reported a significant difference in total body fat but not body weight (Hargrave et al., 2015); and three reported a significant difference in body weight at later, but not early, behavioural tests (Beilharz et al., 2014, Experiments 1 and 2; Tran & Westbrook, 2015). Of the studies reporting a significant difference in body weight: four reported a deficit in place recognition (Beilharz et al., 2014, Experiments 1 and 2; Beilharz et al., 2018; Tran & Westbrook, 2015): one reported a deficit in spontaneous alternation (Hargrave et al., 2015); and one reported a deficit in the RAM (Kanoski & Davidson, 2010). The remaining experiments reported no deficits in place recognition (Ross et al., 2013), spontaneous alternation (Hargrave et al., 2015), or the MWM (Takechi et al., 2017).

Taken together, the experiments included in the present meta-analysis provide equivocal evidence regarding the association between dietary-induced increases in body weight and cognitive performance; increases in body weight and cognitive deficits do co-occur but deficits have been detected in the absence of increases in body weight and cognition has been intact in spite of increases in body weight.

The studies included in the meta-analysis differed with respect to their assessment of diet-induced alterations to metabolic status. A number of studies demonstrating diet-induced deficits report significant differences between control and experimental animals in metabolic parameters including blood glucose level (Arnold et al., 2014; Jurdak et al., 2008; Pathan et al., 2008; Xu et al., 2018), response on a glucose tolerance test (Arnold et al., 2014; Xu et al., 2018) and insulin tolerance test (Xu et al., 2018), plasma insulin level (Beilharz et al., 2014, Experiment 1; Pathan et al., 2008; Spinelli et al., 2017; Valladolid-Acebes et al., 2011), plasma leptin level (Beilharz et al., 2014, Experiment 2; Valladolid-Acebes et al., 2013, Experiment 1), triglycerides (Beilharz et al., 2014, Experiment 2; Jamshed et al., 2014; Jurdak et al., 2008; Moreira et al., 2014; Pathan et al., 2008; Xu et al., 2018), and cholesterol levels (Jamshed et al., 2014; Moreira et al., 2014; Pathan et al., 2008; Xu et al., 2018). However, a number of the included studies also failed to find statistically significant differences in these metabolic parameters (Beilharz et al., 2014, 2018; Gergerlioglu et al., 2016; Jurdak et al., 2008; Kendig et al., 2013; Moreira et al., 2014; Valladolid-Acebes et al., 2011, 2013). Furthermore, dietary-induced alterations in blood glucose (Boitard et al., 2014; Kendig et al., 2013; Scichilone et al., 2016; Takechi et al., 2017; Valladolid-Acebes et al., 2013, Experiment 3), plasma insulin and HOMA (Pratchayasakul et al., 2015; Takechi et al., 2017), and plasma leptin (Boitard et al., 2014; Valladolid-Acebes et al., 2013, Experiment 3) have been reported but in the absence of deficits in hippocampal-dependent learning and memory. Thus,

again, the experiments included in the meta-analysis provide equivocal evidence regarding the association between metabolic changes and cognitive performance.

2.4.6. Mechanisms of Diet-Induced Impairments

There are various mechanisms by which high-fat, high-sugar, or high-fat high-sugar diets can impair hippocampal-dependent forms of cognition (reviewed in Beilharz et al., 2015; Freeman et al., 2014). One such mechanism is neuroinflammation (Guillemot-Legris, & Muccioli, 2017; Johnson, 2015). Several studies have reported that diet-induced impairments are accompanied by increased expression of pro-inflammatory cytokines, such as interleukin-1Beta (IL-1β) mRNA (Beilharz et al., 2014, 2018; Che et al., 2018; Mirzaei et al., 2018; Thirumangalakudi et al., 2008) and protein (Mirzaei et al., 2018), tumour necrosis factor-Alpha (TNF-α) mRNA (Beilharz et al., 2014; Thirumangalakudi et al., 2008) and protein (Che et al., 2018), as well as glial fibrillary acidic protein (GFAP), a marker of glial cell activation, (Che et al., 2018; Thirumangalakudi et al., 2008). However, inconsistent results have been reported in rodents who failed to exhibit diet-induced impairments: some studies failed to detect evidence for pro-inflammatory cytokine expression (Boitard et al., 2014; Takechi et al., 2017) and GFAP (Denver et al., 2018; Silva et al., 2005), whereas others found increased expression of IL-1β and TNF-α protein (Ayabe et al., 2018; Spencer et al., 2017). Thus, the presence of neuroinflammation is not a necessarily condition for observing short-term dietary impairments in hippocampal-dependent spatial learning and memory.

A second mechanism is reductions in neuroplasticity (Morin et al., 2017; Murphey, Dias, & Thuret, 2014). Several studies have reported that diet-induced impairments are associated with reduced long-term potentiation in hippocampal pyramidal neurons (Spinelli et al., 2017) and changes in factors related to neuroplasticity, such as decreases in synapsin-1 mRNA and protein (Molteni et al., 2004), as well as in

BDNF mRNA and protein (Che et al., 2018; Molteni et al., 2004). Consistent with a role for changes in neuroplasticity, some studies failed to detect any changes in BDNF mRNA (Wu et al., 2003) or BDNF protein expression (Woodie & Blythe, 2018; Wu et al., 2003) in rodents who failed to exhibit diet-induced impairments in spatial learning and memory. However, other studies have reported diet-induced impairments, but in the absence of changes to BDNF mRNA (Alzoubi et al., 2013a, 2013b) or BDNF protein expression (Beilharz et al., 2014). Conversely, markers of altered neuroplasticity, such as increased synaptophysin protein (Denver et al., 2018), decreased dendritic spine density, as well as both increases (Ayabe et al. 2018) and decreases (Scichilone et al., 2016) in BDNF protein expression, have been found in rodents who failed to exhibit diet-induced impairments in spatial learning and memory. Taken together, changes in neuroplasticity may play a role in mediating the cognitive impairments induced by relatively short-term dietary exposures but the nature of this role remains to be determined.

Finally, additional mechanisms include altered insulin signaling within the hippocampus (Arnold et al., 2014; Liang et al., 2015; Spinelli et al., 2017; Xu et al., 2018), disruptions to the blood-brain-barrier (Hsu & Kanoski, 2014), and dysbiosis in the gut microbiome arising from reduced bacterial diversity (Beilharz et al., 2018; Magnusson et al., 2015; Noble, Hsu, & Kanoski, 2017a). However, these proposals are relatively recent and they await further investigation (Denver et al., 2018; Pratchayasakul et al., 2015).

2.4.7. Conclusion

In sum, the meta-analysis showed that, despite the inconsistent findings in the literature, diets high in saturated fat or refined sugar can each produce reliable impairments in hippocampal-dependent forms of cognition. It also showed that these impairments can be detected in a range of hippocampal-dependent tasks. These results reveal that the type of dietary manipulation is unlikely to be the primary factor for the

inconsistent findings in the literature. Instead, we propose that the inconsistencies are more likely to be a product of the procedural variations used to assess the impact of short-term diet exposures on cognition. Finally, while no direct statistical comparisons were made in this type of meta-analysis conducted, the weighted effect-sizes suggest that diet-induced impairments are most likely to be detected in rodents fed a high-fat high-sugar diet and tested in the radial arm maze.

Chapter 3: The influence of high-sugar diet on the generalization of a contextual fear memory

3.1. Introduction

Epidemiological studies have shown that high-sugar intake is associated with adverse effects on cognition across the life span. For example, high-sugar intake is negatively correlated with cognitive ability (Abargouei et al., 2012) and academic performance (Bleiweiss-Sande et al., 2019; Burrows et al, 2017b; Edwards et al., 2011a; Park et al., 2012) in children and adolescents. Similarly, sugar intake is negatively correlated with cognitive function assessed using the Mini-Mental State Examination (MMSE) in middle-aged (Ye et al., 2011) and older adults (Chong et al., 2019), with verbal and visual memory in middle-aged adults (Ye et al., 2011), and with increased risk of developing mild cognitive impairment in older adults (Roberts et al., 2012). The hippocampus and cognitive functions dependent on this structure appear particularly vulnerable to the detrimental effect of high-sugar diet consumption. As shown in chapter 2, rats exposed to a high-sugar diet lasting two-months or less were impaired on a number of hippocampal-dependent spatial memory tasks, including the Morris water maze, radial arm maze, and place recognition. Such findings suggest that high-sugar diets disrupt hippocampal processes involved in various aspects of spatial learning and memory.

An important component of hippocampal processing involves the integration of the spatial and featural cues that constitute an environment into a distinct configural representation (Rudy & O'Reilly, 1999, 2001; Rudy, 2015). This representation is encoded by a unique pattern of activity within hippocampal place cells, a so-called hippocampal engram (Anderson & Jeffery, 2003; Bulken et al., 2016; Leutgeb et al., 2004). Once formed, configural representations can act as a Pavlovian conditioned stimulus (CS) and enter into direct association with other stimuli, such as an

unconditioned stimulus (US; Figure 3.1.A), or serve as an occasion setter for the relationships that exist between stimuli in that environment (Nadel & Willner, 1980; Fraser & Holland, 2019; Urcelay & Miller, 2014). Subsequent exposure to a subset of the contextual cues results in activation of the configural representation via a pattern completion process (Rudy et al., 2004) and retrieval of information that has been associated with it (Smith & Bulkin, 2014). Importantly, the distinctive nature of the configural representation allows discrimination between contexts comprised of similar cues, and thus supports behavioural and cognitive flexibility by ensuring only context-specific information is retrieved from memory (Maren, Phan, & Liberzon, 2013).
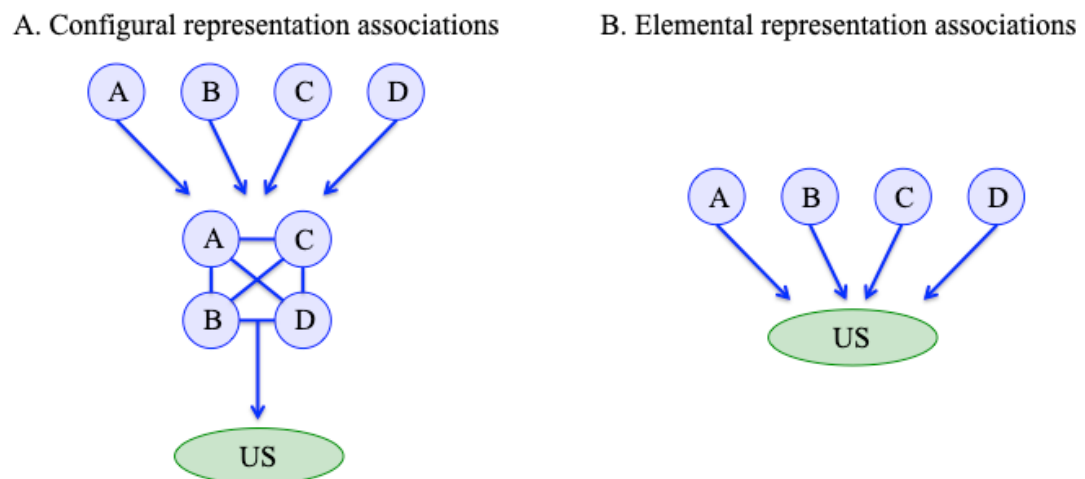
Figure 3.1. Illustration of the hippocampal-dependent configural representation of context and cortical-dependent elemental representation of contexts, and how these two forms of context representation associate with an unconditioned stimulus (US). Contexts are represented by a number of individual features (A-D). **(A)** The formation of configural representations of context involve integration of individual features into a unified representation that functions as a conditioned stimulus (CS). The configural representation can go on and enter into an association with a US. **(B)** Elemental representations of context involve each individual feature functioning as an independent CS that can enter into association with a US.

Rudy and colleagues (Matus-Amat et al., 2004; Rudy & O'Reilly, 1999, 2001; Rudy et al., 2002, 2004; Rudy, 2009) have proposed that in the absence of a functional

hippocampus, context can be represented within neocortical regions. However, these neocortical regions cannot integrate the contextual cues into a configural representation; instead, they process the context in terms of its component elements. Like traditional Pavlovian CSs, these elemental representations compete with one another to associate with environmental stimuli, resulting in associations being formed with only the most salient of the contextual cues (Figure 3.1.B; Rescorla & Wagner, 1972; Wagner, 2008). Consequently, behaviour that is elicited upon subsequent exposure to the context is contingent on the particular cues that are sampled. These elemental representations are also activated by contexts that contain similar elements as the learning context, resulting in retrieval of context-inappropriate information and displays of context-inappropriate behaviour (Maren et al., 2013). Thus, neocortical-dependent elemental representations are often insufficient to support behavioural and cognitive flexibility.

Pavlovian fear conditioning in rodents has been widely used to assess the representation of context by the hippocampal and neocortical systems (Fanselow, 2010). In such conditioning, rats are placed in a context (a distinctive chamber) and administered a brief but aversive foot shock US. Rats quickly learn about the relationship between the context and foot shock, exhibiting this learning when re-exposed to the context in behavioural and autonomic responses indicative of fear in people, such as freezing, potentiated startle, and changes in heart rate and breathing (Carrive, 2000; Rudy et al., 2004). Consistent with the proposal concerning the role of the hippocampus in forming configural representations that individuate the context, normal rats subsequently discriminate the shocked context from a second, similar context, freezing in the former more than the latter. However, rats with hippocampal lesions fail to discriminate between the two contexts, showing just as much freezing in the shocked context as in the second,

similar context (Antoniadis & McDonald, 1999, 2000; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998).

The aim of the present set of experiments was to examine whether the previously reported deficits in hippocampal-dependent spatial memory observed in high-sugar diet exposed rats (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b; Kendig et al., 2013; Kendig, Lin, Beilharz, Rooney, & Boakes, 2014) extend to the formation and retrieval of configural representations of context. The experiments used a context fear generalisation test to evaluate whether rats maintained on a high-sugar diet rely on neocortical-dependent elemental representations of context for associative learning. Both experiments provided rats with access to standard chow, and rats in the high-sugar (HS) diet conditions were provided additional access to a 10% sucrose solution. This concentration is commonly used to study the metabolic and cognitive effects of sugar (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b; Kendig et al., 2013, 2014) as it is similar to that of standard soft drinks (e.g., Coco-Cola) consumed by people (Kendig et al., 2014). If intake of HS diet impairs the hippocampal processes involved in the formation or retrieval of a configural representation of context, then rats maintained on this diet will generalize a context fear memory to a neutral context more than rats maintained on a standard chow diet.

3.2. Experiment 1

In experiment 1, the context fear manipulation was preceded by tests of perirhinal-dependent object and hippocampal-dependent place recognition memories (Figure 3.2.). This was done in order to provide an additional assessment of dietary effects on cognition, as well as to confirm a specific impairment in hippocampal spatial memory function in HS rats prior to examination of hippocampal configural processing. Previous studies have demonstrated intact object recognition but impaired place recognition in rats exposed to

high-sugar diet (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b). These recognition tests rely on the tendency of rats to explore novel items over familiar items (Ennaceur & Delacour, 1988). Moreover, such tests do not require food or water deprivation or other aversive motivators, such as searching for a platform to escape from the pool in the water maze or freezing in anticipation of foot shock. These motivators are likely to induce a physiological stress response. Previous studies have demonstrated increased vulnerability to stress-induced hippocampal injury in rats consuming high energy dies (Sobesky et al., 2014), and stress-induced hyperphagia of energy-dense foods in mice (Bartolomucci et al., 2009). Consequently, the recognition tasks minimise possible confounding variables of the diet-induced hippocampal impairments. The experimental timeline is shown in Figure 3.2.
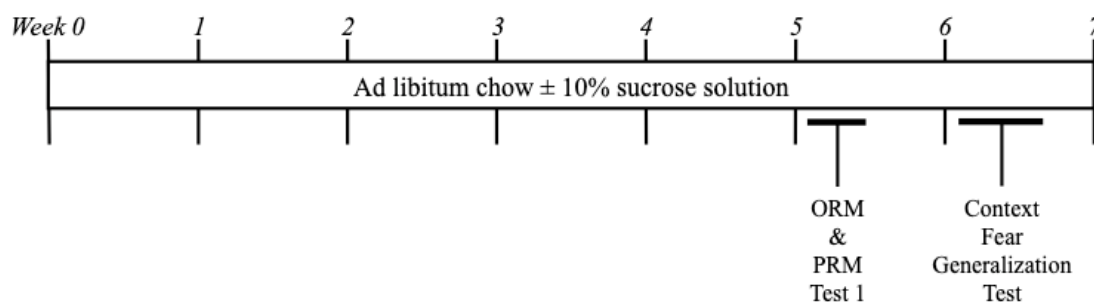
Figure 3.2. Timeline of experiment 1. Rats received free access to chow and water. Rats in the high-sugar condition had additional access to a single bottle of 10% (w/v) sucrose solution. Object (ORM) and place (PRM) memory tests were conducted after five-weeks of diet exposure. The context fear generalization test was conducted after six-weeks of diet exposure.

3.2.1. Method

3.2.1.1. Subjects and Design

Subjects were 32 experimentally naïve, male, Sprague Dawley rats obtained from Animal Resources Centre (Perth, Western Australia). Rats were housed in groups of four in plastic tubs (60 x 40 x 26 cm, L · W · H). The tubs were kept in climate-controlled

colony room (21°C ± 2°C; humidity 55% ± 5%) maintained on a 12-hour light-dark schedule (lights on 07:00 hours). Rats were weight matched across tubs at the beginning of the experiment (weight range 291 - 350 g). After one week of acclimation to the housing conditions, four of the tubs were randomly assigned to the control (diet CD) and four to the high-sugar diet (HS) conditions.

3.2.1.1.1. Diets. All rats had free access to tap water and standard laboratory chow (Gordon's ® Specialty Rodent Feed; Yanderra, New South Wales, Australia; 3.53 kcal/g, 15% energy from fat). Rats in the HS condition were provided with one bottle containing 10% (w/vol) sucrose solution (CSR® White Sugar; Victoria, Australia) in addition to one bottle of tap water. Consumption of food and sucrose solution for each tub was measured daily and was used to calculate a weekly intake of calories per tub. This value was divided by four to calculate an average intake per rat per tub. The unit of analysis for consumption was the tub (n = 4).

3.2.1.2. Object and Place Recognition Memory Tests

3.2.1.2.1. Apparatus. The object and place recognition memory tests were conducted in a square open-field arena (50 x 50 x 60 cm, L · W · H) constructed from black PVC plastic. The arena was surrounded by black curtains that hung from the ceiling to preclude the use of extra-maze cues to locate objects in the place test. The behaviour of each rat was recorded by a camera mounted 185 cm above the arena floor and connected to a DVD recorder located in another room in the laboratory. Three identical copies of commercially available household items (maximum dimensions: 10 x 10 x 20 cm, L · W · H) that varied in shape, material, and texture were used as objects (two for the place task, three for the object task). A photograph of the objects used is available in appendix B. Any item with a lid was emptied, washed, and filled with corncob prior to use to prevent it from being knocked over. A small holding cage (30 x 40 x 30 cm, L · W

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· H) containing corncob bedding was placed on a bench outside the test room to hold rats during the retention period between familiarisation and test.

3.2.1.2.2. Procedure. Rats were pre-exposed to the empty test arena for 10-minutes on two consecutive days in order to reduce any neophobia that might preclude exploration of the objects. The object and place test occurred after five-weeks of experimental diet access, and were conducted in a counterbalanced order such that half the rats received an object test on day one and a place test on day two and the remaining rats received the opposite order.

Each object and place trial consisted of a familiarisation and test phase (Figure 3.3.). In familiarisation, each rat was placed in the arena that contained two identical objects. After five-minutes, the rat was removed and placed in the holding cage for a five-minute retention interval, and the arena and objects were cleaned with 70% ethanol. The rat was then returned to the arena for a three-minute test. On the object test, the arena contained two objects in the same central locations as in familiarisation; one was a copy of the object that was used in familiarisation and the other was a novel object. The positions occupied by the familiar and novel objects were counterbalanced within each group. On the place test, the same two objects used in familiarisation were present, with one in its original central location and the other moved to a new location in the corner of the arena. The corner to which the object was moved was counterbalanced within each group.

Object and place recognition memory was indexed using a novelty preference ratio (Ennaceur & Delacour, 1988), quantified as the time spent exploring the novel object or location divided by the total time spent exploring both objects ($time_{novel}/(time_{novel} + time_{familiar})$). Exploration, measured using Macropod Software $ODLog^{TM}$, was defined as the rat directly facing and sniffing or contacting an object with its whiskers. Proximity,

rearing, biting, climbing and sitting on the object were not scored as exploration. Test results were excluded from statistical analysis if a rat did not make exploratory contact with each object for at least 10-seconds at familiarization or at least 1-second at test. These exclusion criteria were included because it would be invalid to calculate a preference between two objects at test if one object was not explored during familiarisation or at test.
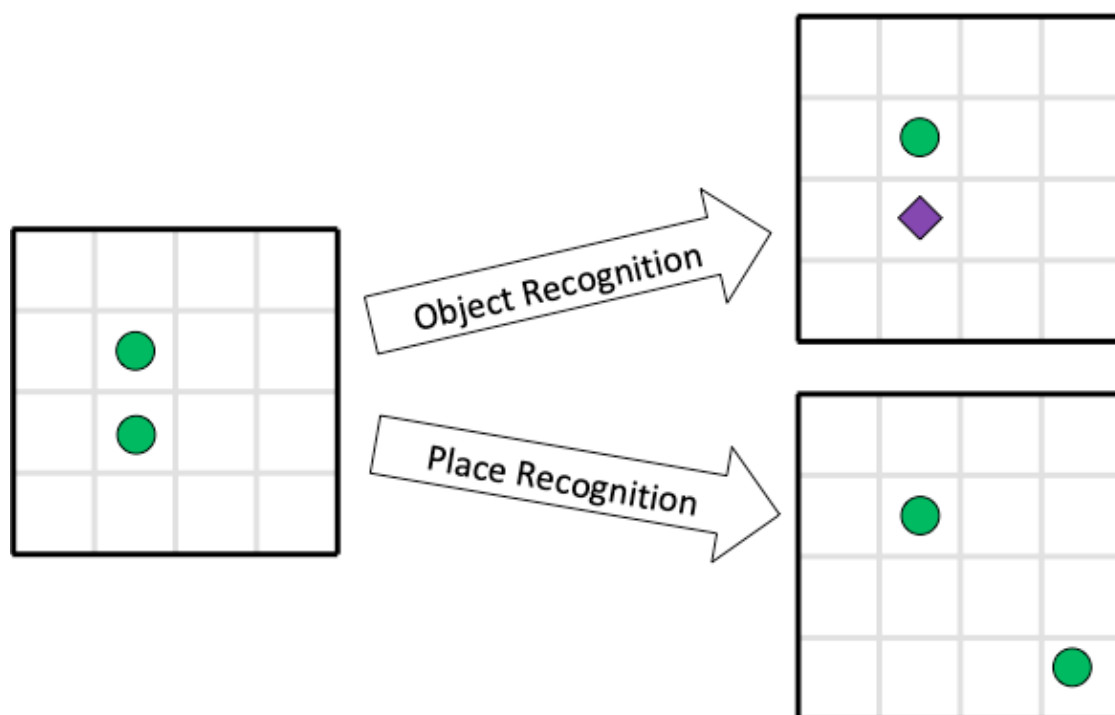
Figure 3.3. Diagram of the object and place recognition memory tests. In the familiarization phase, two identical objects were placed in the centre of the arena. At test, one of the objects was replaced by a new object in the same location (object recognition) or one of the original objects was moved to a new location in the corner of the arena (place recognition).

3.2.1.3. Context Generalisation Fear Conditioning

3.2.1.3.1. Apparatus. The fear generalisation task used two contexts that shared similar features. Conditioning occurred in context A, which consisted of two conditioning chambers (21 x 24 x 20 cm, L · W · H) that were each located in their own compartment of a wooden sound-attenuated cabinet whose walls, floors and ceiling were painted black.

The side walls of the conditioning chambers were made of aluminium and the front, back, and ceilings were made of clear Perspex. The Perspex ceilings were hinged to the top of the chamber and served as the door through which rats were placed into the chamber. The floor consisted of stainless-steel rods (2-mm in diameter, spaced 12-mm apart) through which a foot shock could be delivered, with a removable stainless-steel tray containing corncob bedding underneath. The chamber was illuminated by an infrared light (940 ± 25 nm) to permit observation of the rat, and a camera, mounted on the back wall of the wooden cabinet and connected to a DVD recorder located in another room, was used to record the behaviour of each rat for subsequent scoring.

Generalisation of context fear was tested in context B, which consisted of a single chamber (20 x 23 x 24 cm, L · W · H) located on top of the wooden cabinets housing context A. The side walls and ceiling of the chamber were made from aluminium and painted white, and the front and back walls were made of clear Perspex. The front Perspex wall could be opened to serve as the door through which rats were placed into the context. The floor consisted of stainless-steel rods (8-mm in diameter, spaced 12-mm apart) with a removable stainless-steel tray containing corncob bedding underneath. Illumination was provided by the fluorescent light installed in the room housing the chamber. A camera, mounted to the back of the chamber and connected to a DVD recorder located in another room in the laboratory, was used to record the behaviour of each rat for subsequent scoring.

3.2.1.3.2. Procedure. The fear generalisation test occurred after six-weeks of diet access, and five-days after the object and place recognition memory tests. On each of days one and two, rats were pre-exposed to contexts A and B in four-minute sessions. On day one, half of the rats from each group were exposed to context A in the morning and to context B six hours later in the afternoon; the remaining rats received the opposite

order of context exposure. This order of context pre-exposure was reversed on day two. Rats were pre-exposed to the two contexts to provide them with the opportunity to explore, sample and unify the elemental features that comprise each context into a configural representation, as this has been shown to enhance subsequent fear conditioning (Fanselow, 1990; Rudy & O'Reilly, 1999).

On day three, each rat received a single shocked exposure to context A. The shock (0.8 mA, 0.5 seconds) was delivered 2-minutes following placement of the rat into the chamber. The rat remained in the context for a further 30-seconds following foot-shock before being returned to the colony room. On day four, half of the rats from each group were tested in the previously shocked context A, and the remaining rats were tested for generalization of fear in the non-shocked context B. The duration of each test was four-minutes. Freezing was assessed using a time sampling procedure in which each rat was scored as freezing or not freezing every 2 seconds, and expressed as a percentage of the total number of occasions on which freezing could have occurred.

3.2.1.4. Statistical Analysis

A mixed-model ANOVA (Diet [CD, HS] x Time [Week 1 – 6]) was used to evaluate body weight, total energy intake, and energy intake from chow at each week of the experiment. A repeated measure ANOVA was used to evaluate change in sucrose intake across experimental weeks. Post-hoc independent t-tests were used to examine group differences in body weight and chow intake at each week of the experiment. The unit of analysis for energy intake was the home tub ($n = 4$). In the object and place recognition memory tests, student t-tests were used to evaluate the novelty preference and total exploration time. In the context generalisation test, post-shock levels of freezing and levels of freezing at test were examined using a two-way ANOVA (Diet [CD, HS] x Context [A, B]). A partial eta-squared (η^2) provided by SPSS was used as a measure of

effect size for analysis of body weight, energy intake, and levels of freezing in context fear generalisation tests. An $\eta^2 = 0.01$ is a small effect, $\eta^2 = 0.06$ a medium effect and $\eta^2 = 0.14$ a large effect (Cohen, 1988). For the object and place recognition memory tests, a Cohen's d was calculated as a measure of effect size for analyses comparing performance of CD and HS rats. A d = .2 is a small effect, d = .5 is a medium effect, and d = .8 is a large effect (Cohen, 1988). 95% confidence intervals (CIs) that were provided by SPSS were used as a measure of effect size for assessment of whether novelty preference of CD and HS rats significantly differed from chance in the place recognition memory test.

3.2.2. Results

3.2.2.1. Body Weight and Energy Intake

Figure 3.4.A shows the body weights averaged across each week of the experiment. There was no difference in body weight between groups at baseline (t(3) = .067, p = .947). Body weights in both control and HS diet conditions increased across time, and this increase appeared to be greater for HS than control rats. These observations were confirmed by statistical analysis which revealed a significant main effect of diet (F(1,30) = 6.315, p = .018, η^2 = .174), a significant linear trend for time (F(1,30) =460.845, p < .001, η^2 = .939) and a significant time x diet interaction (F(5,150) = 6.155, p < .001, η^2 = .170). Figure 3.3.A suggests that group differences in body weight are present at week two of the experiment, which was confirmed via post-hoc t-test (t(30) = 1.400, p = .035; CIs [1.53, 37.97]).

Figure 3.4.B shows the total energy intake across each week for CD and HS rats, and the energy intake from chow and sucrose solution for HS rats. The figure suggests that HS rats consumed progressively less energy from chow than control rats. This observation was confirmed by statistical analysis which revealed a significant effect of diet (F(1,6) = 44.102, p < .001, η^2 = .880) and a significant time x diet interaction (F(5,30)

= 6.661, $p < .001$, $\eta^2 = .526$). Follow up tests with a Bonferroni correction showed that the HS rats consumed significantly less chow than CD rats from the second week of the experiment ($t(6) = -5.212$, $p = .002$; CIs [-248.52, -89.73]). The figure also suggests that HS rats' energy intake from sucrose solution increased across experimental weeks, and this was confirmed by statistical analysis which revealed a significant effect of time ($F(5,15) = 4.630$, $p = .009$, $\eta^2 = 607$). Finally, Figure 3.4.B shows that despite having lower energy intake from chow, total energy intake was higher in HS than CD rats and that total energy intake remained stable across experimental weeks. This was confirmed by statistical analysis which revealed a significant effect of diet, ($F(1,6) = 6.927$, $p = .039$, $\eta^2 = .536$), no effect of time, and no time x diet interaction for total energy intake (Fs $\leq$ 1.738). Taken together, the results indicate that rats maintained on HS diet reduced their energy intake from chow across experimental weeks, presumably to compensate for the increasing energy intake from the sucrose solution. However, the reduction in energy from chow was insufficient to counter the increased energy from sucrose, resulting in significantly higher total energy intake in HS rats than control rats.
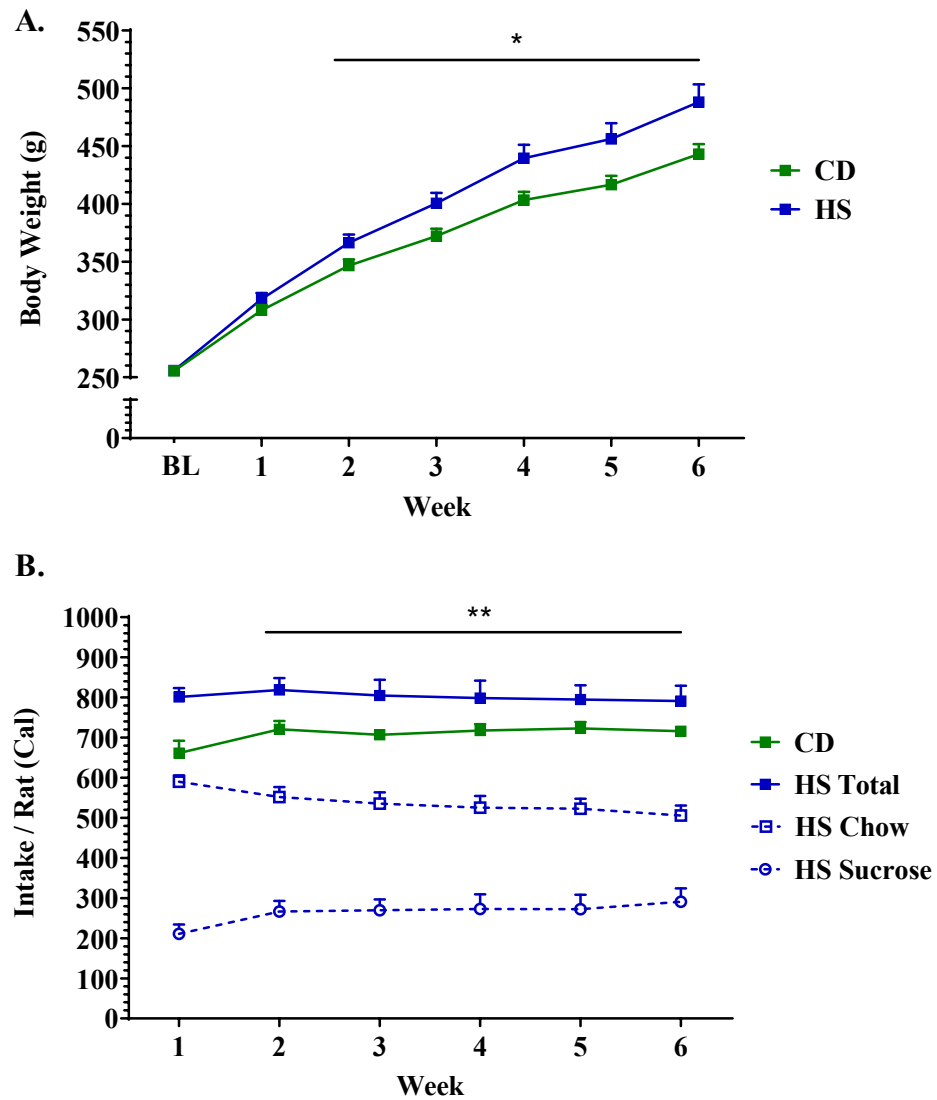
Figure 3.4. (A) Average body weight of rats consuming the control diet (CD) and high-sugar diet (HS) at baseline (BL) and at each week of the experiment. **(B)** Average total energy intake of CD and HS rats across experimental weeks, as well as total energy derived from chow (open blue squares) and 10% sucrose solution (open blue circles) for HS rats. * $p \leq .05$, ** $p \leq .01$.

3.2.2.2. Object and Place Recognition Memory Tests

In the object test, four rats (one CD and three HS) failed to reach criteria for object exploration at familiarization and were excluded from the statistical analysis, leaving 15 rats in the CD and 13 in the HS diet groups. In the place test, four rats (three CD and one HS) failed to reach criteria for exploration at familiarization, and one CD rat was excluded

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as novelty preference was greater than six standard deviations below the group mean. This left 12 rats in the CD and 15 in the HS diet groups.

Figure 3.5.A shows that control and HS diet rats had a similar novelty preference in the object test, however HS rats spent less time than CD rats engaged in object exploration (Figure 3.5.B). These observations were confirmed by statistical analysis that revealed a significant difference in exploration time (t(26) = -2.138, p = .042, d = .71) and no difference in novelty preference (t(26) = -.147, p = .863).

In the place test, the HS rats can be seen to have a lower novelty preference than CD rats (Figure 3.5.C), although the total time spent exploring the objects was similar (Figure 3.5.D). Statistical analysis confirmed a significant difference for novelty preference (t(25) = -2.702, p = .012, d = 1.01) and no difference in exploration time (p = .938). This finding indicates worse place recognition in HS than CD rats. Analysis of the a priori prediction that CD rats would discriminate the novel object location and HS rats would not discriminate the novel object location revealed that novelty preference of CD (t(11) = 7.068, p < .001; CIs [.1469, .2798]) and HS (t(14) = 3.426, p = .004; CIs [.0372, .1615]) rats were significantly different from chance. This indicates HS rats discriminated between the objects in the familiar and novel locations albeit less well than CD rats.
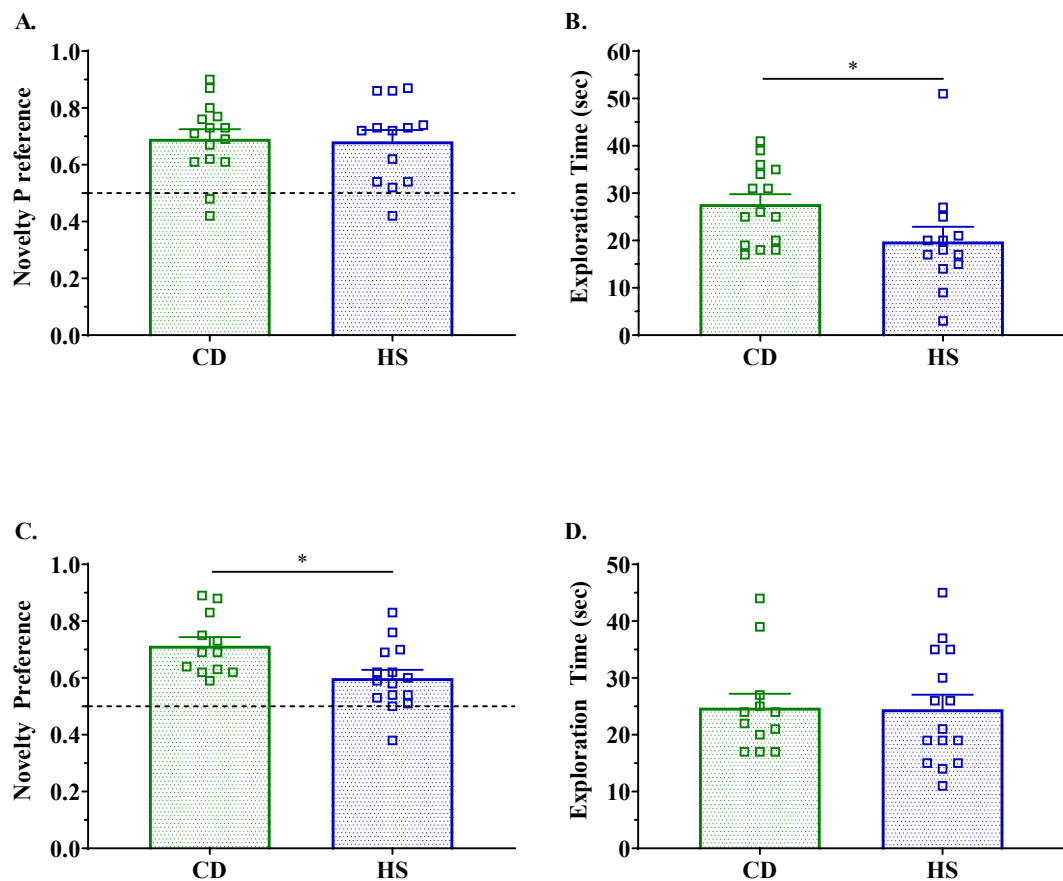
Figure 3.5. (A) Average novelty preference and **(B)** average exploration time in the object recognition test, and **(C)** average novelty preference and **(D)** average exploration time in the place recognition test for rats maintained on control diet (CD) and high-sugar diet (HS). *$p \leq .05$.

3.2.2.3. Context Generalisation Fear Conditioning

Two control rats were excluded from the statistical analysis. One exhibited levels of freezing pre-shock that were greater than four standard deviations above the group mean, and the other rat exhibited test levels of freezing that were greater than four standard deviations above the group mean.

3.2.2.3.1. Conditioning. The post-shock levels of freezing displayed by rats later tested in context A and context B are shown in Figure 3.6.A Examination of the figure suggests that HS rats had a higher level of post-shock freezing than control rats, regardless of the subsequent test context, however this difference was not significant (F = 1.736).

The figure also suggests that rats later tested in context A showed higher levels of post-shock freezing than rats later tested in context B, however this difference was also not significant (F = 2.948). There was no diet x context interaction (F < 1).

3.2.2.3.2. Generalisation Test. Figure 3.6.B shows that rats tested in context A had a higher level of freezing than rats tested in context B. The figure also suggests that HS and CD rats exhibited similar levels of freezing in the previously shocked context A, but HS rats froze more than CD rats in context B. Statistical analysis confirmed a significant effect of context ($F(1,26) = 16.084$, $p < .001$, $\eta^2 = .382$) and a trend toward a diet x context interaction that failed to reach significance ($F(1,26) = 3.943$, $p = .058$). There was no effect of diet ($F = 3.670$). These results indicate that HS rats did not exhibit significantly greater levels of freezing than control rats in the non-shocked context B.

A.

B.
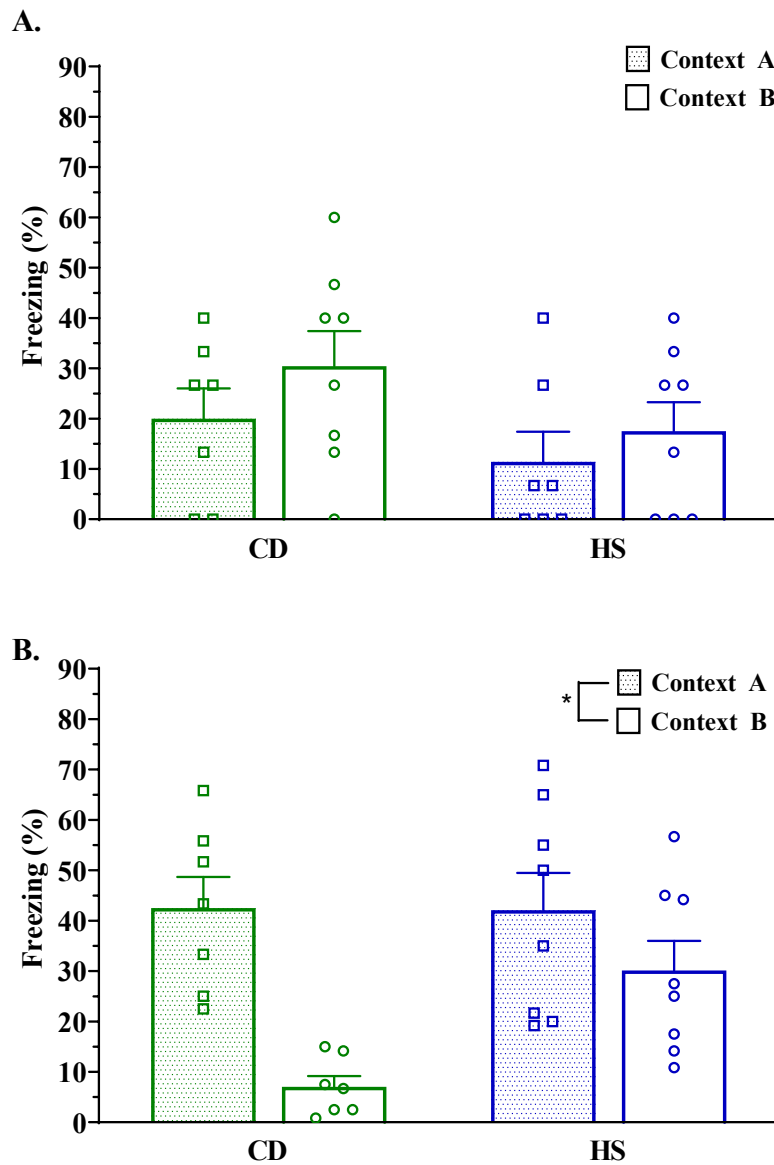
Figure 3.6. (A) Average level of freezing post-delivery of shock for control diet (CD) rats and high-sugar diet (HS) rats that were later tested in the conditioning context (A) and the similar context (B). **(B)** Average level of freezing during fear context fear test in context A and context B.

3.2.3. Discussion

Rats maintained on HS diet procured significantly more total energy than control rats, despite obtaining significantly less energy from chow. This pattern of results suggests that HS rats compensated for the energy obtained from the sucrose solution by reducing their intake of the chow diet, which has been observed in previous studies using

ad libitum (Beilharz et al., 2014, 2016a, 2016b) and restricted (Abbott et al., 2016; Kendig et al., 2013) access to 10% sucrose solution. However, this compensation was not sufficient to prevent a significant increase in total energy consumed across experimental weeks and, as a consequence of this, HS rats gained significantly more weight than control rats.

In the object and place memory tests, the novelty preferences of both HS and control rats were significantly greater than chance, indicating discrimination of the novel object and novel location. While performance on the perirhinal-dependent object memory test was comparable across diet conditions, performance on the hippocampal-dependent place memory test was impaired in HS when compared to control rats. As total exploration time on the place recognition test was similar between the conditions, the deficit in HS rats was not due to an effect of sugar on motivation or induced hyperactivity. Rather, the HS diet appears to have adversely affected the hippocampal substrates underlying place recognition memory. This finding is consistent with previous research that has demonstrated impaired place recognition memory in rats consuming 10% sucrose solution for as little as one week (Beilharz et al., 2014, 2016a, 2016b). As such, the deficit in place recognition memory confirmed that HS diet had influenced hippocampal function prior to undertaking the generalisation task.

In the context fear generalization test, the level of freezing was comparable across the two diet conditions in the previously shocked context A. However, HS diet rats exhibited greater levels of freezing than control rats in the non-shocked context B. Statistical examination revealed a trend toward generalisation of fear from context A to context B in the HS rats, however this failed to reach significance. Nevertheless, the trend suggests that control and HS rats may differ in their generalisation of fear from a shocked context to a similar context.

The behaviour of the control rats suggests that they formed a context fear memory in the shocked context A, but did not generalise this fear memory to the similar context. The absence of generalisation replicates previous findings observed in hippocampal intact rats (Antoniadis & McDonald, 1999, 2000) and mice (Frankland et al., 1998). The behaviour of control rats is therefore consistent with the proposal that they formed hippocampal-dependent configural representations across context pre-exposure, associated the representation of context A with shock, and then used their representations to discriminate between the contexts A and B at test (Rudy & O'Reilly, 1999. 2011; Rudy, 2015).

The intact fear conditioning in HS rats is also consistent with previous findings in hippocampal lesioned rats (Antoniadis & McDonald, 1999, 2000) and mice (Frankland et al., 1998), however the absence of greater generalisation is inconsistent with this research. There are two possible explanations for these results. The first is that the HS rats used the same strategy as the control rats; that is, they formed configural representations of the contexts during pre-exposure and used the two representations to discriminate between context A and B at test. However, if the control and HS rats both used configural representations for associative learning and discrimination of the two contexts, it is unlikely that the HS rats would exhibit such a marked increase in fear when tested in the similar context. That said, it could be that the configural representation formed by the HS rats was sufficiently accurate as to allow the discrimination but not as accurate as that formed by the chow rats, as evidenced by their respective levels of freezing in the similar context.

The second explanation is that the HS rats were unable to develop hippocampal configural representations, relying instead on associations between elemental features of the conditioning context and shock. Reliance on elemental associations would have

resulted in transfer of the shock association to the similar features in context B, and thus elicitation of the fear memory (Antoniadis & McDonald, 1999, 2000; Frankland et al., 1998). Support for this explanation comes from the trend toward greater generalisation in HS rats. Although non-significant, the trend suggests that CD and HS rats may differ in their generalisation of fear from a shocked context to a similar context, and that the contexts used were not sufficiently similar to detect such differences in generalization. Another possible reason for the failure to detect a significant group difference was the use of a between-subject design. While between subject designs offer a more conservative assessment of group differences, they may also result in differences being missed (Charness, Gneezy, & Kuhn, 2012). As such, if the size of the generalisation effect in HS rats is small, the present experiment may not have been designed in a manner that would allow detection of the hypothesised dietary effect. The assessment of the level of freezing of each rat in both context A and B using a within-subject design would provide a more sensitive measure of rats' ability to differentiate the two contexts, and thus be more aligned with the research question of interest.

3.3. Experiment 2

There were two aims of experiment 2. The first was to examine generalisation of a context fear memory in control and HS rats using a within subject design. Previous research has demonstrated an impairment in hippocampal-dependent place recognition memory after one week of HS diet consumption, and a progressive worsening of this deficit with longer diet exposure (Beilharz et al., 2014). Therefore, the second aim of experiment 2 was to assess the effects of duration of exposure to the HS diet on generalisation of a context fear memory. The experimental timeline is shown in Figure 3.7.
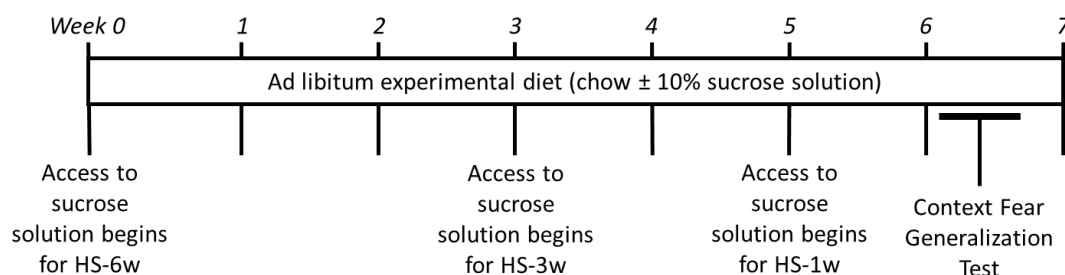
Figure 3.7. Timeline of experiment 2. Rats were provided *ad libitum* access to standard chow and water for the duration of the experiment. Rats in the high-sugar (HS) diet conditions were provided *ad libitum* access to 10% sucrose solution in addition to chow. Rats maintained on high-sugar (HS) diet for six-weeks (HS-6w) had access to sucrose solution at the start of the experiment. Rats maintained on HS diet for three-weeks (HS-3w) had access from the start of week three. Rats maintained on HS diet for one week (HS-1w) had access at the start of week five. The context fear generalisation test was conducted during week six of the experiment.

3.3.1. Method

3.3.1.1. Subjects and Design

Subjects were 48 experimentally naive rats of the same sex and strain, obtained from the same source and housed under the same conditions as experiment 1. There were 16 rats in the chow and sugar conditions. Rats were weight matched across tubs at the beginning of the experiment (weight range 329 - 414 g) and, after one week of acclimation to the housing conditions, tubs randomly assigned to control diet (CD), or high-sugar diet for one (HS-1w), three (HS-3w), or six-weeks (HS-6w).

3.3.1.1.1. Diets. The CD and HS diets were the same as those used in experiment 1. Access to the sucrose solution started six-weeks, three-weeks, or one week prior to the context fear generalisation test for rats in the HS-6w, HS-3w, and HS-1w conditions, respectively (see Figure 3.7). Consumption of food and sucrose solution for each tub was measured daily and was used to calculate a weekly intake of calories per tub. This value was divided by four to calculate an average intake per rat per tub. The unit of analysis was the tub (n = 3).

3.3.1.2. Context Generalisation Fear Conditioning

3.3.1.2.1. Apparatus. Context A and context B were the same chambers used in experiment 1.

3.3.1.2.2. Procedure. The fear generalisation test occurred after one, three, or six-weeks of HS diet access. Pre-exposure to contexts A and B (days 1 and 2) and conditioning in context A (day three) were conducted in the same manner as described in experiment 1. On day four, half of the rats from each group were tested in the previously shocked context A, and the remaining rats were tested for generalization of fear in the non-shocked context B. On day five, rats tested in context A were now tested in context B and vice versa. The duration of each test was four-minutes. Freezing was scored every 2 seconds as described in experiment 1. A context discrimination ratio, calculated by dividing the freezing percentage in context A by the total freezing percentage in both contexts ($Freezing_{contextA}$ / ($Freezing_{ContextA}$ + $Freezing_{ContextB}$). The ratio was used as an index of generalisation of context fear memory from context A to context B, with ratios higher than 0.5 indicating greater freezing in context A than context B (Huckleberry, Ferguson, & Drew, 2016).

3.3.1.3. Statistical Analysis

One-way ANOVA was used to examine baseline body weight. A mixed-model ANOVA (Diet [CD, HS-1w, HS-3w, HS-6w] x Time [Week 1 – 6]) was used to evaluate body weight, total energy intake, and energy intake from chow at each week of the experiment. Post-hoc Tukey tests were used to follow up any significant differences. One-way ANOVA was used to evaluate differences in energy intake from sucrose solution across the three HS diet conditions during experimental week six. The unit of analysis for energy intake was the tub ($n = 3$).

One-way ANOVA was used to examine post-shock freezing. A mixed-model ANOVA (Diet [CD, HS-1w, HS-3w, HS-6w] x Context [Context A, Context B] x Test Order [A→B, B→A]) was used to evaluate the level of freezing in context A and context B across the four diet conditions, and to examine the effects of the order of testing in the two contexts. Two-way ANOVA (Diet x Test Order) assessed context discrimination ratios, and one sample t-tests were used to examine whether the discrimination ratios differed significantly from 0.5 chance level. All significant outputs from the ANOVAs were followed up with post-hoc independent t-tests. ANOVAs and t-tests were conducted using IBM SPSS statistics 26 and $p \leq \alpha = .05$ was considered significant. 95% confidence intervals (CIs) were calculated for post-hoc tests. A partial eta-squared (η^2) provided by SPSS was used as a measure of effect size for all analyses. An $\eta^2 = 0.01$ is a small effect, $\eta^2 = 0.06$ a medium effect and $\eta^2 = 0.14$ a large effect (Cohen, 1988).

3.3.2. Results

3.3.2.1. Body Weight and Energy Intake

Figure 3.8.A shows there was no difference in body weight between groups at baseline ($F < 1$). The figure further suggests that the body weight of rats in all diet conditions increased across experimental weeks, and that the rate of increase was not influenced by diet. Statistical analysis confirmed a significant linear trend for time ($F(1,44) = 1420.050, p < .001, \eta^2 = .970$), and no significant effect of diet nor diet x time interaction (Fs ≤ 1.062). This indicates that the body weight of rats was not significantly influenced by consumption of the HS diet.

Figure 3.8.B shows the total energy intake from chow and sucrose solution for CD and HS rats. Examination of the figure suggests that HS-6w rats consumed less energy from chow than CD, HS-3w, and HS-1w rats in each week of the experiment. Rats in the HS-1w and HS-3w conditions consumed comparable energy from chow as CD rats

until they received access to sucrose solution, at which time energy intake from chow decreased. Statistical analysis confirmed a significant effect of diet ($F(3,8) = 26.985$, $p < .001$, $\eta^2 = .910$) and a significant diet x time interaction ($F(15,40) = 34.011$, $p < .001$, $\eta^2 = .927$). Statistical analysis further revealed a significant effect of time ($F(5,40) = 95.219$, $p < .001$, $\eta^2 = .922$), which likely reflects a decrease in energy intake from chow in the three HS diet conditions across the experiment. Post-hoc Tukey tests confirmed that HS-6w rats consumed significantly less energy from chow than CD, HS-1w, and HS-3w rats across the experimental period (largest $p = .004$; CIs [-241.54, -53.53]). Post-hoc analyses also revealed that HS-3w rats consumed significantly less energy from chow than CD rats ($p = .032$; CIs [-197.33, -9.31]).

It can also be seen in Figure 3.8.B that rats in the three sucrose conditions consumed similar amounts of energy from the sucrose solution during the common week six of the experiment. Statistical analysis confirmed no difference between diet conditions ($F < 1$), which indicates that the level of sucrose consumption was not influenced by the length of exposure to the sucrose solution.

Figure 3.8.C shows total energy intake for CD and HS rats in each week of the experiment. The figure shows that HS-6w rats had higher energy intake than CD rats across all-weeks of the experiment, as well as higher intake than HS-3w and HS-1w rats before these groups were provided access to sucrose solution. It can also be seen that access to the sucrose solution resulted in a marked increase in total energy intake in both HS-3w and HS-1w rats to levels greater than HS-6w rats. Statistical analysis partially supported these observations. The analysis revealed no effect of diet ($F = 2.700$), a significant effect of time ($F(5,40) = 8.729$, $p = .001$, $\eta^2 = .522$) and confirmed a significant quadratic trend for time x diet interaction ($F(3,8) = 6.004$, $p < .001$, $\eta^2 = .692$). Post-hoc Tukey tests revealed the source of the interaction was the marked increase in energy

intake in HS-3w rats when compared to the weighted average energy intake in the other diet conditions in experimental week four (F_c = 5.318; $F(1,8)$ = 26.472; CIs [39.87, 197.94]) and the absence of any differences by the final week of the experiment (F < 1). The increase in total energy intake in HS-1w rats in experimental week six failed to reach significance when compared to the weighted average energy intake of the other diet conditions (F = 3.656). These results indicate that total calorie intake of rats in the HS conditions changed across-weeks of the experiment, and that this change was a consequence of access to sucrose solution in addition to the chow diet.
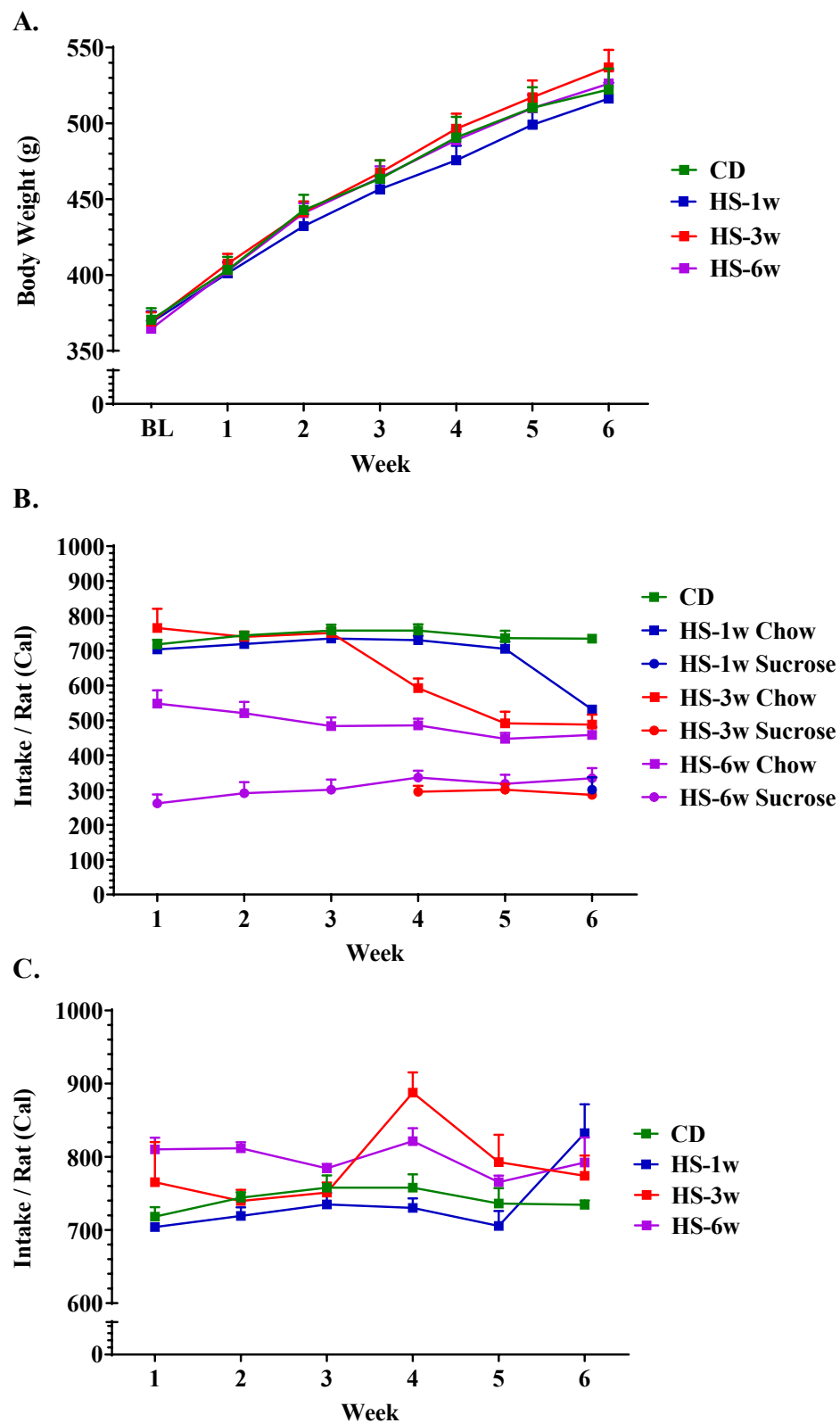
Figure 3.8. (A) Average body weight of rats consuming the control diet (CD), and high-sugar diet for one week (HS-1w), three-weeks (HS-3), and six-weeks (HS-6w). **(B)** Energy intake procured from chow diet and 10% sucrose solution across experimental weeks. **(C)** Total energy intake across experimental weeks.

3.3.2.2. Context Generalisation Fear Conditioning

One HS-6w rat was excluded from statistical analysis as it exhibited post-shock levels of freezing that were greater than two standard deviations above the group mean. One CD rat was euthanized on the day of conditioning due to illness. This left n = 11 CD and 11 HS-6w rats for inclusion in statistical analysis.

3.3.2.2.1. Conditioning. Figure 3.9. shows that rats in all diet conditions exhibited comparable levels of post-shock freezing, which was confirmed by statistical analysis (F = 1.210).
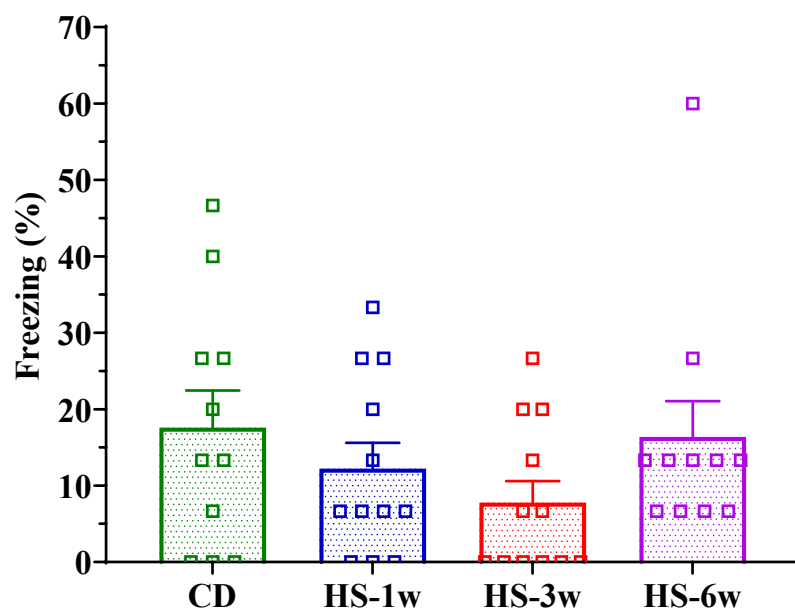
Figure 3.9. Average levels of freezing after the delivery of shock expressed by rats consuming control diet (CD) and high-sugar diet for one week (HS-1w), three-weeks (HS-3w) and six-weeks (HS-6w).

3.3.2.2.2. Generalisation Test. The levels of freezing in context A and context B by rats that received A➔B test order and rats that received B➔A test order are shown in Figure 3.10.A. The figure shows that rats exhibited higher levels of freezing in context A than context B, regardless of test order. The figure also shows that the difference in level of freezing in context A and B was greater in rats that received A➔B test order than B➔A

test order. Statistical analysis confirmed an effect of context ($F(1,38) = 30.870$, $p < .001$, $\eta^2 = .448$) and a significant context x test order interaction ($F(1,38) = 5.270$, $p = .027$, $\eta^2 = .122$). There was no effect of diet or test order, and no diet x context, diet x test order, nor diet x test order x context interaction ($Fs \leq 1.104$).

A discrimination ratio, shown in Figure 3.10.B, was calculated to examine the size of the difference in freezing to context A and B between rats that received different test order. Statistical analysis revealed that discrimination ratios were significantly higher in rats that received A➔B test order than rats that received B➔A test order ($F(1,38) = 12.696$, $p = .001$, $\eta^2 = .250$). This indicates that the difference in context freezing was larger in rats that received A➔B test order than rats that received the B➔A test order. In order to assess whether rats that received B➔A test order discriminated between the two contexts, we compared the discrimination ratio of each group to chance. After Bonferroni correction for multiple comparisons, $p \leq \alpha = .0125$ was considered significant. T-tests revealed that the ratio for CD rats was significantly different from chance ($t(4) = 6.917$, $p = .002$; CIs [.083, .194]), but the ratio for all HS diet conditions did not differ from chance (all $p \geq .218$).

A.

B.
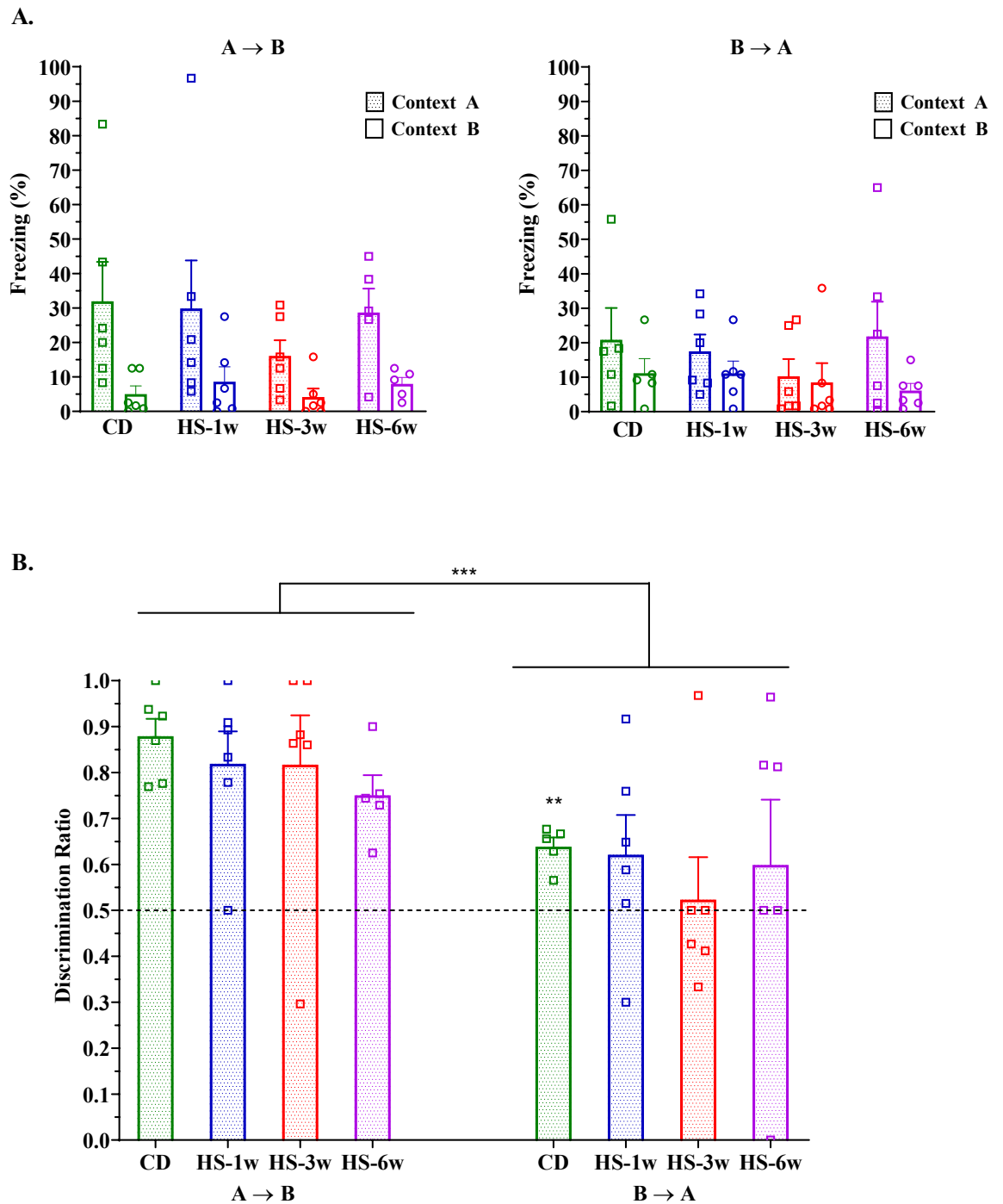
Figure 3.10. (A) Average level of freezing in the conditioning context (A) and similar context (B) for rats that were tested in the context A then context B (A➜B) or context B then context A (B➜A). **(B)** Average context discrimination ratio. The hyphenated line at 0.5 indicates chance level performance. (CD = control diet; HS-1w = one week high-sugar (HS) diet; HS-3w = three-weeks HS diet; HS-6w = six-weeks HS diet.) * p ≤.05, ** p ≤ .01, *** p ≤ .001.

3.3.3. Discussion

Rats maintained on HS diet for one, three, or six-weeks had comparable body weight with control rats maintained on standard chow. This is inconsistent with the results of experiment 1, but is consistent with the results reported in previous research that has used *ad libitum* access to 10% sucrose solution (Beilharz et al., 2014, 2016a, 2016b; Jurdak et al., 2008; Kendig et al., 2014; Woodie & Blythe, 2018). Total energy intake of rats maintained on the HS diet was similar to control rats, despite consuming less energy from chow once access to the 10% sucrose solution was provided. This pattern of energy intake may explain the absence of a difference in body weight between the control and experimental diet groups.

The pattern of energy intake from chow and sucrose solution differed across the four experimental diet conditions. Firstly, there was a difference in the intake of energy procured from chow by the HS rats and the control rats. HS-6w rats had lower energy from chow across all-weeks of the experiment; the HS-1w and HS-3w rats also procured less energy from chow once provided with access to the 10% sucrose solution. Secondly, total energy intake was increased in HS rats compared to control rats. The increase in total energy intake was observed once HS rats were provided with access to the 10% sucrose solution. This pattern of intake suggests that HS rats in all diet conditions compensated for the increased energy obtained from the sucrose solution by reducing their intake of energy from chow.

In the context fear generalisation test, rats exhibited significantly higher levels of freezing in the previously shocked context A than the non-shocked context B, regardless of diet condition and test order. The context discrimination ratios of rats that received the A➔B test order were significantly greater than the ratios of rats that received the B➔A test order, and were greater than chance level, indicating rats in all diet conditions

successfully discriminated the two contexts. However, for the B→A test order rats, statistical analysis revealed that only the ratio of control rats differed significantly from chance. Ratios of HS rats in all diet conditions did not differ significantly from chance. These findings suggest that when rats were tested in shocked context A before context B, they were able to successfully discriminate the two contexts and this reduced the generalisation of fear to context B. However, rats that were tested in context B and then in context A had greater difficulty discriminating the contexts. Nevertheless, control rats maintained their ability to discriminate the two contexts, whereas HS rats were less able to do so, resulting in generalization. Notably, the different length of exposure to high-sugar diet did not appear to influence the generalization effect.

The context discrimination in the control rats is consistent with the proposal that they formed hippocampal-dependent configural representations across context pre-exposure, associated the representation of context A with shock, and then used their representations to discriminate between contexts A and B on test. Importantly, while the control rats that received B→A test order had poorer performance than control rats that received A→B test order, they retained their ability to discriminate the two contexts. This finding is consistent with previous research in mice that demonstrated greater generalisation of fear when mice were tested in a neutral context before the conditioning context than mice that received the opposite order (Keiser et al., 2017). Taken together, the performance of control rats indicates that the configural representations formed in pre-exposure were sufficient to discriminate between the two contexts and thus reduce generalisation of fear to contexts comprised of similar features.

The discrimination ratios of HS rats that received B→A test order suggests that these rats were unable to discriminate the two contexts and thus generalised the conditioned fear memory formed in shocked context A to the non-shocked context B.

There was no evidence that longer exposure to the HS diet produced greater fear generalisation, with rats maintained on HS diet for one, three, or six-weeks exhibiting generalisation of context fear. This finding is inconsistent with previous research that suggests a progressive worsening of HS diet-induced impairments in hippocampal-dependent cognition with longer diet exposures (Beilharz et al., 2014).

The intact fear conditioning in context A accompanied by greater generalization of conditioned fear to similar context B that is observed in HS rats that received B➔A test order is consistent with previous research in rats (Antoniadis & McDonald, 1999, 2000) and mice (Frankland et al, 1998) with hippocampal damage. One explanation for the generalisation of fear is that the HS rats were unable to develop hippocampal-dependent configural representations, relying instead on associations between elemental features of context A and shock that would transfer the shock association to the similar features in context B, thus eliciting a fear memory. A reliance on elemental representations would also account for the reduced freezing observed in context A in HS rats that received B➔A test order. Activation of the shock association by the similar features would result in these features undergoing extinction. When these rats were subsequently tested in context A, only a subset of the elemental features that were associated with shock at conditioning would have retrieved the fear memory. Consequently, this would result in lower freezing in context A than would be observed had rats been tested in context A before B.

However, a second possible explanation of the reduced discrimination ratio in HS rats that received B➔A test order is that this reflects reduced freezing in context A rather than increased freezing in context B. While all rats were observed to exhibit significantly greater freezing in context A than context B, this difference was smaller in rats that received B➔A test order than rats that received A➔B test order. If HS rats are using

elemental representations for associative learning, any associations formed in context A that are activated in context B at test would be extinguished. Consequently, any fear expressed in context A would be reduced as only a subset of the initially conditioned associations would remain intact on the subsequent test in context B, resulting in reduced retrieval of a context fear memory. As the discrimination ratio is calculated by dividing level of freezing in context A by the combined level of freezing in both contexts, lower levels of freezing in context A alone would be sufficient to produce a reduced discrimination ratio in rats that received B➔A test order. As such, the interpretation that a reduced discrimination ratio is reflective of increased generalisation should be treated with caution.

The discrimination between the two contexts in HS rats that received A➔B test order is inconsistent with research in hippocampal lesioned rodents (Antoniadis & McDonald, 1999, 2001; Frankland et al., 1998). There are at least two explanations for this finding. The first is that HS rats used a similar process as control rats to guide their performance. That is, they formed a configural representation of context A and B and used these representations to discriminate the two contexts at test. While this is possible, an equal number of rats from each diet condition were randomly allocated to the two test orders, and it seems unlikely that all rats allocated to the A➔B test order would have intact configural processing and all rats allocated to the B➔A test order would have impaired configural processing. A second explanation is that HS rats that received A➔B test order were unable to form configural representations and thus used a similar process as HS rats that received B➔A test order. That is, they formed associations between the elemental features of context A and shock. These elemental associations would retrieve the conditioned fear memory during test in context A. The absence of shock during test would result in the elemental associations activated by context A undergoing extinction.

When the rats are subsequently tested in context B, the similar features would activate the extinguished associations, resulting in a low level of freezing in context B.

The results of the present experiment suggest that rats maintained on HS diet may generalise a context fear memory to contexts that are comprised of features that are similar to the conditioning context. However, this generalisation appears conditional on rats being tested in the similar context prior to the conditioning context. Furthermore, there are a number of possible explanations for the behaviour of HS rats that received A→B test order and B→A test order. Consequently, the present experiment provides inconclusive evidence to support the hypothesis that rats rely on elemental representations of context and precludes any conclusions about the effect of HS diet on hippocampal configural processing.

3.4. Experiment 1 & 2 - Ancillary Analysis

The results of Experiment 1 suggested a trend toward HS rats exhibiting significantly greater generalisation of fear from a shocked context to a similar context when compared to control rats, and that we failed to detect this due to insufficient number of rats. In support of this hypothesis, the results of Experiment 2 suggested that HS rats generalise a context fear memory to a similar context when they are tested in the similar context before the conditioning context. Therefore, to increase power, the data from the CD and HS-6w rats from the first day of testing in experiment 2 were combined with the data from CD and HS rats in experiment 1. This increased the sample size for statistical analysis to 13 CD and 13 HS rats that were tested in context A, and 12 CD and 14 HS rats that were tested in context B. Statistical analysis was conducted using SPSS, and a partial eta-squared (η^2) provided by SPSS was used as a measure of effect size. An $\eta^2 = 0.01$ is a small effect, $\eta^2 = 0.06$ a medium effect and $\eta^2 = 0.14$ a large effect (Cohen, 1988).

We first assessed whether the levels of freezing exhibited by CD and HS rats in context A and context B differed across the two experiments. A mixed-model ANOVA (Experiment [1, 2] x Diet [CD, HS] x Context [A, B]) revealed a main effect of experiment ($F(1,44) = 5.476$, $p = .024$, $\eta^2 = .111$), but no significant diet x experiment, context x experiment, or diet x context x experiment interactions (Fs ≤ 2.740). These results indicated that the CD and HS rats exhibited significantly more freezing in experiment 1 than experiment 2, but that the difference in freezing between the two experiments was comparable across CD and HS rats and comparable across the two contexts. As the difference experiments were comparable across diet and context, we continued with the planned analysis of freezing levels at test collapsed across the two experiments.

The levels of freezing at test were examined using a two-way ANOVA (Diet [CD, HS] x Context [A, B]). The level of freezing exhibited by CD and HS rats in context A and context B is shown in Figure 3.11. Examination of the figure suggests that rats in both diet conditions exhibited similar levels of freezing in context A, and that HS rats exhibited approximately twice the level of freezing as CD rats in context B. Statistical analysis partially supported these observations and revealed a significant effect of context ($F(1,48) = 21.780$, $p < .001$, $\eta^2 = .312$), but no main effect of diet nor diet x context interaction (Fs ≤ 1.429). These results indicate that HS diet rats did not exhibit significantly greater levels of freezing than control rats in the non-shocked context.
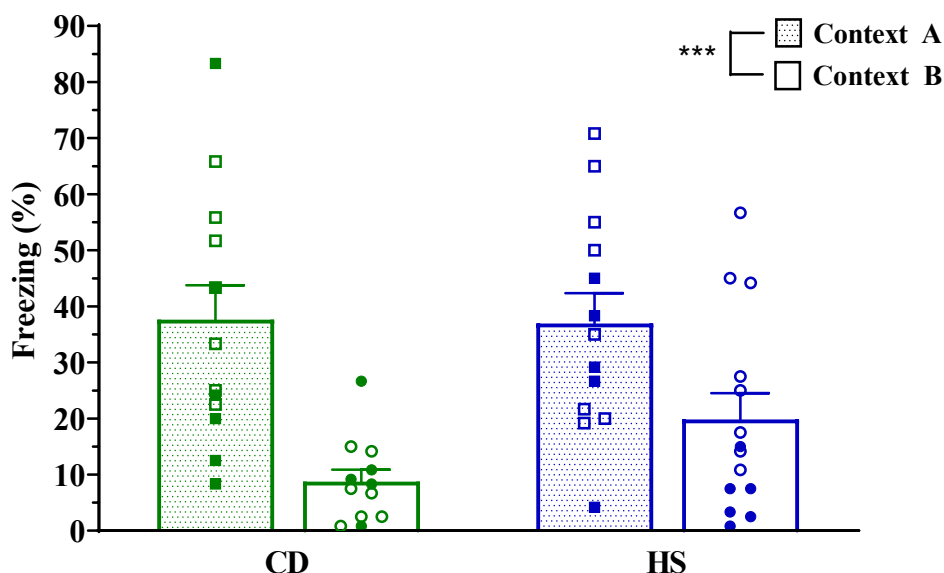
Figure 3.11. Average level of freezing for rats maintained on control diet (CD) and high-sugar diet (HS) in the conditioning context (A) and similar context (B) during context fear test. The open circles/squares are from rats in experiment 1, and the filled circles/squares are from rats in experiment 2. *** $p \le .001$.

Combining the data from Experiments 1 and 2 in the ancillary analysis did little to change the pattern of results that were observed in the context fear generalisation test in Experiment 1. Both the control and HS rats exhibited significantly greater levels of freezing in the shocked context A than the non-shocked context B. While the HS rats were observed to show greater levels of freezing in non-shocked context B than control rats, this difference was not significant. In fact, increasing the sample size for statistical analysis removed the trend toward a diet x context interaction that was observed in experiment 1 and confirmed that that HS rats showed comparable generalisation of fear to the similar context as the control rats. The results of the present experiment are inconsistent with the results of experiment 2, which suggested that HS rats are more likely to generalise a context fear memory when they are tested in the similar context without prior testing in the shocked context. Thus, the finding of the ancillary analysis suggests

that the use of a between subject design may be inappropriate for assessing the present hypothesis as it may result in important and real patterns being missed.

3.5. Chapter 3 Discussion

In Experiment 1, rats maintained on HS diet gained more body weight and consumed more calories than CD rats. However, in experiment two there was no significant difference between CD rats and rats maintained on HS diet for one, three, or six-weeks. It is therefore unclear why the difference in energy intake between control and HS rats differed across the two experiments. One possible explanation is that the difference is due to environmental effects. However, as rats in both experiments were housed under the same conditions in the same colony room, it is unlikely that the difference is a consequence of environmental factors that have been demonstrated to influence energy intake and body weight such as temperature (Rowe & Rolls, 1982), day/night length (Kersten, Strubbe, & Spiteri, 1980), or number of rats housed together (Harrington & Coscina, 1983). A second possibility is that the difference across experiments is due to age effects; differences in body weight gain and energy intake have previously been noted between adolescent and adult rats consuming a high-sugar diet consisting of chow and 10% sucrose solution (Kendig et al., 2013). However, as both experiments used adult rats that differed in age by a few-weeks, it is unlikely that age effects would influence energy intake and body weight gain. The final possibility is the difference in energy intake between control and HS rats across the two experiments. In experiment 1, HS rats consumed significantly more energy than control rats but in experiment 2 the control and HS rats had comparable energy intake. This difference likely explains why HS rats in Experiment 1, but not Experiment 2, gained significantly more weight than control rats.

In Experiment 1, performance on the perirhinal-dependent object recognition test was comparable in the two diet conditions, but performance on the hippocampal-dependent place recognition test was worse in the HS than the control condition. The finding of intact object recognition memory and impaired place recognition memory is consistent with previous research examining these two types of recognition memory in high-sugar diet exposed rats (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b). Total exploration time on the place recognition test was similar between the two dietary conditions, suggesting that the deficit in the HS rats was not due to an effect of the sugar on motivation or induced hyperactivity. Rather, consumption of the sugar appears to have adversely affected the hippocampal substrates underlying place recognition memory but had no detectable effect on the perirhinal substrates that mediate object recognition memory. It is important to note here that we are not suggesting a double dissociation in the effect of the high-sugar diet across the two tests; rather, the results suggest that the effect of high-sugar diet appears specific to hippocampal-dependent cognition. It is also important to note that we cannot rule out that the deficit in the place recognition test is a consequence of the diet-induced increase in body weight observed in HS rats. However, previous studies using a 10% sucrose solution diet manipulation have observed this deficit in the absence of significant effects of the diet on body weight (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b). This evidence suggests that the impairment in place recognition memory observed in HS rats in experiment 1 could be a consequence of the increased sugar intake alone.

The context fear generalisation task was used to assess the effect of a high-sugar diet on hippocampal-dependent configural processing. The hypothesis tested was that such a diet would bias rats towards the use of elemental representations of context, rather than configural ones, for associative learning. The results of the experiments provided

mixed support for this hypothesis. Experiment 1 provided evidence of a trend toward greater generalisation of fear in HS rats compared to control rats. However, after the addition of more subjects to the analysis in Experiment 3, this trend was no longer present. This finding indicates there was no effect of HS diet on generalisation of context fear to a similar context, and suggests that HS rats do not rely on elemental representations of context.

However, the results of Experiment 2 did provide some evidence that rats maintained on a HS diet for one, three, or six-weeks were impaired in discriminating between contexts comprised of similar features, resulting in a generalisation of contextual fear from a previously shocked context to a neutral context. This generalisation was only present when rats were tested using a within subject design, and when tested in the neutral context (B) before the shocked context (A). However, another possible explanation for the generalisation observed in Experiment 2 is that the low context discrimination ratio reflects reduced expression of fear in the shocked context on test day two, rather than an increased expression of fear in the non-shocked context. Overall, the results preclude any strong conclusions about the influence of HS diet on configural processing.

The mixed evidence in the context generalisation experiments suggests that diet-induced impairments in configural processing may be small and that their detection contingent on the type of memory task used. One limitation of the present experiments is the use of a fear generalisation conditioning procedure, which assesses the behavioural implications of deficits in configural processing, rather than specifically assessing the formation of context representation within the neocortical or hippocampal systems. Consequently, the generalisation tests may not provide a sufficiently sensitive measure of the influence of HS diet on configural processing.

Fanselow (2010) proposes that the fundamental assessment of whether rats use configural or elemental representations of context is whether context pre-exposure facilitates acquisition of a contextual fear memory when the rat is later fear conditioned with an immediate shock upon placement in the context. Rats that are capable of configural processing are able to rapidly retrieve the representation via pattern completion and associate this representation with the foot shock. In contrast, rats that rely upon elemental associations due to hippocampal damage do not have the capacity to form or rapidly retrieve a configured context representation for associatively learning; hence, these rats exhibited reduced freezing within the context at test when compared to hippocampal intact animals. If the consumption of HS diet does bias rats toward the use of elemental associations for learning, rats consuming such a diet would presumably not benefit from context pre-exposure when conditioned with an immediate shock. From the perspective of the Pavlovian conditioning literature, such a finding would provide more conclusive evidence of diet-induced disruption in hippocampal-dependent configural processing (Fanselow, 2010; Rudy, 2009)

3.5.1. Conclusion

The present set of experiments demonstrate that HS diet produces impairments in hippocampal-dependent place recognition memory. However, there was inconsistent evidence regarding the effect of diet on generalisation of context fear. Consequently, we are not able to draw a conclusion on whether rats maintained on HS diet use elemental or configural representations of context for associative learning. As such, further research is required to examine diet-induced impairments in configural processing using a CPFC task that is particularly sensitive to hippocampal damage.

Chapter 4: Effect of high-sugar and/or high-fat diets on Context Pre-exposure Fear Conditioning

4.1. Introduction

The detrimental effect of high-fat and/or high-sugar diet on physical health is well documented (Afshin et al., 2019). A growing body of research demonstrates that such diets also have an adverse effect on cognition, particularly cognition that is dependent on the hippocampus. Experimental studies with people (Attuquayefio et al., 2016, 2017) and rodents (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b, 2018; Kanoski & Davidson, 2010; Tran & Westbrook, 2015) have demonstrated deficits in hippocampal-dependent cognition, with relative sparing of cognition that is dependent on other brain regions, following high-fat and/or high-sugar diet manipulation. Furthermore, evidence from some rodent studies suggests that the deficits in hippocampal-dependent cognition that accompany high-fat high-sugar diet may change with prolonged dietary exposure (Beilharz et al., 2014, 2018), however most studies have failed to show this effect (Kanoski & Davidson, 2010; Leigh et al., 2020a, 2020b; Tran & Westbrook, 2015, 2017). These findings indicate that diet-induced impairments in hippocampal-dependent cognition occurs rapidly, and suggest that the level of impairment remains stable across time.

The hippocampus plays an important role in coding place information (O'keefe & Nadel, 1978). Chapter 2 of this thesis reviewed the evidence for an impairment in hippocampal place coding in rodents maintained on diets high in fat, sugar, or both, on a number of spatial memory tasks, including the Morris water maze, radial arm and radial water maze, spontaneous alternation task, and place recognition task. There was evidence of diet-induced impairments on all tasks, with the largest impairments found for the radial arm and radial water maze tasks. There was also evidence to suggest that the effect size

of the impairment was larger in rodents consuming both high-fat and sugar than rodents consuming either fat or sugar in isolation, however all three diets were found to produce impairments with a medium effect size.

The respective impact of consuming a diet high in fat and/or high in sugar remains debated. Few experimental studies have directly compared the influence of consuming fat or sugar either alone or in combination on place memory, and those studies that have made direct comparisons between diet manipulations have found inconsistent results. For example, Beilharz et al (2014, 2016) found a comparable deficit in place recognition memory in rats consuming a high-fat diet, a high-sugar diet or a high-fat high-sugar diet. Hargrave and colleagues (2015) reported an impairment in spontaneous alternation by rats consuming a high-fat high-sugar but not a high-fat diet. Finally, impairments in learning to locate the hidden platform in the Morris water maze have been observed in rats consuming a high-sugar but not a high-fat diet (Jurdak et al., 2008), but the reverse has also been reported (Gergerlioglu et al., 2016). Thus, there is no clear evidence whether the diet-induced impairment changes as a function of whether fat or sugar is consumed, either alone or in combination.

One important aspect of hippocampal place is the integration of the multi-sensory cues that comprise a context into a configural representation (Rudy & O'Reilly, 1999, 2001; Rudy, 2015). This representation acts as a Pavlovian conditioned stimulus (CS) that can be associated with an unconditioned stimulus (US), and thus influence behaviour upon subsequent exposure to that context (Fanselow, 2010; Maren et al, 2013). However, the sensory cues comprising a context can also be encoded independently of each other by cortical brain regions (Rudy & O'Reilly, 1999, 2001; Rudy, 2015). When this occurs, these cues compete with one another such that only the most salient cues become associated with the US. Thus, behaviour elicited upon subsequent exposure to the context

depends on the particular cues sampled: if the sampled cues are those that entered into associations, then conditioned responses are elicited; if the cues sampled are not those that entered into association, then no such conditioned responses occur (Rescorla & Wagner, 1972).

Chapter 3 examined the influence of high-sugar diet on the use of hippocampal-dependent configural representations of context in a context fear generalisation procedure. The results of those experiments provided inconsistent evidence of fear generalisation. The between-subject design used in experiment 1 failed to detect any differences between control and high-sugar (HS) diet rats in fear generalisation. However, the within-subject design used in experiment 2 suggested an order effect such that the HS rats generalised more when tested in the similar context and then in the conditioning context, but not when they were tested in the opposite order. The results of experiment 2 further suggested that the deficit in hippocampal-dependent cognition after HS diet access was observable after one week of HS diet access, and was comparable across rats exposed to the diet for one, three, or six-weeks. The inconsistent evidence of fear generalisation precluded any definitive conclusions about the influence of consuming a high-sugar diet on the processing of contextual information by the neocortical or hippocampal systems. Nevertheless, the results did suggest that control and HS rats differed in the way they used contextual information for associative learning, and that the context fear generalisation task may not be sufficiently sensitive to detect any effects of diet on hippocampal configural processing.

One way to assess the formation and use of a configural representation of context is context pre-exposure fear conditioning (CPFC). CPFC is a variant of standard context fear conditioning that involves three distinct stages separated from each other by 24-hour intervals: (1) context pre-exposure, (2) conditioning with a foot shock delivered

immediately, or shortly after, placement in the context, and (3) context fear test (Fanselow, 1986, 1990). Importantly, CPFC is critically dependent on intact hippocampal function. Inactivation or lesioning of the hippocampus either prior to (Matus-Amat et al., 2004; Rudy et al., 2002) or following (Chang, Chen, & Liang, 2008) the pre-exposure or conditioning stages results in a significant reduction in the expression of context fear at test. The role of the hippocampus in CPFC is attributed to its capacity for the formation of a configural representation of the conditioning context (Fanselow, 1986, 1990). Research demonstrates that rats pre-exposed to the conditioning context show higher levels of freezing at test than control rats that do not receive pre-exposure (Fanselow, 1990), rats that are pre-exposed to a different context (Landeira-Fernandez, Fanselow, Decola, & Kim, 1995), or rats that are pre-exposed to the elements of the conditioning context but in a different configuration from that present at conditioning and test (Rudy & O'Reilly, 1999, 2001). The configural representation formed by the hippocampus is rapidly retrieved via pattern completion from a subset of the available cues and associated with foot shock during conditioning (Fanselow, 1986, 1990; Rudy & O'Reilly, 1999, 2001). Together, this research indicates that the acquisition of a context fear memory in CPFC is critically dependent on the formation of a configural representation of the conditioning context by the hippocampus.

Sobesky and colleagues (2014) have used CPFC to examine the effect of consuming high-fat diet containing either 42% or 60% energy from fat on hippocampal-dependent configural processing. Pre-exposure consisted of a five-minute exposure to the context followed by five 30-second exposures; the inter-exposure interval was 30-seconds and rats spent this time in their home cage. The five-minute pre-exposure was used to allow rats to form a configural context representation, and the subsequent brief pre-exposures were used to establish the distinctive transportation bucket as a retrieval

cue for the context representation (Barrientos, Hein, Frank, Watkins, & Maier, 2012). Rats received an immediate shock when placed into the context on day two and tested for context fear (freezing) on day three. At test, rats maintained on 60% fat diet exhibited significantly less freezing than rats maintained on a control diet. Rats maintained on 42% fat diet also froze less than control rats but more than the rats maintained on the 60% fat diet, however these differences were not significant. From these results, Sobesky et al. concluded that rats maintained on a 60% fat diet, but not a 42% fat diet, were impaired in their ability to use configural representations of context for associative learning. However, as Sobesky et al. did not include a control condition that were not pre-exposed to the context and did not report post-shock levels of freezing, it cannot be determined whether differences in level of freezing at test were due to differences in strength of conditioning on day two. Nevertheless, the results demonstrate that consumption of a 60% fat diet, but not a 42% fat diet, disrupts the acquisition of a context fear memory in CPFC, suggesting that configural processing may be disrupted in rats exposed to high energy diets. Furthermore, these results contrast with the evidence of differential use of contextual information in rats consuming a high-sugar diet for one, three, or six-weeks presented in chapter 3, and thus suggests that deficits in configural processing may be differentially impacted by fat and sugar intake.

A number of factors are proposed to mediate diet-induced deficits in hippocampal-dependent cognition. One such factor is alterations in glucose regulation and insulin sensitivity. However, evidence of alterations in these metabolic parameters in rodents consuming short term high-fat and/or high-sugar diets is inconsistent. Some studies have reported differences in blood glucose levels (Arnold et al., 2014; Jurdak et al., 2008; Kendig et al., 2013; Pathan et al., 2008; Xu et al., 2018), plasma insulin levels (Beilharz et al., 2014; Pathan et al., 2008; Spinelli et al., 2017; Valladolid-Acebes et al.,

2011), and responses on a glucose tolerance test (Arnold et al., 2014; Xu et al., 2018) between rats fed chow and those fed a diet high in fat, sugar, or both fat and sugar. Furthermore, these differences have been associated with deficits in hippocampal spatial cognition. For example, Beilharz et al. (2014) reported increased plasma insulin concentration in rats fed a high-fat high-sugar diet during the third week of diet access, and that this increase was negatively correlated with performance in a place recognition memory task conducted in the same week; however, there was no metabolic disturbance observed in rats fed high-sugar diet alone. Jurdak et al. (2008) have also demonstrated a negative correlation between the area under the curve in a glucose tolerance test and escape latency in a Morris water maze in rats consuming high-sugar diet for five-weeks, but no correlation with escape latency in high-fat diet rats. However, a number of studies have failed to find significant differences from control rats in plasma insulin concentration in rats fed high-sugar diet (Beilharz et al., 2014) or high-fat diet (Valladolid-Acebes et al., 2011, 2013) or blood glucose levels in rats fed high-sugar diet (Gergerlioglu et al., 2016) or high-fat diet (Gergerlioglu et al., 2016; Moreira et al., 2014). Furthermore, dietary-induced alterations in blood glucose (Boitard et al., 2014; Kendig et al., 2013; Scichilone et al., 2016; Takechi et al., 2017; Valladolid-Acebes et al., 2013) and plasma insulin (Pratchayasakul et al., 2015; Takechi et al., 2017) have been reported but in the absence of deficits in hippocampal-dependent learning and memory. Therefore, further examination of the role of any changes in glucose regulation and insulin sensitivity in mediating deficits in hippocampal learning and memory is required.

The present experiment had four aims. The first was to use CPFC to examine the hypothesis that rats maintained on a diet that is high in sugar, fat, or both sugar and fat, are biased toward use of elemental representations of context for associative learning. The second was to examine whether impairment in hippocampal place memory changes

with duration of exposure to these diets. Two object and place recognition memory tests were conducted prior to CPFC testing; one was conducted after four-weeks of diet access and the second set of tests was conducted one week later (Figure 4.1.). These time points were selected as much of the previous research using the place recognition memory task has examined change in place memory across the first three-weeks of dietary intake (e.g. Beilharz et al., 2014, 2018; Tran & Westbrook 2017), but less is known about changes that occur after this time. The object and place memory tests were additionally used to confirm that the diet manipulation had impaired hippocampal-dependent memory before assessment of configural processing using the CPFC. The third aim of the present experiment was to examine the influence of high-sugar (HS), high-fat (HF), or a HFHS diet on the place recognition memory and the CPFC tasks. The inclusion of HF and HFHS diet in addition to HS diet allowed a test of whether the HFHS diet produces a more pronounced deficit in hippocampal place memory than either component alone. The final aim was to assess whether consumption of a HS, HF, or HFHS diet influences peripheral glucose homeostasis and insulin function, and whether any alterations in these parameters were associated with diet-induced deficits in the two tasks.
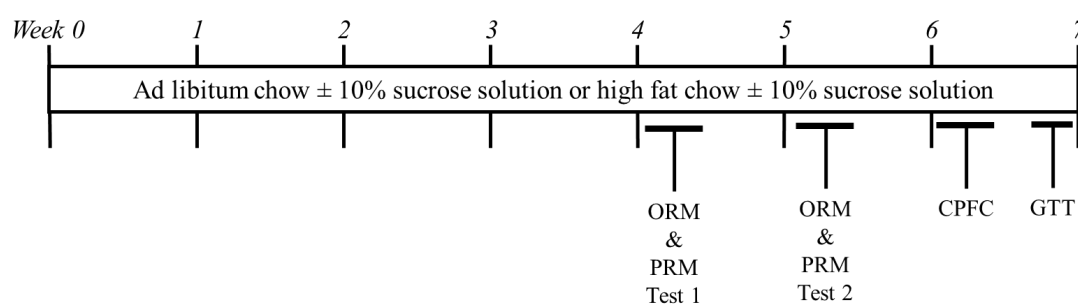
Figure 4.1. Experimental timeline. Rats were provided *ad libitum* access to chow (control diet), chow supplemented with 10% sucrose solution (high-sugar diet), high-fat chow (high-fat diet), or high-fat chow supplemented with 10% sucrose solution (high-fat high-sugar diet) for six-weeks. Object recognition memory (ORM) and place recognition memory (PRM) tests were conducted after four-weeks and five-weeks of diet access. A context pre-exposure fear conditioning (CPFC) test was conducted after six-weeks of diet access. A glucose tolerance test (GTT) was conducted three days later.

4.2. Method

4.2.1. Subjects and Design

Subjects were 64 experimentally naive rats of the same sex and strain, obtained from the same source, and housed under the same conditions as rats used in chapter 3. Rats were weight matched across tubs at the beginning of the experiment (weight range 224 - 314 g). After one week of acclimation to the housing conditions, four tubs were randomly assigned to the control diet (CD), four to the high-sugar diet (HS), four to the high-fat diet (HF), and four to the high-fat high-sugar diet (HFHS) conditions. Two rats assigned to the HF diet were euthanized due to illness prior to behavioural testing, leaving n = 14 in the HF diet condition.

4.2.1.1. Diets

All rats had free access to tap water for the duration of the experiment. CD and HS rats had *ad libitum* access to standard laboratory chow (Gordon's ® Specialty Rodent Feed; Yanderra, New South Wales, Australia; 3.53 kcal/g, 15% kcal from fat). The rats in the HF and HFHS conditions had *ad libitum* access to a semi-purified high-fat rodent chow (Specialty Feeds® SF04-001; 4.59 kcal/g, 40% kcal from fat). Rats in the HS and HFHS conditions were provided with one bottle containing 10% (w/vol) sucrose solution (CSR® White Sugar; Victoria, Australia; 3.82 kcal/g) in addition to one bottle of tap water. The consumption of food and sucrose solution for each tub was measured three times per week and was used to calculate a weekly intake of calories derived from chow and sucrose solution for each tub (4 rats per tub; one HF tub with 2 rats). The unit of analysis was the tub (n = 4).

4.2.2. Object and Place Recognition Memory Tests

4.2.2.1. Apparatus

The object and place recognition memory tests were conducted using the same apparatus as experiment 1 in chapter 3.

4.2.2.2. Procedure

The first object and place recognition memory tests were conducted after four-weeks of diet and the second tests one week later. Rats were familiarized with the test arena in daily 10-minute sessions across two consecutive days before the first object and place recognition memory tests in week four but not week five. The order of the object and place tests was counterbalanced such that half of the rats in each of the four groups received an object test first and a place test one day later, while the remaining rats received the place test first and the object test one day later. The tests were conducted and the data scored as previously described in experiment 1 in chapter 3.

4.2.3. Context Pre-exposure Fear Conditioning (CPFC)

4.2.3.1. Apparatus

CPFC was conducted in the chambers described in chapter 3. The conditioning context continued to be the chambers assigned as context A and the similar context was assigned as context B.

4.2.3.2. Procedure

CPFC was examined after six-weeks of diet access. The CPFC procedure is shown in Figure 4.2. On day one, each rat was pre-exposed to context A for four-minutes. On day two, each rat was returned to context A and administered two brief foot shocks (0.8 mA, 0.5 sec) delivered 5 seconds and 6.5 seconds following placement in the context. The rats were removed from the chamber 30-seconds after the second shock. On day three, context fear memory was assessed in context A. We examined the specificity of

the context fear memory by testing rats in similar context B on day four. Both the context fear and generalisation tests last for four-minutes and the tests were conducted under extinction. Freezing was used as an index of context conditioned fear and its generalization. It was scored as previously described in chapter 3.
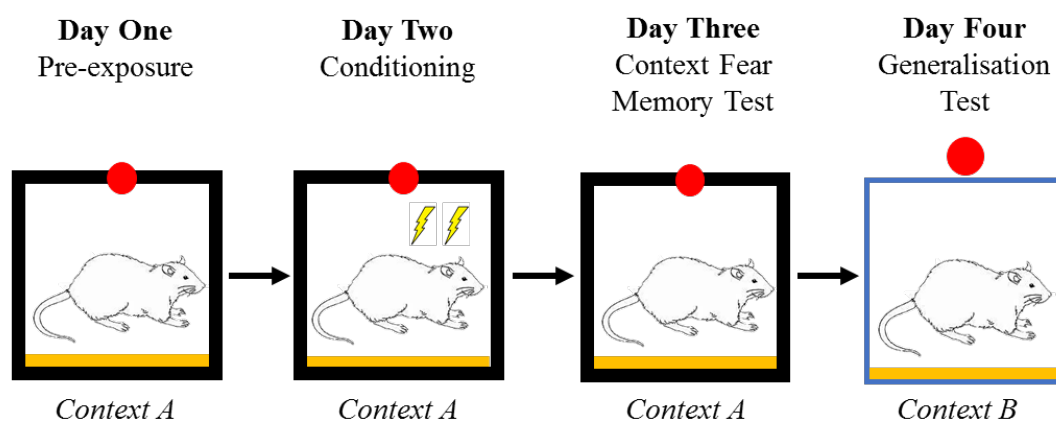
Figure 4.2. Diagram of the context pre-exposure fear conditioning (CPFC) test procedure. Rats were pre-exposed to context A on day one for four-minutes before conditioning on day two with two brief aversive foot shocks delivered shortly after placement in the chamber. Formation of a context fear memory was assessed in context A on day three, followed be examination of the generalisation of the context fear memory to a novel context B on day four.

4.2.4. Glucose Tolerance Test (GTT)

A glucose tolerance test was conducted during week six of diet access, three-days after the CPFC generalisation test. Rats in all conditions were fasted for 12-hours overnight but with free access to water. Following this fast, the tip of the rat tail was cut and baseline glucose was measured from approximately 5 uL blood (Accu-Chec; Roche Diagnostics, IN). Immediately following baseline glucose test, a glucose bolus (1 uL/g body weight; 20% (w/v) glucose dissolved in distilled water) was delivered by intraperitoneal (i.p.) injection to each rat. Blood glucose was assessed from approximately 5 uL blood collected via tail nick at 15-, 30-, 45-, 60-, and 120-minutes post-bolus injection.

To assess peripheral insulin response to the glucose bolus, 10 rats were randomly selected from each diet condition and 50 uL of blood was collected in 500 uL microvette tubes at baseline, and 15- and 60-minutes post-bolus injection. Blood was centrifuged (12 000 rcf, 12-minutes) and plasma supernatant was pipetted into fresh eppendorf tubes. Plasma samples were stored at -20ºc. Plasma insulin concentration was assessed using an Enzyme-Linked Immunosorbent Assays (ELISA) that was conducted as per manufacturer instructions (CrystalChem®, Illinois, USA).

4.2.5. Statistical Analysis

Two-way ANOVAs (chow [standard, high-fat] x sucrose access [water, 10% sucrose solution]) were used to examine body weight at baseline, and mixed-model ANOVAs (chow x sucrose access x time [weeks 1 – 6]) were used to examine average body weight and energy intake in each week of the experiment. Performance on the object recognition, place recognition, and CPFC tests were assessed using planned orthogonal contrasts that compared (1) control diet to the weighted average of HS, HF, and HFHS diet, (2) HFHS to the weighted average of HS and HF, and (3) HS to HF diet. The first contrast examined whether exposure to any of the experimental diets affected task performance; the second contrast examined whether the combination of high-fat and high-sugar affected performance more than these components in isolation; and the final contrast examined whether the consumption of HS or HF diet had a differential impact on task performance. Mixed-model ANOVAs (chow x sucrose access x time [minute]) was used to assess blood glucose level and plasma insulin concentration across time in the glucose tolerance tests. Two-way ANOVAs (chow x sucrose access) were used to examine the area under the curve (AUC) for blood glucose level and plasma insulin concentration. Pearson's correlations were used to examine the *a priori* prediction that blood glucose and plasma insulin concentration would correlate negatively with

performance on hippocampal-dependent memory tasks. The data used for Pearson's correlations (r) were blood glucose AUC, plasma insulin AUC, novelty preference from the place recognition memory test conducted in week five, and CPFC context fear memory test. Rats that were excluded from statistical analysis of the memory tests or the statistical analysis of the glucose tolerance test data were excluded from the correlations.

ANOVAs and Pearson's correlations were conducted using IBM SPSS statistics 26 and Bonferroni contrasts were conducted using PSY (Bird, Hadzi-Pavlovic, & Isaac, 2000). A $p < \alpha = .05$ was considered significant for all tests and the appropriate F-critical is stated for analyses using contrasts. A partial eta-squared (η^2) provided by SPSS was used as a measure of effect size for all analyses. A $\eta^2 = 0.01$ is a small effect, $\eta^2 = 0.06$ a medium effect and $\eta^2 = 0.14$ a large effect (Cohen, 1988). For contrasts used to assess performance on hippocampal-dependent tasks, 95% Confidence Intervals [lower bound, upper bound] are provided as a measure of effect size. For Pearson's correlations, a correlation of $r \leq 0.3$ is taken to be a small effect and $r \geq 0.5$ a large effect (Cohen, 1992).

4.3. Results

4.3.1. Body Weight and Energy Intake

Figure 4.3.A shows that body weight was comparable across groups at baseline. Statistical analysis confirmed that there were no significant differences among the rats allocated to the four groups ($F = 1.152$). Analysis of the average body weight across experimental weeks revealed a significant main effect of chow ($F(1,58) = 12.312$, $p = .001$, $\eta^2 = .175$), a significant linear trend for time ($F(1,58) = 1238.295$, $p < .001$, $\eta^2 = .955$), and a significant linear trend x chow interaction ($F(1,58) = 22.532$, $p < .001$, $\eta^2 = .280$). This indicates that body weight increased for rats in all diet conditions, and that the increase was greater in rats consuming high-fat chow than standard chow. There was no

effect of access to sucrose solution nor a time x sucrose access interaction (Fs < 1), indicating that sucrose consumption did not influence body weight gain.

Energy intake from chow and sucrose solution is shown in Figure 4.3.B. Examination of the figure suggests that energy intake from chow was lower in CD and HS rats provided with standard chow than in the HF and HFHS rats. The figure also suggests that rats provided with the 10% sucrose solution consumed less energy from chow than rats that did not have access to the solution, and that the decrease in energy intake from chow became more pronounced across experimental weeks. Statistical analysis confirmed that rats with access to standard chow consumed significantly less energy from chow than rats with access to the high-fat chow ($F(1,12) = 6.986$, $p = .021$, $\eta^2 = .368$) and that sucrose access decreased energy intake from chow ($F(1,12) = 46.918$, $p < .001$, $\eta^2 = .796$). Statistical analysis also revealed a significant linear trend for time ($F(1,12) = 12.907$, $p = .004$, $\eta^2 = .518$) and a time x sucrose access interaction ($F(5,60) = 4.125$, $p = .003$, $\eta^2 = .256$), suggesting that HS and HFHS rats' energy intake from chow decreased across weeks. There was no interaction between time x chow nor between chow x sucrose access (Fs ≤ 1.159).

As shown in Figure 4.3.B, energy intake from consumption of the sucrose solution appeared to be comparable across the HS and HFHS groups. To control for multiple comparisons, a Bonferroni correction was made to the alpha level such that a p < α = .025 was significant. Statistical analysis confirmed no effect of chow nor time x chow interaction (Fs < 1). The analysis also revealed a significant quadratic trend for time ($F(1,6) = 18.759$, $p = .005$, $\eta^2 = .758$), which likely reflects a modest increase in sucrose intake across experimental weeks one to five and a decrease in energy intake in week six due to 12-hour food restriction for the glucose tolerance test.

Figure 4.3.C shows total energy intake across the experimental weeks. Total energy intake in the HFHS rats was higher than the energy intake of CD, HS, and HF rats across all experimental weeks. The total energy intake by HS and HF rats was comparable across the first two-weeks of the experiment, and greater than the total energy intake of CD rats. From week three of the experiment, total energy intake of HS rats was comparable with that of CD rats, however the total energy intake of HF rats remained relatively stable. Total energy intake decreased in the final week of experiment for all diet conditions, and this decrease appeared to be greater in HF and HFHS rats than CD and HS rats. These observations were partially confirmed by statistical analysis. Analysis confirmed total energy intake was higher in rats consuming high-fat chow than standard chow ($F(1,12) = 9520.038$, $p < .001$, $\eta^2 = .987$), a significant linear effect of time ($F(1,12) = 2422.549$, $p < .001$, $\eta^2 = .995$), and a time x chow interaction ($F(1,12) = 2598.937$, $p < .001$, $\eta^2 = .995$). However, there was no time x chow x sucrose access interaction ($F < 1$). There was also no effect of sucrose solution access, and no time x sucrose access, nor chow x sucrose access interactions (Fs ≤ 2.083). Taken together, these results indicate that rats provided access to sucrose solution reduced their energy intake from their respective chow source, presumably to compensate for the increasing energy intake from the sucrose solution. The reduction in energy from chow was sufficient to counter the increased energy from sucrose in HS rats and HFHS rats.
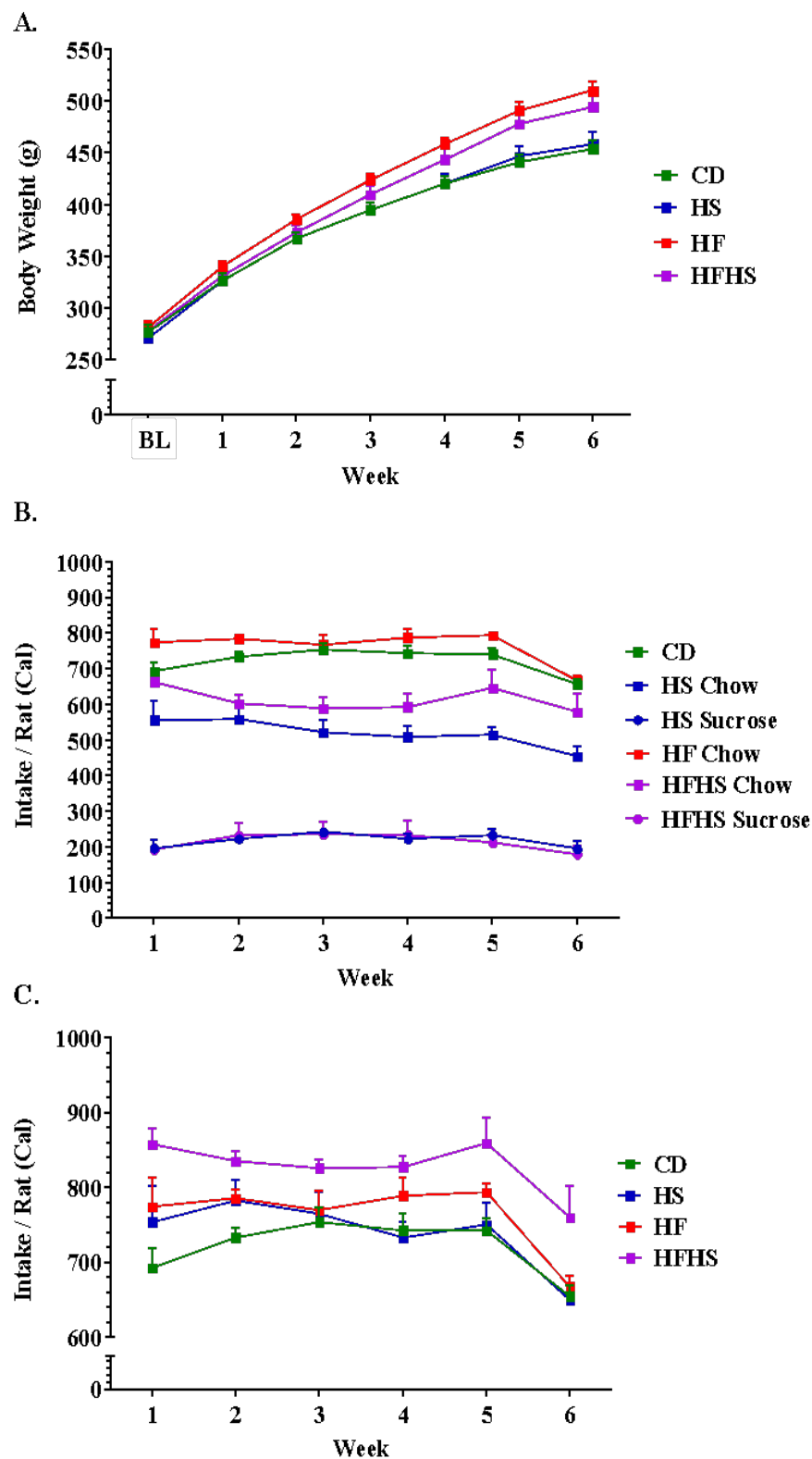
Figure 4.3. Average **(A)** body weight, **(B)** energy intake from chow and sucrose solution, and **(C)** total energy intake for rats consuming control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar diet (HFHS).

4.3.2. Object and Place Recognition Memory Tests

Two rats were excluded from statistical analysis of the object recognition memory tests: one CD rat who knocked over an object during test 2, and one HFHS rat who explored one object for less than one second during test 2. Six rats were excluded from statistical analysis of the place recognition tests as they explored one object for less than once second at test: one HF rat and one CD rat from test 1, and one HF rat, one HS rat, and two CD rats from test 2.

Figure 4.4.A shows the novelty preference for the object recognition memory tests 1 and 2, and Figure 4.4.B. shows the exploration times for tests 1 and 2. The figure shows that CD, HS, HF, and HFHS rats had a similar novelty preference in object tests 1 and 2 (F_c = 4.013; Fs $\leq$ 2.195), and spent similar amounts of time in object exploration on each of the tests (Fs $\leq$ 2.481).
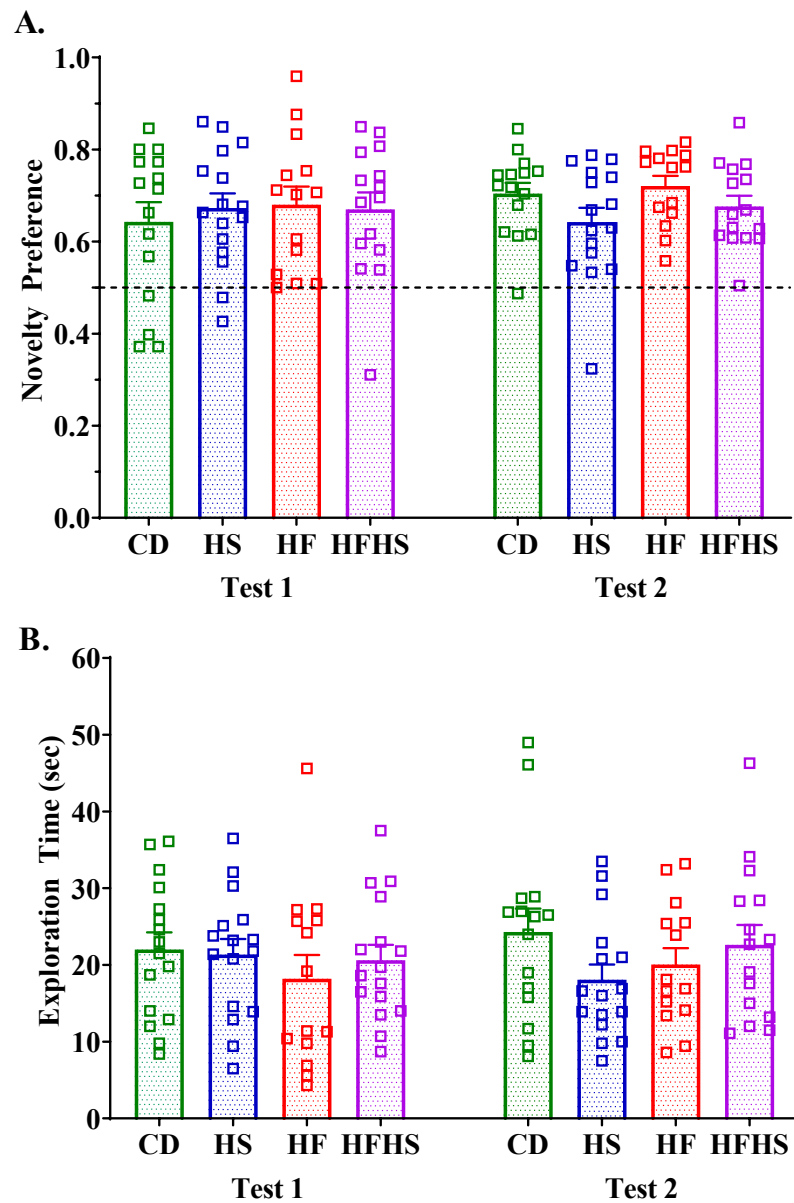
Figure 4.4. (A) Average novelty preference in the object recognition memory tests conducted after four-weeks (test 1) and five-weeks (test 2) of access to the control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar diet (HFHS). **(B)** Average exploration time in object recognition memory tests 1 and 2.

The novelty preference and exploration times in the place recognition memory tests are shown in Figure 4.5.A and 4.5.B, respectively. The figure shows that rats consuming HS, HF, and HFHS diet had a lower novelty preference than CD rats on both tests 1 and 2. Statistical analysis revealed a significant difference in novelty preference between CD rats and the weighted average of HS, HF, and HFHS rats ($F_c = 4.027$; $F(1,52)$

= 18.419; CIs [-0.176, -0.064]). However, there were no significant difference in novelty preference between HFHS rats and the weighted average of HS and HF rats, nor between HS and HF rats (Fs < 1). time spent in exploration of the objects did not differ significantly across place recognition memory tests 1 and 2 (Fs ≤ 2.829), however the exploration time of HFHS rats was significantly greater than the weighted average exploration time of HS and HF rats ($F(1,52)$ = 10.734; CIs [2.305, 9.591]). There was no difference in exploration time between CD rats and the weighted average exploration time of HS, HF, and HFHS rats, nor was there a difference in exploration time between HFHS rats and the weighted average exploration time of HS and HF rats, nor between the HS and HF rats (Fs ≤ 1.120). For both test 1 and test 2, the novelty preference of CD rats was significantly greater than chance (t(12) ≥ 4.644, p ≤ .001), however the novelty preference of HS (t(14) ≤ 1.153, p ≥ .268), HF (t(11) ≤ 4.392, p ≥ .191), and HFHS (t(15) ≤ 1.349, p ≥ .197) rats did not significantly differ from chance. These results indicate that CD rats successfully discriminated between the novel and the old object locations in test 1 and test 2, while HS, HF, and HFHS rats failed to do so on either test. Taken together, the results demonstrate that HS, HF, and HFHS diets impair hippocampal processes underlying place recognition memory, that this impairment does not change over time, and does not differ as a function of whether sugar or fat is consumed alone or in combination.
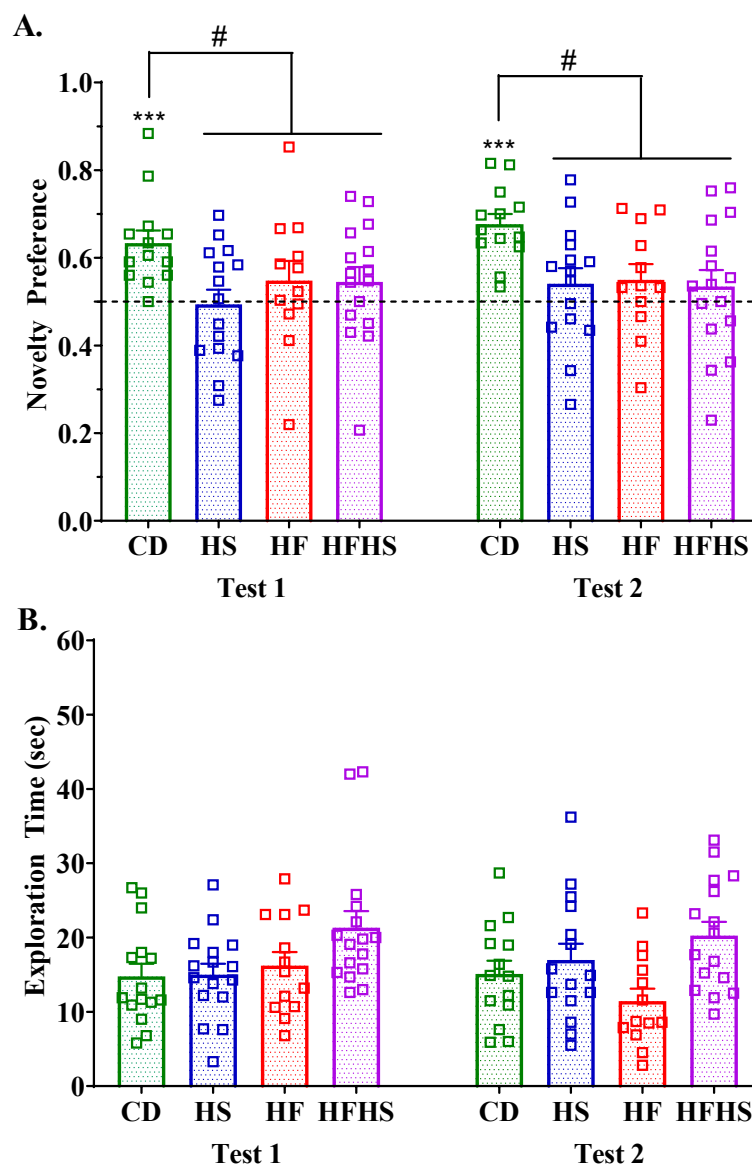
Figure 4.5. (A) Average novelty preference in the place recognition memory tests conducted after four-weeks (test 1) and five-weeks (test 2) of access to the control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar diet (HFHS). **(B)** Average exploration time in place recognition memory tests 1 and 2. $^{\#}$ F $\geq$ F$_c$ = 4.016, *** $p \leq .001$.

4.3.3. Context Pre-Exposure Fear Conditioning

The data from three rats were excluded from all analyses of the CPFC data: one HFHS rat was excluded due to a computer malfunction at the time of conditioning resulting in extended exposure to context A prior to shock delivery; one CD and one HS

diet rat were excluded as their level of freezing was greater than 2 standard deviations above the group mean in the 30 seconds post-shock on the conditioning day. One CD rat was excluded from statistical analysis of the fear generalisation data as the level of freezing was greater than 2 standard deviations above the group mean, but was included in all other analyses.

4.3.3.1. Conditioning

Figure 4.6. shows average level of freezing post-shock. Examination of the figure suggests that HF rats exhibited lower levels of post-shock freezing than CD, HS, and HFHS rats, and that HS rats exhibited higher levels of freezing than CD rats. The statistical analysis revealed a significant difference in post-shock freezing between HS and HF rats (F_c = 4.016; $F(1,55)$ = 4.224; CIs [0.224, 17.807]). The weighted average freezing of HS, HF, and HFHS rats compared to CD rats was not significantly different, nor was the difference between the weighted average freezing of HS and HF rats compared to HFHS rats (Fs < 1).
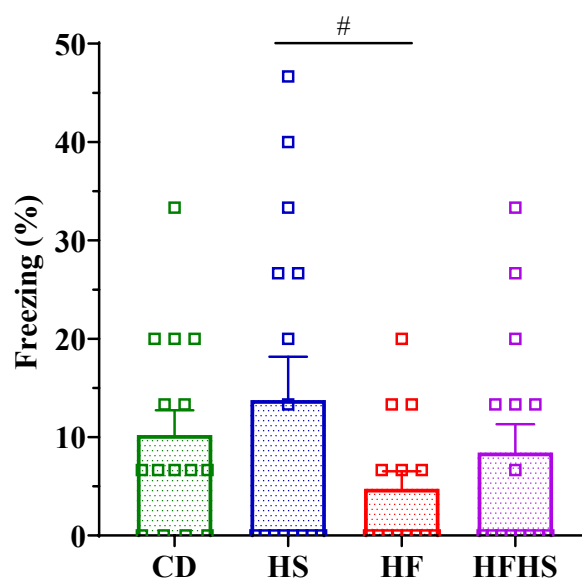
Figure 4.6. Average level of post-shock freezing at time of conditioning for rats consuming the control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar diet (HFHS). [#] $F \geq F_c$ = 4.016.

4.3.3.2. Context Fear Test

Figures 4.7.A and 4.7.B show average level of freezing at test in the conditioned context, and at test in the neutral context, respectively. Examination of Figure 4.7.A shows that all rats, regardless of diet, exhibited comparable levels of freezing when tested in context A, and this was confirmed by statistical analysis (Fs < 1). Examination of Figure 4.7.B suggests that HS, HF, and HFHS rats exhibited comparable levels of freezing in context B, and that this was greater than the level of freezing in the CD rats. Statistical analysis partially supported these findings; the freezing by HS and HF diet rats were not significantly different, nor was the weighted average freezing of HS and HF diet rats compared to HFHS diet rats (Fs < 1). However, statistical analysis also revealed there was no significant difference between the weighted average freezing of HS, HF, and HFHS rats compared to CD rats (F_c = 4.020; F ≤ 2.322).
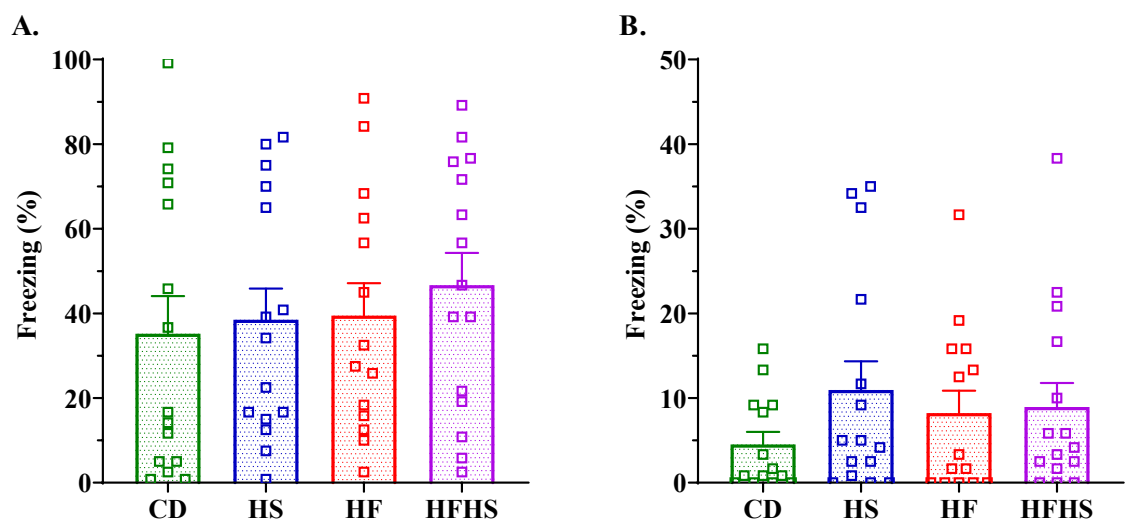
Figure 4.7. (A) Average level of freezing at test in the conditioning context for rats in the control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar (HFHS) conditions. **(B)** Average level of freezing at test in a similar non-shocked context.

4.3.4. Glucose Tolerance Test

The data from one HFHS and one HF rat were excluded from statistical analysis of blood glucose levels as their AUC was greater than 2 standard deviations above the group mean. Figure 4.8.A shows the average blood glucose concentration for each measurement time point during the GTT. It can be seen in the figure that there was no difference in blood glucose concentration at baseline after the 12-hour fast. This observation was confirmed by statistical analysis (Fs ≤ 1.041). The figure shows that blood glucose levels increased in all groups after injection of the glucose bolus and this increase was larger in HF and HFHS rats than in CD and HS rats. Blood glucose peaked in CD rats 15-minutes post-injection and at 30-minutes in HS, HF, and HFHS rats. The blood glucose levels decreased toward baseline levels, and this decrease appeared to be more rapid for CD and HS rats than for HF and HFHS rats. Statistical analysis partially confirmed these observations. Analysis revealed a significant main effect of chow ($F(1,56) = 4.178$, $p = .046$, $\eta^2 = .069$), a quadratic effect of time ($F(1,56) = 591.348$, $p < .001$, $\eta^2 = .914$), and a significant time x chow interaction ($F(5,280) = 3.588$, $p = .004$, $\eta^2 = .060$). However, there was no effect of sucrose access, and no time x sucrose access nor time x chow x sucrose access interactions (Fs < 1).

Figure 4.8.B shows the average area under the curve (AUC) for blood glucose concentration across the GTT. Observation of the figure suggests that the AUC for HF and HFHS rats was higher than the AUC for CD and HS rats. The AUC of HF and HFHS rats appears comparable, as does the AUC for CD and HS rats. These observations were confirmed by statistical analysis which revealed a significant effect of chow ($F(1,56) = 5.372$, $p = .024$, $\eta^2 = .088$), and no effect of sucrose access nor chow x sucrose access interaction (Fs <1).

The average plasma insulin concentration at baseline, and 15-minutes and 60-minutes post glucose bolus injection is shown in Figure 4.8.C. The figure shows that the plasma insulin concentration was higher in the HF and HFHS rats than the CD and HS rats at baseline after the 12-hour fast. However, baseline insulin concentration was comparable in the HF and HFHS rats, and comparable in the CD and HS rats. Statistical analysis confirmed a significant effect of chow ($F(1,35) = 11.380$, $p = .002$, $\eta^2 = .245$), and no effect of sucrose access nor chow x sucrose access interaction (Fs < 1). Plasma insulin concentration increased in all groups after injection of the glucose bolus, peaking at 15-minutes post-injection. The increase in plasma insulin concentration was greatest in HF rats. The HFHS rats also appear to have a greater increase in plasma insulin concentration than CD and HS rats, which appear to have a comparable insulin concentration. Statistical analysis confirmed a main effect of chow ($F(1,35) = 21.102$, $p < .001$, $\eta^2 = .376$), a significant quadratic effect of time ($F(1,35) = 32.266$, $p < .001$, $\eta^2 = .480$), and a significant chow x sucrose access interaction ($F(1,35) = 4.245$, $p = .047$, $\eta^2 = .108$). There was no effect of sucrose access and no time x chow access, nor time x sucrose access, nor time x chow x sucrose access interactions (Fs $\leq$ 1.995).

Figure 4.8.D shows the average AUC for plasma insulin concentration during the first 60-minutes of the GTT. The figure shows that the AUC for HF rats was larger than the AUC for CD, HS, and HFHS rats. The AUC for CD and HS rats appears comparable, while the AUC for HFHS rats appears to be lower than the AUC for HF rats. Statistical analysis confirmed a significant effect of chow ($F(1,35) = 18.556$, $p < .001$, $\eta^2 = .346$) and a significant chow x sucrose access interaction ($F(1,35) = 5.136$, $p = .030$, $\eta^2 = .128$). There was no effect of sucrose access ($F = 3.526$).
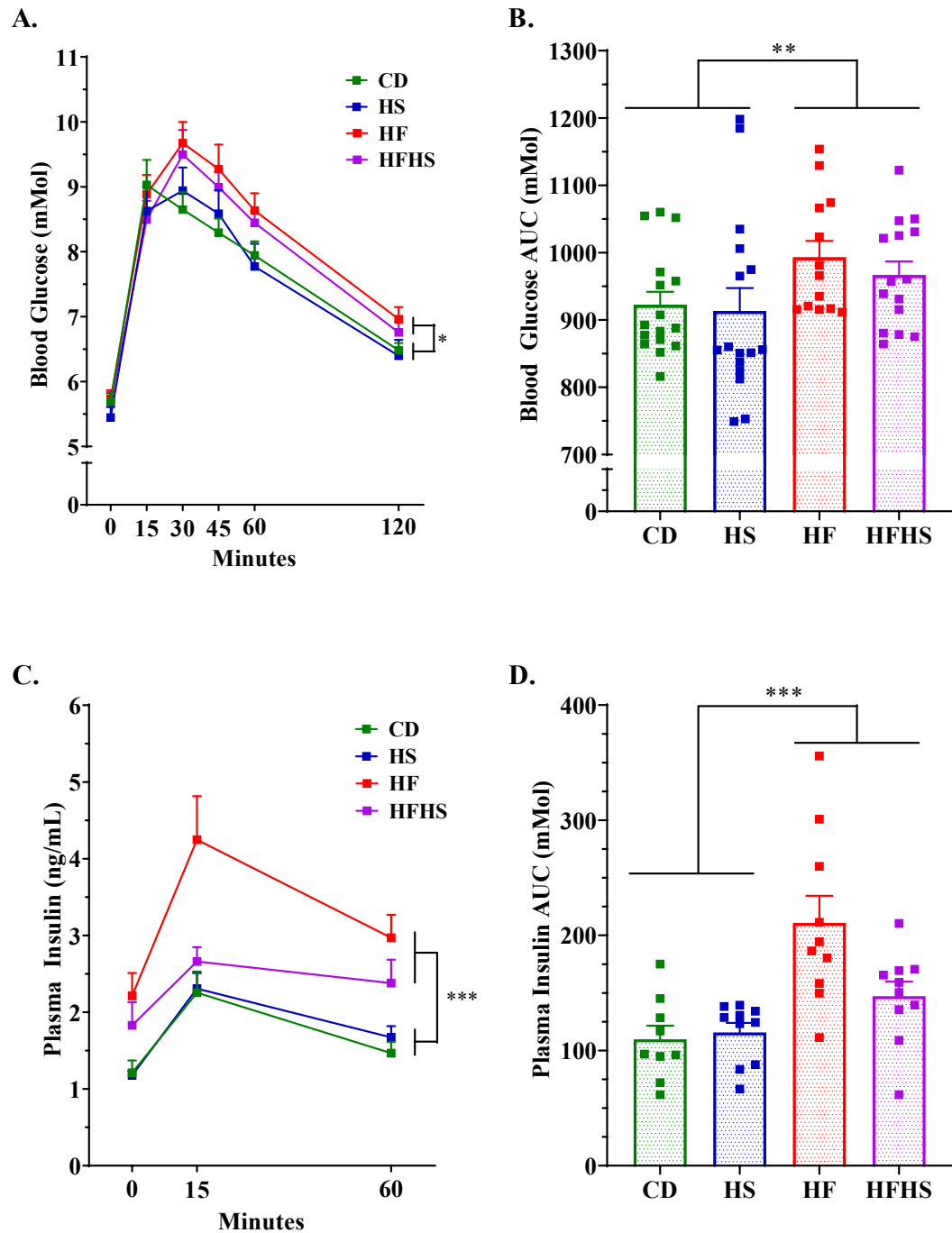
Figure 4.8. (A) Average blood glucose level across the glucose tolerance test (GTT). **(B)** Average area under the curve for blood glucose levels across the GTT. **(C)** Average plasma insulin concentration in the first 60-minutes of the GTT. **(D)** Average area under the curve for plasma insulin concentration during the first 60-minutes of the GTT. (CD = Control diet; HS = high-sugar diet; HF = high-fat diet; HFHS = high-fat high-sugar diet). ** $p \leq .01$, *** $p \leq .001$.

4.3.5. Pearson's Correlations

Pearson's correlations were used to examine the *a priori* prediction that blood glucose and plasma insulin concentration would correlate negatively with performance on the hippocampal-dependent memory tests. Statistical analysis revealed a significant positive correlation between blood glucose AUC and novelty preference on the place recognition test conducted in week five of diet access ($r = .542$, $p = .045$, n = 14; Figure 4.9.), but no correlation between plasma insulin AUC and place recognition novelty preference ($r = -.182$, $p = .666$, n = 8; Table 4.1). There were no correlations between blood glucose AUC or plasma insulin AUC and performance in the place recognition memory test for HS, HF, or HFHS rats (Table 4.1). There were also no correlations between blood glucose AUC or plasma insulin AUC and level of freezing in the CPFC memory test.
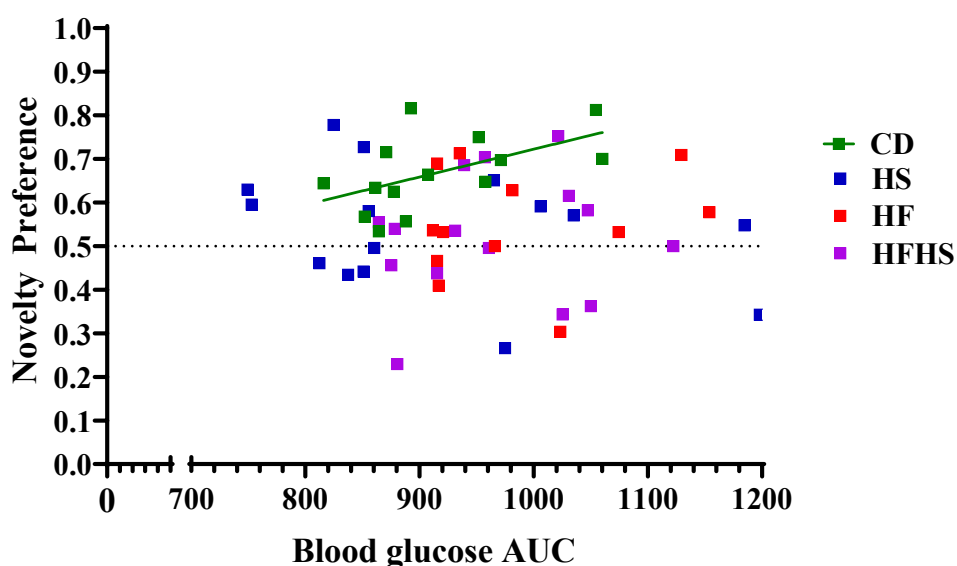
Figure 4.9. Pearson's Correlation between novelty preference in the place recognition memory test conducted in experiment week five and area under the curve (AUC) for blood glucose levels during the glucose tolerance test conducted in experiment week six. (CD = Control diet; HS = high-sugar diet; HF = high-fat diet; HFHS = high-fat high-sugar diet).

Table 4.1. Pearson's correlation between metabolic parameters and hippocampal-dependent cognition. Correlations were conducted between blood glucose area under the curve (AUC), plasma insulin AUC, novelty preference in the place recognition memory test, and context fear memory in the context pre-exposure fear conditioning test for rats fed control diet (CD), high-sugar diet (HS), high-fat diet (HF), and high-fat high-sugar diet (HFHS). * $p \leq .05$.

			Blood glucose AUC	Plasma insulin AUC	Novelty preference
CD rats	Plasma insulin AUC	r	.141		
		p-value	.717		
		N	9		
	Novelty preference	r	.542*	-.182	
		p-value	.045	.666	
		N	14	8	
	CPFC fear memory	r	.449	.217	.296
		p-value	.096	.605	.325
		N	15	8	13
HS rats	Plasma insulin AUC	r	.555		
		p-value	.096		
		N	10		
	Novelty preference	r	-.338	-.116	
		p-value	.218	.766	
		N	15	9	
	CPFC fear memory	r	-.094	.238	.098
		p-value	.739	.508	.740
		N	15	10	14
HF rats	Plasma insulin AUC	r	-.329		
		p-value	.387		
		N	9		
	Novelty preference	r	.142	.142	
		p-value	.659	.715	
		N	12	9	
	CPFC fear memory	r	-.338	-.114	-.066
		p-value	.259	.770	.831
		N	13	9	13
HFHS rats	Plasma insulin AUC	r	.636		
		p-value	.065		
		N	9		
	Novelty preference	r	.130	.63	
		p-value	.644	.653	
		N	15	10	
	CPFC fear memory	r	-.128	.114	.173
		p-value	.664	.754	.538
		N	14	10	15

4.4. Chapter 4 Discussion

By the end of the experimental period, HF and HFHS rats had gained significantly more weight and consumed significantly more energy than control and HS rats. There was no difference in body weight or total energy intake between HF and HFHS rats, nor between control and HS rats. These results indicate that consumption of the high-fat chow significantly increased body weight and total energy intake, and that access to the 10% sucrose solution had no effect on either of these measures. The increased body weight and energy intake observed in HF and HFHS rats compared to control rats is consistent with previous studies that have used a similar length high-fat diet (Alzoubi et al., 2013a, 2013b; Boitard et al., 2014; Jurdak et al., 2008; Pathan et al., 2008; Woodie & Blythe, 2018) and high-fat high-sugar diet (Kanoski & Davidson, 2010). The absence of an effect of sucrose solution on body weight and energy intake replicates the results observed in HS rats in experiment 2 in chapter 3 of this thesis, and is consistent with previous research that has used a similar duration of high-sugar diet (Woodie & Blythe, 2018).

Total energy intake was greater in HFHS rats than rats in the other dietary conditions which were similar to each other. A different pattern of energy intake was observed between rats consuming chow alone and rats consuming sucrose solution in addition to chow. For chow alone groups, energy intake was significantly greater in HF rats than control rats due to the increased energy content of the high-fat chow. Similarly, the HFHS rats procured significantly greater energy from chow than did the HS rats, however they procured significantly less energy from their chow source when compared to HF and control rats. Both the HS and HFHS rats procured similar energy from sucrose solution, indicating there was no influence of chow on the amount of sucrose solution consumed. The pattern of intake observed in the present experiment indicates HFHS and HS rats compensated for the energy obtained from sucrose solution by reducing their

energy intake from the solid chow diet. This replicates the findings of experiment 2 in chapter 3 of this thesis, and is in line with previous studies that have supplemented chow diet (Kendig et al., 2013; Abbott et al., 2016) or high-fat diet (Soto et al., 2015) with a 10-15% (w/v) sucrose solution.

Performance on the object recognition tests did not change between tests 1 and 2, and there were no differences in novelty preference between rats in the four dietary conditions. In the place recognition memory tests, however, the performance of HS, HF, and HFHS rats was significantly worse than control rats at both tests 1 and 2. There was no evidence of a difference in place recognition memory between the HS, HF, and HFHS rats nor evidence of a decrease in place recognition memory across the two tests. The novelty preference of control rats was significantly greater than chance in both tests, indicating successful discrimination of the novel object location. However, the novelty preferences of HS, HF, and HFHS rats did not differ from chance on either test, indicating that rats in these diet conditions were unable to discriminate the object moved to the new location from the one remaining in the old location.

The findings in the object and place recognition memory tests are consistent with the results obtained in experiment 1 of chapter 3 as well as those from previous studies using diets that are high in sugar or high in both fat and sugar (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b, 2018; Leigh et al., 2020a, 2020b; Tran & Westbrook, 2015, 2017). The results indicate that the consumption of any of these diets has no detectable effect on perirhinal-dependent object recognition memory but does impair the hippocampal-dependent spatial recognition memory. The results also suggest that the deficit in spatial memory does not differ as a function of consuming sugar or fat, either alone or in combination, and that the deficit does not worsen with longer diet exposure. It is important to note here that we are not suggesting a double dissociation in the effect

of diets high in fat, sugar, or both, across the two tests; rather, the results suggest that the effect of high-fat and/or high-sugar diets appear specific to hippocampal-dependent cognition.

The finding of a comparable deficit in place memory across the experimental diet conditions is consistent with previous research that has compared place recognition memory in rats consuming a diet high in fat, sugar, or both fat and sugar (Beilharz et al., 2014, 2016a, 2016b). It is also consistent with the results of the meta-analysis in chapter 2, which suggests that the effect size of the diet-induced impairment in hippocampal-dependent memory in rodents consuming high-fat and/or high-sugar diets is comparable. However, this finding is inconsistent with previous research that has failed to find consistent deficits between rodents exposed to high-fat and/or high-sugar diets in hippocampal spatial memory tasks including the MWM (Gergerlioglu et al., 2016; Jurdak et al., 2008) and spontaneous alternation task (Hargrave et al., 2015). The reason for the inconsistent finding of comparable deficits in HS, HF, an HFHS diet exposed rats across the place recognition memory test, MWM, and spontaneous alternation task is unclear. However, one reason may be that performance in these tasks is scored differently and these differences may result in floor and/or ceiling effects that mask true differences. For example, the MWM uses an interval variable (time) that has no "chance" level of performance to assess performance, whereas the place recognition memory test uses a ratio scale (novelty preference) that includes a "chance" level of performance; the rats in the present experiment performed at chance level in both place recognition memory tests, and this may confound the ability to detect differences in place memory across the HS, HF, and HFHS rats due to floor effects.

Previous research has provided mixed evidence of a worsening in place recognition memory in rats consuming high-sugar and high-fat high-sugar diets across

the first three-weeks of diet access (e.g. Beilharz et al., 2014, 2018; Tran & Westbrook, 2017). The present experiment failed to detect any worsening of this impairment between test 1 at four-weeks of diet exposure and test 2 at five-weeks of diet exposure. The absence of a worsening in the diet-induced impairment in place recognition memory is consistent with previous research in rats maintained on high-fat high-sugar diet; these studies demonstrated a stable diet-induced impairment in hippocampal-dependent place recognition memory across three-weeks of diet access (Tran & Westbrook, 2017) and spatial navigation through a radial arm maze across 90 days of diet access (Kanoski & Davidson, 2010). While the results of the present experiment suggest diet-induced impairments do not change across time, this interpretation should be treated with caution as the absence of a progressive worsening in place recognition memory is likely a consequence of floor effects. Future research that examines diet-induced changes in hippocampal dependent memory should be undertaken using behavioural tasks that are less likely to be influenced by floor effects, such as a spontaneous alternation task. Similar to the object and place recognition memory tests, the spontaneous alternation task relies on preference to explore novel over familiar environments. Consequently, this task does not require the use of appetitive or aversive motivators, and can also be undertaken at multiple time points during an experimental period by using a different maze for each test.

In the CPFC, rats in all diet conditions showed comparable levels of freezing in the shocked context and in the similar context. As the formation of a fear memory in CPFC has been shown to be dependent on the hippocampus (Matus-Amat et al., 2004; Rudy et al., 2002), the absence of a difference in freezing between control and experimental diet rats suggests that rats in all diet conditions formed a configural representation of the contextual cues during pre-exposure on day one, associated this

representation with shock on day two, and used this representation to retrieve the fear memory on day three. The intact formation of a context fear memory in HS, HF, and HFHS rats replicates the findings of previous research by Sobesky et al. (2014) that used a 42% high-fat diet, and extends the results of their research to diets that are high in sugar and both fat and sugar.

After six-weeks on their respective diets, there was considerable variation in blood glucose level and plasma insulin concentration across measures and between dietary conditions. Firstly, blood glucose levels after a 12-hour fast were comparable across all diet conditions, however plasma insulin levels were significantly greater in HF and HFHS rats than control and HS rats. The increased concentration of plasma insulin, but not blood glucose level, in the fasted HF and HFHS rats may be a consequence of chronic exposure to dietary fatty acids in the high-fat and high-fat/high-sugar diets, which have been demonstrated in previous research to increase basal insulin secretion (Bollheimer, Skelly, Chester, McGarry, & Rhodes, 1998). The concentration of circulating dietary fatty acids was not assessed in the present experiment and should be undertaken in future research to examine this hypothesis.

Secondly, HF and HFHS rats had higher blood glucose and plasma insulin levels than control and HS rats in the GTT. The results obtained from the GTT suggest that consumption of high-fat chow, but not sucrose solution, resulted in altered insulin sensitivity that may have contributed to impaired metabolism of a glucose load. The influence of fat, but not sugar, on blood glucose and insulin concentration is consistent with a growing body of evidence which suggests that high-fat or high-fat and high-sugar diets result in earlier and more pronounced metabolic impairments than high-sugar diets (Matias et al., 2018; Perazza et al., 2020; Ramos-Romero et al., 2018; Rodríguez-Correa, González-Pérez, Clavel-Pérez, Contreras-Vargas, & Carvajal, 2020; Small, Brandon,

Turner, & Cooney, 2018), which may be a consequence of fat-induced increases in adiposity and circulating free fatty acids that stimulate insulin secretion and induce beta-cell apoptosis (Boden, 2003; Boland, Rhondes, & Grimsby, 2017).

Finally, the correlations between the AUC of blood glucose level and AUC of plasma insulin concentration were not significant for any dietary condition. However, there was a trend toward correlation for rats consuming the high-sugar and high-fat/high-sugar diets. This suggests that the relationship between blood glucose level and plasma insulin levels may only be present in subjects when the diet intervention contains a high-sugar component. Importantly, however, these correlations are based on a low sample size, and the data may be underpowered. As such, future research should be conducted to examine the association between blood glucose and plasma insulin in diet-exposed rats.

Examination of the correlations between measures of glucose metabolism and cognition revealed that the blood glucose AUC during the GTT was positively correlated with performance on the place recognition test conducted in week five in control rats. However, there were no correlations between blood glucose AUC or plasma insulin AUC and hippocampal-dependent memory in HS, HF, and HFHS rats. This suggests that blood glucose levels may mediate performance on the place recognition memory tasks in control rats fed chow but not in rats fed the high energy diets. However, it may also be the case that the observation of a positive association between blood glucose level and memory performance in control rats, but not high energy diet rats, reflects a Type I error. While this possibility cannot be discredited, the observed relationship is consistent with the notion that blood glucose levels play an important role in memory function (Benton & Owens, 1993; Stollery & Christian, 2015), and replicates experimental research that demonstrates improved spatial memory function upon the administration of glucose in both humans (e.g. Mohanty & Flint, 2001; Stollery & Christian, 2016) and rodents (e.g.

Greenwood & Winocur, 2001; Winocur & Gagnon, 1998). The consistency between the results reported in the present experiment and that in the available experimental literature suggests that it is unlikely that a Type I error has occurred here.

The finding of no correlation between measure of glucose metabolism and cognition fail to replicate those reported by Beilharz et al. (2014), who found a negative correlation between plasma insulin and performance on the place recognition memory test, and those reported by Jurdak et al. (2008), who found a negative correlation between glucose AUC and escape latency in the Morris water maze. The failure to replicate these associations may reflect differences in metabolic outcomes due to the use of different dietary manipulations that vary significantly in their macro- and micronutrient content. Specifically, Beilharz et al. used a dietary manipulation consisting of store-bought "junk" foods (e.g. cakes, biscuits, pies, and dim sums) and Jurdak et al. used a manipulation consisting of standard chow supplemented with a 32% sucrose solution; these diets contrast considerably with the nutritionally complete semi-purified high-fat diet and 10% sucrose solution supplement to chow utilised in the present experiment. Previous research has demonstrated variable metabolic responses in rodents exposed to diets that differ in their composition of macronutrients and micronutrients, as well as to diets that differ in their sources of fat and sugar (Bollheimer., 2006; Buettner, Schölmerich, & Bollheimer, 2007; Hintze, Benninghoff, Cho, & Ward, 2018; Rodríguez-Correa et al., 2020; Sadowska & Bruszkowska, 2019). Hence, the failure to replicate the correlation between blood glucose or plasma insulin and performance in hippocampal-dependent memory tests may reflect the intrinsic variability in this assay due to different impact of diet composition on metabolic parameters.

Finally, a notable finding from the present experiment is that despite all experimental diet groups showing a deficit in hippocampal-dependent place recognition

memory, diet-induced changes in body weight, fasted blood glucose level, and insulin sensitivity in the GTT were only observed in rats consuming high-fat or high-fat/high-sugar diet, but not high-sugar diet alone. This suggests that if the effect of diet on body weight and glucose metabolism may mediates the diet-induced impairments in hippocampal-dependent cognition, it is unlikely that this is the driving factor across all diet conditions. Further examination of this should be undertaken in future studies.

4.4.1. Conclusion

The results of the present study suggest that consumption of high-sugar and/or high-fat diet negatively impacts the hippocampal substrates that mediate place memory, while leaving the substrates that mediate hippocampal configural processing relatively intact. The results further suggest that such diets produce comparable impairments in hippocampal place memory, and that these impairments are relatively stable after four-weeks of diet access; however, these findings may be an artefact of the task used to assess place memory, thus the conclusions should be treated with caution. Finally, the results suggest that performance on the object and place recognition memory tasks are not mediated by blood glucose levels in rats consuming a high-sugar and/or high-fat diet. The results also demonstrate that high-fat, but not high-sugar, intake disrupts insulin action.

Chapter 5: General Discussion

5.1. Summary of main findings

The present thesis examined the effect of relatively short-term, high-fat and/or high-sugar diet consumption on hippocampal-dependent cognition in rats. It began by asking whether the discrepant findings from studies that have examined the relationship between short-term dietary interventions and cognitive impairment using spatial memory tasks were due to differences in experimental design (chapter 2). It attempted to answer this question by subjecting these studies to a meta-analysis, specifically assessing the contribution of the type of diet and/or task. The meta-analysis confirmed that a brief exposure to a diet high in fat and/or sugar, lasting two-months or less, impairs performance in a number of hippocampal-dependent spatial memory tasks. It also revealed that all dietary manipulations yielded medium effect sizes. Although unable to make direct comparisons, the size of the hedge's *g* indicated that the largest diet effect was produced by diets high in fat and sugar, followed by high-fat and high-sugar diets. The analysis also revealed a dietary effect on all the hippocampal-dependent tasks with a large effect size observed in the radial arm or radial water mazes, and medium effect sizes in the MWM, spontaneous alternation, and place recognition memory tasks.

The experimental work involved exposing rats to diets high in either fat, sugar or both fat and sugar. This showed that rats fed high-fat chow had significantly greater weight gain, total energy intake, and blood glucose levels and plasma insulin levels in a GTT, than rats consuming standard chow (chapter 4). Rats provided with access to the sucrose solution reduced their intake of chow. However, sucrose consumption had mixed effects on body weight and total energy intake; apart from experiment 1 (chapter 3) where it increased body weight and energy intake, the provision of sucrose failed to change body weight or energy intake relative to control rats just fed chow in most of the experiments

(e.g. experiment 2, chapter 3; chapter 4). As diet-induced changes in body weight gain, energy intake, and metabolic parameters have already been discussed in detail each experimental chapter, these finding will not be discussed in further detail here.

Rats maintained on a high-sugar, high-fat, or high-fat high-sugar diet for four or five-weeks exhibited impaired spatial memory, as indexed by a lower novelty preference in the short-term place recognition memory test than control rats fed chow. This preference among rats fed the high-sugar diet in experiment 1 of chapter 3 was significantly different from chance, indicating that such rats retained some ability to discriminate between the novel and familiar locations. In contrast, the novelty preference among rats fed any of the high energy diets (high-sugar, high-fat, or high-fat high-sugar) in chapter 4 did not differ from chance, indicating that they were unable to discriminate the novel and familiar locations. The place recognition test in chapter 4 also revealed that the impairment in spatial memory remained stable across two tests conducted one week apart, and was comparable across the three experimental diet conditions.

Finally, there was mixed evidence of an effect of high-sugar, high-fat, and high-fat high-sugar diet on hippocampal-dependent configural representations of context. In the context fear generalisation task (chapter 3), HS rats did not differ from control rats in their generalisation of a context fear memory, as indexed by similar levels of freezing in both the conditioning and similar contexts, when a between-subject design was used. However, when a within-subject design was used, there was evidence that HS rats exhibited increased generalisation of context fear when rats were first tested in the similar context then the conditioning context, but not when HS rats were tested in the opposite order. In the context pre-exposure fear conditioning test (chapter 4), HS, HF, and HFHS rats showed comparable levels of freezing as control rats at test, indicating that rats fed the high energy diets were just as able as those fed chow to form a context fear memory.

5.2. Diet-Induced Cognitive Impairments

5.2.1. Interpretation of Meta-analysis Findings

A detailed discussion of the meta-analysis findings has been provided in chapter 2, thus only a brief discussion is presented here. The meta-analysis revealed that rats fed a diet either high in fat, sugar or both fat and sugar were impaired in spatial learning and memory tasks relative to control rats fed a chow diet that was typically starch based and low in saturated fat and sugar. Each of the three types of high energy diets produced an impairment that was of medium effect size. The impairment was observed across all the tasks used to assess spatial learning and memory, with a large effect size in studies using the radial arm and radial water maze and a medium effect size in those using the MWM, place recognition, and spontaneous alternation tasks. These findings suggest that differences in the composition of the diet and/or the behavioural task used to assess the dietary effects on spatial learning and memory are unlikely to be the single or primary factor responsible for the inconsistent findings in the literature. Rather, the inconsistent findings are likely a consequence of procedural differences in the tasks used to assesses spatial cognition. For example, studies using the MWM differed in whether the rats were familiarised with swimming prior to training, the inclusion of visible platform trials before hidden platform trials, the number of acquisition training sessions, the number of trials per acquisition session, the length of an acquisition trial, the intertrial interval (ITI), the intersession interval, the time between final acquisition trial and probe test, and the length of probe test.

Such procedural differences can affect what the rats learn in the maze. For example, an important procedural variable for successful spatial memory acquisition is the duration of the interval between trials. A routine finding is that long intervals, "spaced training", leads to more robust memory than shorter intervals, "massed training" (Smolen,

Zhang, & Byrne, 2016), in both rats (see Commins, Cunningham, Harvey, & Walsh, 2003) and mice (see Genoux et al., 2002). Consistent with this evidence, spaced trials produce better memory than massed ones in the Morris water maze (e.g., Porte, Buhot, & Mons, 2008) and place recognition tasks (e.g. Seese, Wang, Yao, Lynch, & Gall, 2014). Such differences in training protocols are likely to contribute to the inconsistent evidence of a relationship between high-fat and/or high-sugar diets and cognitive impairment.

Procedural variations can also affect the reliance on the hippocampus for successful performance, and thus increase or decrease the likelihood of detecting high-fat and/or high-sugar diet-induced cognitive impairments (e.g., Tran & Westbrook, 2017; Vorhees & Williams, 2006, 2014). For example, a considerable body of research suggests that the hippocampus is critical for successful performance in tasks that can only be solved based on recollection (or recall) processes, whereas tasks that can be solved based on familiarity processes are supported by cortical regions such as the perirhinal cortex (see Fortin, Wright, & Eichenbaum, 2004, and Sauvage, Fortin, Owens, Yonelinas, & Eichenbaum, 2008). Tran and Westbrook (2018) have recently demonstrated that rats fed a high-fat high-sugar diet comprised of store-bought discretionary foods are impaired in their ability to detect novelty in an object recognition memory task. Performance in this task is typically unaffected by high energy diets (e.g., Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b, 2018; Leigh et al., 2020a, 2020b; Tran & Westbrook, 2015, 2017). These differences in the effects of a high energy diet on object recognition may be due to whether recollection- or familiarity-based judgements are required for successful performance. In the study by Tran and Westbrook, the test objects were equally familiar but differed in their relative recency, rather than relative novelty. Under these conditions, successful performance involved rats recalling which object they had explored more recently, whereas the task demands in a standard object recognition memory test simply

requires rats to detect whether an item has or has not been encountered before (i.e. a familiarity-based judgement). Tran and Westbrook found that rats maintained on a high-fat high-sugar diet for three-weeks were able to successfully discriminate the novel and familiar objects in a standard object recognition memory task, but were unable to discriminate the remote and recent objects in the object recency memory task. These results demonstrate that the diet impaired rats object recognition memory when performance was based on hippocampal-dependent recall processes, but had no impact when performance was based on hippocampal-independent familiarity processes. Such findings therefore demonstrate that manipulation of task demands can change the reliance on a functioning hippocampus, and thus change the likelihood of detecting diet-induced cognitive impairments.

Similarly, the flexible use of allocentric (i.e. world-centred), but not egocentric (i.e. body-centred), navigation in a spatial memory task is mediated by the hippocampus (see Grech, Nakamura, & Hill, 2018; e.g. McDonald & White, 1994; Packard & McGaugh, 1996). For example, Rinaldi et al. (2020) trained mice to navigate through a four-arm cross-maze for a food reward using either an allocentric or an egocentric navigation strategy, and found that expression of the immediate early gene *Zif-268* was increased in the hippocampus of mice trained using allocentric navigation strategies but not in mice trained using egocentric navigation strategies. Hargrave et al. (2016) reported that rats fed a high-fat high-sugar diet shifted from an allocentric "place" navigation strategy to an egocentric "response" strategy to locate a food reward in a Y-maze task. Together, these studies demonstrate another way in which procedural variations that influence rodents' ability to use different navigation strategies to successfully perform a task can influence the involvement of the hippocampus and, consequently, affect the ability to detect diet-induced impairments in a spatial memory task.

While procedural differences in the assessment measures are likely responsible for the inconsistencies reported in the literature, there are a number of other biological variables that may account for the observed relationship between diet and cognition that were not examined in the meta-analysis. For example, rats and mice, as well as different strains within these species, can perform differently on hippocampal-dependent behavioural tasks (see Hok, Poucet, Duvelle, Save, & Sargolini, 2016; Keeley et al., 2015). Similarly, sex differences in hippocampal-dependent spatial learning and memory are well documented in both humans and rodents (reviewed in Keeley et al., 2015; Koss & Frick, 2017; Yagi & Galea, 2018). These differences in species, strain, and/or sex, could interact with dietary manipulations to affect performance on hippocampal-dependent tasks (e.g. Abbott et al., 2016; Bollheimer., 2007; Kendig et al., 2014; Stöckli et al., 2017; West et al., 1992, 1995). There is also evidence that adolescents may be more susceptible to the effects of dietary manipulations on hippocampal-dependent learning and memory than adults (see Noble & Kanoski, 2016), and that rodents with greater susceptibility to diet-induced body weight gain are more susceptible to diet-induced impairments than rodents that are not susceptible to body weight gain (e.g. Kanoski et al., 2010; Kanoski & Davidson, 2010; Hargrave et al., 2016; McNay et al., 2010). A qualitative analysis of the studies included in the meta-analysis yielded equivocal evidence that such variables contributed to inconsistencies in the literature; but such variables could well be involved.

One way to provide a quantitative measure of the impact of these variables is through the use of a meta-regression analysis. This is a subgroup analysis that allows the effect of both continuous and categorical variables to be investigated simultaneously and therefore allows researchers to examine the impact of covariates (moderators) on the effect size for the relationship between diet and cognition, using regression-based

techniques (Bellavance, Dionne, & Lebeau, 2009; Stanley & Jarrell, 2005). Covariates of interest can be included as continuous variables (e.g. age, biological factors such as body weight and metabolic parameters, concentration of dietary fat and/or sugar, diet duration, procedural details for assessment measures) or categorical variables (e.g. sex, diet type), and thus allow for the role of a broad range of covariates to be examined.

Meta-regressions have several advantages over meta-analyses (see Tatsioni & Ioannidis, 2017). One is that meta-regressions show whether covariates explain any of the heterogeneity of dietary effects on cognition between studies. Hence, they could be used to determine whether inconsistencies within the rodent diet literature are due to factors such as the biological variables of age, sex, species/strain, or body weight play a role above the dietary components alone. The meta-regression could also determine whether the type and concentration of fat or sugar consumed, or the length of diet exposure are critical variables in diet exposure. A second advantage of using a meta-regression analysis is that it would allow variables that were excluded in the present meta-analysis, such as diet duration and age of diet access, to be included as co-variates. This would increase the number of studies in the meta-regression, improving the reliability and validity of the analysis (Thompson & Higgins, 2002). Most critically, however, the meta-regression would allow for assessment of the heterogeneity within the diet literature that arises from procedural differences across spatial memory tasks, and thus help to identify the conditions under which high-fat and/or high-sugar diet induced cognitive impairments are observed.

5.2.2. Interpretation of Experimental Findings

The thesis also examined the influence of high-fat and/or high-sugar diet on hippocampal-dependent configural processing of contextual cues. It did so by using two Pavlovian conditioning tasks in which successful performance has been demonstrated to

be dependent on an intact hippocampus: a context fear generalisation test (chapter 3; Frankland et al., 1998) and a context pre-exposure fear conditioning test (chapter 4; Fanselow, 1986, 1990). Object and place recognition memory tests were conducted prior to these tasks in two of the three experiments (experiment 1 of chapter 3 & chapter 4) to confirm that the dietary manipulation had selectively impaired spatial cognition. The object and place recognition memory tests were selected for two reasons; firstly, lesioning and inactivation studies have demonstrated performance to be dependent on the perirhinal cortex and hippocampus, respectively (Barker, Bird, Alexander, & Warburton, 2007; Mumby, Gaskin, Glenn, Schramek, & Lehmann, 2002). Secondly, these tests rely on a rodent's natural tendency to explore novelty and therefore successful performance does not require the use of aversive or appetitive motivators that may interact with the experimental diets to influence cognition (e.g., Bartolomucci et al., 2009; Sobesky et al., 2014).

The results of the recognition memory tests confirmed that rats maintained on a high-sugar diet (chapters 3 & 4), high-fat diet (chapter 4), or high-fat high-sugar diet (chapter 4) exhibited a selective impairment in hippocampal-dependent spatial memory, as evidenced by poorer performance than control rats in the place recognition memory test but comparable performance in the perirhinal-dependent object recognition memory test. The dissociable effect of the experimental diets on object and place recognition memory observed in the present thesis replicates the pattern of results reported by previous research that has used these recognition memory tests to assess the relationship between diet and cognition. Such studies have reported disrupted place, but not object, recognition memory in rats fed a high-sugar diet (Abbott et al., 2016; Beilharz et al., 2014, 2016a, 2016b), high-fat diet (Beilharz et al., 2016a), or high-fat high-sugar diet (Beilharz et al., 2014, 2016b 2018; Leigh et al., 2020a, 2020b; Kendig, Westbrook, & Morris, 2019;

Tran & Westbrook, 2015, 2017) for durations lasting a few days (Beilharz et al., 2014, 2018; Tran & Westbrook, 2015, 2017), two to three-weeks (Abbott et al., 2016; Beilharz et al., 2016a, 2016b; Kendig et al., 2019; Leigh et al., 2020a, 2020b; Tran & Westbrook, 2015, 2017), or six-weeks (Leigh et al., 2020a, 2020b; Tran & Westbrook, 2017). Furthermore, the deficits in place recognition memory are consistent with the results of the meta-analysis; specifically, these findings demonstrate that high-fat and/or high-sugar diets produce an impairment in hippocampal-dependent spatial memory, and that diet-induced deficits are comparable regardless of whether fat and sugar is consumed alone or in combination. Importantly, the impairment in hippocampal-dependent spatial memory was not a consequence of a lack of motivation or altered locomotion behaviour, as rats in the experimental diet conditions spent equivalent amounts of time exploring the objects at test as the control rats. Thus, the selective deficit in place recognition memory observed in experimental rats in chapters 3 and 4 suggests that consumption of high-fat and/or high-sugar diet disrupted the neural substrates within the hippocampus that mediate spatial learning and memory, while leaving the neural substrates within cortical regions that mediate object memory intact.

Despite evidence of an impairment in hippocampal-dependent spatial memory, there was mixed evidence of an effect of the dietary manipulations on the formation and use of a hippocampal-dependent configural representation of context. In the context fear generalisation tests (chapter 3), the between-group design revealed that rats fed sugar or chow showed more fear (freezing) when tested in the conditioned context than in the similar, non-conditioned context; but there was no interaction between diet and context, indicating there were no differences between control and sugar fed rats in fear generalisation. However, the within-subject design in experiment 2 suggested an order effect such that the sugar fed rats generalised more when tested in the similar context then

the conditioned context, as indexed by a discrimination ratio that did not differ from chance, but not when they were tested in the opposite order. Furthermore, in the context pre-exposure fear conditioning test (chapter 4), rats fed a high-fat, high-sugar, or a high-fat high-sugar diet did not differ from rats fed chow when tested in the conditioned context, suggesting that all groups were able to form the configural representation of context during pre-exposure that is required for subsequent association with foot shock.

The evidence of increased fear generalisation in rats that were tested first in the similar context and then in the previously shocked context (experiment 2, chapter 3) is consistent with previous research that has examined context fear generalisation in hippocampal-lesioned rats (Antoniadis & McDonald, 1999, 2000) and mice (Frankland et al., 1998). However, the absence of fear generalisation in the sugar fed rats tested using a between-subject design (experiment 1, chapter 3) and tested in the shocked context and then in the similar context (experiment 2, chapter 3) does not replicate these previous findings (Antoniadis & McDonald, 1999, 2000; Frankland et al., 1998). Similarly, the ability of rats fed the high energy diets to form a context fear memory that was comparable to that of control rats on the context pre-exposure context conditioning test (chapter 4) is not consistent with the results of previous experiments in rats with hippocampal lesions or subjected to hippocampal inactivation (Chang et al., 2008; Matus-Amat et al., 2004; Rudy et al., 2002). However, this result does replicate the performance of rats consuming a high-fat diet (42% energy from fat) for 12-weeks prior to the context pre-exposure conditioning (Sobesky et al., 2014). Taken together, the results from the place recognition memory tests and the Pavlovian conditioning studies suggest that the high-fat and/or high-sugar diet-induced impairment in spatial memory may not extend to configural processing of context.

Evidence from lesioning and inactivation studies demonstrates that spatial memory in the place recognition memory test (Mumby et al., 2002), context discrimination in the fear generalisation test (Antoniadis & McDonald, 1999, 2000; Frankland et al., 1998), and the formation of a context fear memory in the context pre-exposure test (Chang et al., 2008; Matus-Amat et al., 2004; Rudy et al., 2002; Rudy & O'Reilly, 1999) are dependent on an intact hippocampus. Thus, there are a number of possible explanations for the results obtained in the experimental chapters of this thesis. The first is that the experimental diet did impair hippocampal-dependent configural processing and that experimental rats were able to use cortical-dependent elemental representations of context to guide their performance in the Pavlovian conditioning tests. This hypothesis can be readily applied to the results of the fear generalisation tests in chapter 3. In these tests, rats were given two intermixed pre-exposures to the conditioning (A) and similar (B) contexts prior to fear conditioning. Elemental accounts of discriminative learning propose that repeated, intermixed pre-exposure to two or more compound stimuli (e.g. AX → BX → AX → BX) that are comprised of unique (A and B) and common (X) features alters the elements selected for attentional processing (Gibson, 1969; Mitchell, Nash, & Hall, 2008). According to such accounts, attention paid to the common features (X) declines relative to the attention paid to the unique features, because the common features are presented twice as frequently. Subsequent discrimination between reinforced AX trials and non-reinforced BX trials is therefore enhanced because attention is directed at the unique features (A and B) rather than the common features, allowing positive associations to be formed between A and the reinforcer and negative ones between B and non-reinforcement (see Lavis, Kadib, Mitchell, & Hall, 2011). The two contexts used in the fear generalisation tests differed on a number of cues and rats received multiple exposures to these contexts, potentially

contributing to the use of elemental strategies for successful context discrimination by experimental rats.

However, the explanation that rats were able to use an elemental strategy to form a context fear memory in the context pre-exposure study is more difficult to support. The literature demonstrates that hippocampally lesioned rats are unable to form a fear memory in this task (Chang et al., 2008; Matus-Amat et al., 2004; Rudy et al., 2002). Furthermore, Rudy and O'Reilly (1999) demonstrated that hippocampal intact rats that receive pre-exposure to the individual elements of a conditioning context separately are unable to form a context fear memory in the task. These results suggest that conditioning in the context pre-exposure task does not accrue to the individual elements of the context, but rather only accrues to a configural representation of all of the cues. Thus, it is unlikely that rats maintained on high-sugar, high-fat, or high-fat high-sugar diet would be able to use elemental representations of context to form a fear memory comparable to that observed in the control rats.

Nevertheless, there is one procedural variable that may have supported the use of elemental representations by experimental rats in the context pre-exposure task. This is the use of two shocks, rather than a single shock, during conditioning. Two shocks were selected based on previous findings in which rats exhibited conditioned fear to a pre-exposed context rather than an immediately shocked context (Bae, Holmes & Westbrook, 2015). However, the context pre-exposure effect has typically been observed using a single shock. Moreover, fear conditioning is greater in rats conditioned with two shocks than rats conditioned with a single shock (Landeira-Fernandez et al., 2006). Similar findings have been reported in research using hippocampal lesioned rats (e.g., Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006). In the study by Wiltgen et al., rats received dorsal hippocampus or sham lesions prior to standard context fear conditioning

with a single shock delivered 48 seconds after placement into the context or three shocks delivered at equal intervals across the 48 second conditioning period. At test, Wiltgen et al. found that sham rats exhibited significantly greater freezing than lesion rats in the single-shock condition but sham and lesion rats performed equivalently in the three-shock condition. These results suggest that increasing the number of shocks delivered at conditioning produces a stronger fear memory in both hippocampal intact and lesioned rats. Importantly, the length of the conditioning procedure used by Wiltgen et al. (48 seconds) is similar to the timeline used in the present experiment (approximately 36 seconds). Thus, the use of two shocks in the present context pre-exposure study may have supported formation of a context fear memory in experimental rats that used a cortical-dependent elemental representation of context. One caveat, however, to this explanation is that the time interval between the two shocks was brief, lasting 0.5 seconds; as such, the rats may not have treated the two shocks as separate events but as a single (intense) shock.

There are two ways to assess the hypothesis that rats consuming the high-sugar, high-fat, or high-fat high-sugar diets used elemental representations in the Pavlovian conditioning tests. The first is to replicate the context fear generalisation test using a single, or even no, pre-exposures to the conditioning and similar contexts. Reducing the number of pre-exposure sessions would minimise rats experience with the two contexts, and thus remove the opportunity for rats to alter their attentional processing of the unique (A and B) and common (X) features. Hence, if the ability of experimental rats to discriminate the contexts was a consequence of shifting their attention to the unique features of each context, it would be expected that experimental rats would show increased generalisation to the similar non-conditioned context relative to control rats if one, or no, pre-exposure sessions were used. A second way to assess the hypothesis is to

replicate the context pre-exposure fear conditioning test using a single shock during conditioning. As demonstrated by Wiltgen et al. (2006), rats with hippocampal lesions are unable to form a context fear memory when a single shock is delivered during conditioning. Thus, if the ability of experimental rats to form a context fear memory was a consequence of the use of two shocks, it would be expected that experimental rats would show a reduced context fear memory relative to control rats when a single shock was used.

A second, and perhaps more likely, explanation of the Pavlovian conditioning results is that the experimental rats formed configural representations of context, but that these representations differed from those of control rats. One hypothesis is that the representations differed quantitatively; that is, experimental rats formed representations albeit less efficiently (e.g., more slowly) than control rats. Such a hypothesis can be readily applied to the results of the context fear generalisation tests. Research has demonstrated that hippocampal-intact rats acquire a context fear memory after as little as 20-seconds of exposure to a conditioning context in a standard fear conditioning test (Fanselow, 1986, 1990). Thus, the two pre-exposures to the conditioning and similar contexts would presumably provide experimental rats with multiple opportunities to form a distinct configural representation of the conditioning and similar contexts that could be used to discriminate between the two contexts at test. The hypothesis can also be applied to the context pre-exposure test results. The four-minute pre-exposure to the conditioning context in this study may have provided rats with sufficient time to form a configural representation of the context that can support the formation of a context fear memory.

One way to examine the hypothesis that rats consuming high-fat and/or high-sugar diet use a quantitatively different (i.e., less efficient) process for context learning than control rats is to compare the slope of the placement-to-shock function between the

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experimental and control rats (Fanselow, 2010). A longer placement-to-shock interval results in better context fear conditioning than a short one (e.g. Fanselow, 1986, 1990; Kiernan & Westbrook, 1993; Wiltgen et al., 2006). This phenomenon is attributed to the longer interval providing rats sufficient time to explore the multiple individual context cues and form a configural representation of the context that enters into association with the shock (Fanselow, 1986). Wiltgen et al. demonstrated that hippocampal intact and lesioned rats show parallel placement-to-shock functions, but that hippocampal lesioned rats show a rightward shift in the function. This rightward shift indicates that hippocampal lesioned rats require longer pre-exposures to form a sufficient representation of a context that can be used in associative learning. Thus, if rats maintained on high-fat and/or high-sugar diet retain the ability to form a configural representation of context, but do so less efficiently than control rats, it would be anticipated that a rightward shift in the placement-to-shock function would similarly be observed.

A second hypothesis is that experimental rats formed a configural representation of context that was qualitatively different to that formed by the control rats. Pearce and colleagues have proposed that one the most critical roles of the hippocampus in formation of a configural representation of context is the processing of the spatial relationship between the elemental features (Aggleton & Pearce, 2001; George, Ward-Robinson, & Pearce, 2001; George & Pearce, 2003; Haselgrove, George, & Pearce, 2005). Support for this proposal can be found in a number of recently published functional magnetic resonance imaging (fMRI) studies that have examined the role of the hippocampus in context fear conditioning in humans (see Glenn, Risbrough, Simmons, Acheson, & Stout, 2018). These studies used a context fear conditioning paradigm that included two feature-identical virtual reality scenes (i.e. contexts) that differed in the arrangement of the features. This procedure is designed such that discrimination between the conditioning

context (CS+) and a neutral control context (CS-) cannot be achieved using an elemental approach or a feature-alone configural approach; rather, participants are required to process the unique spatial relationship between the features to form a spatially configured context representation. The results of these studies demonstrated that fear responding, as indexed by skin conductance responses (SCRs), was significantly greater in the CS+ trials than the CS- trials, and that the increased SCRs were associated with increased activation of the hippocampus during CS+ trials than CS- trials (Baeuchl, Meyer, Hoppstädter, Diener, & Flor, 2015; Stout et al., 2018; Stout, Glenn, Acheson, Simmons, and Risbrough., 2019).

Stout and colleagues (2018, 2019) have demonstrated that the demands placed on configural processing of spatial information influence whether the hippocampus is recruited during context fear conditioning. In the first study, Stout et al. (2018) examined hippocampal activation during context fear conditioning in feature-identical contexts (configural condition) or contexts comprised of a single element (elemental condition). Stout et al. demonstrated that SCRs were significantly greater in the CS+ trials than the CS- trials for both the configural and elemental conditions. However, a significant increase in hippocampal activation during CS+ trials when compared to the CS- trials was only observed in the configural condition. In the second study, Stout et al. (2019) examined how manipulating the demand placed on configural processing of the spatial relationship between elements influenced hippocampal activation. In this study, all contexts were comprised of multiple features, and differed in terms of how many features overlapped between the CS+ and CS- contexts. The results demonstrated that hippocampal activation was greatest in conditions that placed high demand on configural processing (i.e. feature-identical CS+ and CS- contexts) and lowest in conditions that placed low demand on configural processing (i.e. different discrete elements between the

CS+ and CS- contexts). Taken together, these results suggest that the hippocampus plays a role in the formation of configural representations of context, but is particularly important for processing and incorporating the spatial structure of the context into these representations. Thus, rats consuming a high-fat and/or high-sugar diet may have formed spatially deplete representations of context that are sufficient to support acquisition of a context fear memory in the context pre-exposure test (chapter 4) and discrimination between contexts in the fear generalisation test (chapter 3).

The hypothesis that rats fed the high energy diets form a qualitatively different representation of context compared with control rats may account for the apparent dissociable effect of high-fat and/or high-sugar diet on spatial memory in the place recognition memory test and configural processing in the two Pavlovian fear conditioning tests. The place recognition memory test and the Pavlovian conditioning tests may differ in the cognitive demands placed on the rats. The primary difference is the type of information that needs to be processed for successful memory formation. The place recognition memory task requires rats to use geometric (i.e. spatial) information, such as distance and angles between objects and between objects and the arena wall, to learn the location of the objects at familiarisation and thus discriminate when one of the objects has been moved at test (Doeller, King, & Burgess, 2008; Poulter, Kosaki, Sanderson, & McGregor, 2020). In contrast, the Pavlovian fear conditioning tests require rats to bind contextual cues - such as smell, texture, illumination, colour, and shape – into a unified representation that can be rapidly retrieved for associative learning (chapter 4) or for discrimination between similar contexts (chapter 3). While geometric information is present within the contexts used for Pavlovian conditioning, featural cues are available for configural processing; such cues are not, however, available in the place recognition memory test. Thus, rats that process the featural context cues but not the geometric cues

would presumably form a configural representation of context, albeit one that is spatially impoverished when compared to the representation formed by control rats. Nevertheless, the feature-alone configural representation would presumably be sufficient for use in associative learning and discrimination between the two contexts, and thus support the performance of rats in the context pre-exposure and context fear generalisation tests, respectively.

In support of this explanation, Tran and Westbrook (2015) have previously demonstrated a selective impairment in the use of geometric information, with sparing of the use of featural information, in rats exposed to a high-fat high-sugar diet for three-weeks. Rats completed a place recognition task in three arenas: a standard arena, comprised of uniform black walls; a cued arena, comprised of four differentially patterned walls that provided a unique featural cue in each corner of the arena; and a scrambled arena, comprised of the same pattern features as the cued arena however arranged in such a way as to ensure that there were no unique cues in each corner. Successful discrimination of the object location in the standard and scrambled arenas was exclusively dependent on the use of geometric information, however successful discrimination in the cued arena could be achieved by processing either geometric information or featural information. Tran and Westbrook found that rats fed a high-fat high-sugar diet were impaired relative to control rats in their ability to discriminate the location of the novel object when tested in the standard arena and the scrambled arena, however performed in line with control rats when tested in the cued arena. Thus, the availability of the unique featural information in the corners of the cued arena allowed the rats fed the high-fat high-sugar diet to successfully perform the place recognition memory task. Such results support the idea that diet-exposed rats may be able to form qualitatively different (i.e. feature-alone) configural representations of context when compared to control rats, and

use these feature-alone representations to successfully perform the Pavlovian fear conditioning tests.

The idea that rats maintained on a high-fat and/or high-sugar diet perform the Pavlovian conditioning tasks by using feature-alone configural representations of context may be examined in two ways. Firstly, a context fear generalisation test that is designed to mimic the feature-identical context fear conditioning paradigm that has been utilised in experimental research using humans (Baeuchl et al., 2015; Stout et al., 2018, 2019). Murawski and Asok (2017) have recently used a CPFC task to demonstrate in rodents that LCD screens can be incorporated into context fear conditioning to manipulate the visual stimuli of contexts. In this study, rats were pre-exposed to a conditioning chamber that was surrounded by four LCD screens; for one group of rats, the screens displayed a distinct visual scene that was later presented at conditioning (context A) and a second group of rats were presented with a different visual scene (context B). A third group of rats were pre-exposed to a standard conditioning chamber that was not surrounded by LCD screens (context C) and served as a control group. Rats pre-exposed to context A exhibited significantly greater levels of freezing at test when compared to rats pre-exposed to context B or context C, and rats pre-exposed to context B and C did not differ from one another. Thus, the results of this study suggest that it would be possible to use LCD screens to generate contexts that systematically differ in their elemental features and/or the spatial arrangement of the elemental features, and use this to examine context fear generalisation in rats consuming a high-fat and/or high-sugar diet.

A second possible way to follow up on the hypothesis that rats use feature-alone configural representations of context is examination of performance across a set of discrimination tasks that systematically manipulate the reliance on the spatial-relationship between elemental features for successful performance. For example, Sanderson, Pearce,

Kyd, and Aggleton (2006) examined the performance of hippocampal intact and lesioned rats during re-learning in one of three configural discrimination tasks that were matched for task difficulty, but differed in the reliance on the use of spatial-relationships between the elements for successful performance. Discrimination learning was undertaken in a rectangular shaped water maze. The escape platform was attached to either the left or right side of one of the maze end walls, and was always located underneath a reinforced stimulus (S+). Both the S+ and the nonreinforced stimulus (S-) were located on the end wall throughout training, and the location of the S+ appeared on an equal number of occasions on the left and right side of the end wall in a random order. Sanderson et al. found that rats with hippocampal lesions were impaired relative to sham control rats in a structural discrimination task in which the S+ and S- were comprised of similar elements that differed in their spatial arrangement (e.g. A|B+ vs mirror image B|A-). However, both sham and hippocampal lesion rats showed comparable performance in a transverse patterning discrimination task and a biconditional discrimination task. These results demonstrate that an intact hippocampus is required for successful performance in tasks that require configural processing of the spatial arrangement of elements but not when configural processing of the elements alone is required. Thus, this task provides a spatial learning and memory protocol for assessment of configural processing of both geometric and featural cues in rats consuming a high-fat and/or high-sugar diet.

5.3. Limitations and Future Directions

A major limitation of the present thesis is that it did not examine neural mediators of the spatial memory deficit observed in rats consuming a short-term high-fat and/or high-sugar diet. As reviewed in the introduction of this thesis, a number of peripheral and neural mechanisms have been proposed as mediators. These include dysbiosis in the gut

microbiome (Noble et al., 2017a), disrupted glucose regulation and insulin sensitivity within the periphery and the CNS (Greenwood & Winocur, 2005), peripheral and central inflammation (Leigh & Morris, 2020), and BBB disruption (Hsu & Kanoski, 2014). However, much of the evidence supporting these mechanisms as mediators of diet-induced cognitive impairments are based on correlational evidence; this limits the conclusions that can be drawn about a causal relationship of diet-induced changes in peripheral and central markers of health on cognitive impairments. At present, diet-induced gut dysbiosis is one of the few proposed mechanisms with evidence that supports a causal relationship of diet on cognitive impairments. Bruce-Keller and colleagues (2015) subjected normal adult mice to microbiome depletion using antibiotic treatment followed by transplantation with microbiota obtained from mice that had been maintained on a high-fat diet (60% energy from fat) or a standard chow diet for 10-weeks. Two-weeks after the transplantation, mice that received microbiota from the high-fat diet mice demonstrated significantly reduced time in the open arms of an elevated plus maze, reduced time in the inner zone of an open field, and reduced conditioned freezing to a tone CS, when compared to mice that received microbiota from chow-fed mice. Bruce-Keller et al. additionally found disrupted markers of intestinal permeability, increased levels of circulating endotoxins, and increased expression of inflammatory markers within the periphery and the prefrontal cortex in mice that received the high-fat diet microbiota. Importantly, there was no significant difference in body weight between the two groups of mice during the depletion, transplantation, or behavioural testing stages of the experiment, indicating that the altered behaviour in mice transplanted with high-fat diet microbiota was not a consequence of alterations in body weight. Thus, the data demonstrate that high-fat diet-induced manipulations of the gut microbiome not only impairs cognition, but may also induce peripheral and CNS inflammation that has been

implicated in mediating diet-induced deficits. Such evidence points to gut dysbiosis as an explicit mediator of diet-induced cognitive impairments that should be more closely examined in future studies.

The evidence from the meta-analysis and the place recognition memory tests in chapter 4 of a comparable deficit in spatial memory in rats receiving high-sugar, high-fat, and high-fat high-sugar diets suggests that similar mechanisms may mediate high energy diet-induced cognitive impairments. However, very few studies have systematically examined whether there are similarities and differences in the underlying mechanisms of diet-induced cognitive impairment between dietary fat and sugar intake. While cognitive impairments are reported after brief exposure to high-fat or high-sugar diet consumption, the mechanisms underpinning such impairments may differ considerably. For example, increased markers of inflammation have been reported after brief exposure to both a high-fat diet and a high-sugar diet (e.g. Ayabe et al., 2018; Beilharz et al., 2016a; Hsu et al., 2015). However, the pathways by which this increase occurs may be different between the two dietary sources, with increased serum lipids from fat intake most likely producing inflammation in high-fat diet fed rodents (Vachharajani & Granger, 2009), and disrupted glucose regulation and insulin sensitivity most likely producing inflammation in high-sugar diet fed rodents (Pickup & Crook, 1998). Thus, the underlying pathways of potential mediators of diet-induced cognitive impairments should be more closely examined, particularly in brief diet exposure manipulations where potential confounding factors, such as increased body weight and metabolic disturbances, are minimised or even eliminated.

In addition to examining the pathways underlying mediators of diet-induced impairments, it is important for future studies to examine how high-fat and/or high-sugar diets may selectively impair the use of geometric information but not featural

information. The hippocampus is a highly heterogenous and complex structure; a detailed description of hippocampal neuroanatomy is beyond the scope of this thesis and can be found elsewhere (Amaral & Lavenex, 2006), however a brief description will be provided for the purpose of clarity in the following argument. The hippocampus is traditionally divided into four distinct subregions: the dentate gyrus (DG) and three subdivisions (CA3, CA2, and CA1) of the cornu Ammonis (CA) area (Lorente de Nó, 1934; Amaral & Lavenex, 2006). These subregions are defined on the basis of anatomical, physiological, and functional differences that have been observed between these regions (Alkhadi, 2019; Cembrowski & Spruston, 2019; Hunsaker & Kesner, 2008; Kesner, Lee, & Gilbert, 2004). In addition to the DG and CA subregions, the hippocampus is also segregated by physiological and functional differences along a number of axes: dorso-ventral, proximo-distal, raustro-caudal, and medial-lateral, and functionally lateralized between the left and right hemisphere (Amaral & Lavenex, 2006).

The DG and CA subregions form the hippocampal circuit through which information flows unidirectionally from the cortex through the hippocampus and back to the cortex (Figure 5.1.; Amaral & Lavenex, 2006). The hippocampus receives cortical input from the entorhinal cortex (EC), which is segregated into the medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC; Knierim, Neunuebel, & Deshmukh, 2014). From the MEC and LEC, information flows through the hippocampus via a direct or an indirect pathway (Witter, Groenewegen, Da Silva, & Lohman, 1989). The direct pathway, termed the Temporoammonic (TA) pathway, is comprised of axons from layer III of the EC that project directly to CA1 neurons. The indirect pathway, termed the Trisynaptic pathway, is comprised of axons from layer II of the EC that project via the Perforant pathway (PP) to granule cells in the DG (first synapse), whose mossy fibres project to pyramidal neurons in the CA3 (second synapse), which in turn project to the

pyramidal neurons in the CA1 region via Schaffer collaterals (third synapse). However, it is important to note that while the TA and Trisynaptic pathways are the predominant efferent pathways, information can also be passed directly from layer II of the EC to CA3 via the PP.
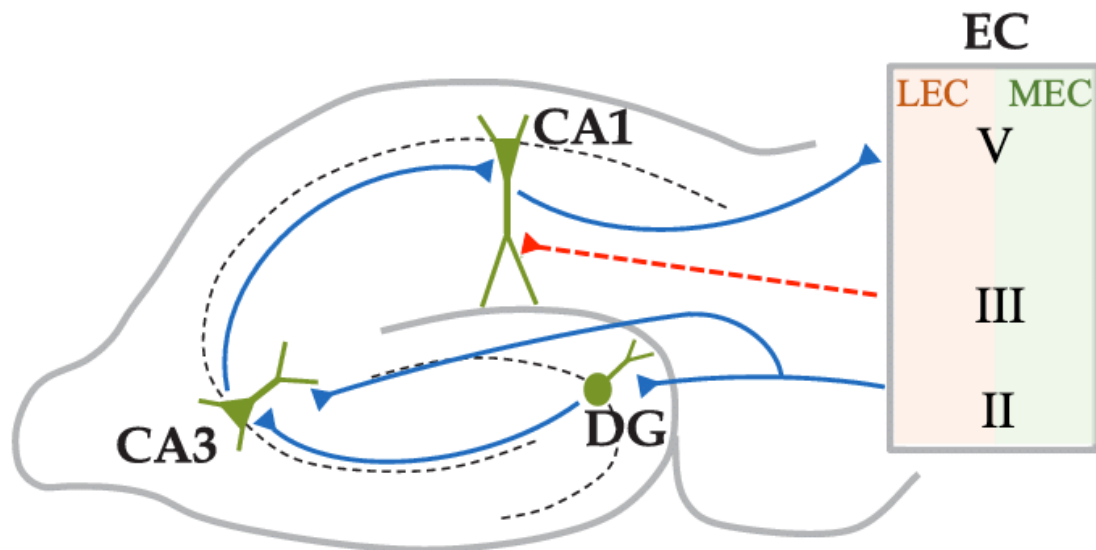
Figure 5.1. Schematic representation of hippocampal circuit. Cortical input to the hippocampus occurs via the entorhinal cortex (EC), which can be divided into the medial EC (MEC) and lateral EC (LEC). The Temporoammonic pathway (broken red line) contains axons from layer III of the EC that project to neurons in cornu Ammonis 1 (CA1). The Trisynaptic pathway (solid blue lines) contains axons from layer II of the EC that project via the Perforant pathway (PP) to granule cells (green circle) in the dentate gyrus (DG), whose mossy fibres project to pyramidal neurons (green triangle) in cornu Ammonis 3 (CA3), which project to the pyramidal neurons in the CA1 region via Schaffer collaterals. The PP also projects from layer II of the EC directly to CA3. Information flows from CA1 back to the cortex via layer V of the EC. Figure adapted from López-Madrona, Matias, Pereda, Canals, and Mirasso (2017).

The heterogeneity within the hippocampus supports parallel information processing via a range of diverse neural circuits that can be recruited depending on the specific task demands. Indeed, a growing body of literature now demonstrates a dissociation between hippocampal subregions in mediating different types of cognition that are dependent on this brain structure. For example, there is evidence that the hippocampal subregions differentially contribute to the acquisition and retrieval of a

context fear memory (Daumas et al., 2005; Hunsaker & Kesner, 2008; Lee & Kesner, 2004b), a context fear extinction memory (Ji & Maren, 2008), and spatial memory in a modified Hebb-Williams maze task (Jerman, Kesner, & Hunsaker, 2006) and a radial arm maze task (Lee & Kesner, 2003). Furthermore, processing of geometric information is heavily dependent on the DG, whereas featural information is predominantly processed within the CA3 and CA1 subregions (Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; Leutgeb, Leutgeb, Moser, & Moser, 2007).

There is also evidence that lesioning information processing pathways within the hippocampus may differentially impact hippocampal-dependent cognition. For example, lesioning the mossy fibres between DG and CA3 impairs acquisition but not retrieval of a spatial memory in a modified Hebb-Williams maze, whereas lesioning the direct EC-CA3 PP has the opposite effect (Lee & Kesner, 2004a). Ferbinteanu and colleagues (1999) have shown that lesions of the medial PP (MPP) that projects directly from EC to CA3 impairs spatial learning and memory in the MWM, however has no influence on the ability to discriminate between contexts in a Pavlovian context fear conditioning task. Conversely, lesioning of the lateral PP (LPP) between EC and CA3 had no effect on MWM performance while facilitating discriminative fear conditioning. Similarly, Hunsaker and colleagues (2007) examined the effects of lesioning the MPP and LPP efferents between the EC and the dorsal DG, the EC and dorsal CA3, or the EC and dorsal CA1. They found that lesioning any of the MPP projections impaired place recognition memory, whereas lesioning any of the LPP projections impaired object recognition memory. Finally, a recent study found that lesioning of the ventral hippocampal commissure, which supports contralateral communication between the CA3 and the CA1 subregions in the left and right hippocampi, disrupted long term spatial memory in the

MWM and spatial working memory in a Y-maze, but had no effect on acquisition and retrieval of a context fear memory (Jordan, Tong, & Pytte, 2018).

Few studies have directly compared the effect of high-fat and/or high-sugar diets on the various hippocampal subregions and information signalling pathways. However, those that have provide evidence that the impact of dietary fat and sugar intake may not be uniform across the hippocampus. For example, Hernandez et al. (2019) maintained rats on a control diet or a calorically-matched high-fat diet (75% energy from fat) diet for 12-weeks, and found significantly reduced mRNA expression of 40 genes in the DG, but not in the CA3 or CA1 subregions. Of the 40 genes that were altered by the high-fat diet, 21 coded for proteins that contribute to glutamatergic signalling; eight of these genes were associated with presynaptic glutamate regulation, six were associated with postsynaptic excitation, and seven were associated with postsynaptic plasticity. Thus, the high-fat diet disrupted genes involved in neuronal excitability and synaptic plasticity within DG but not in other subregions. However, other studies have demonstrated susceptibility within the CA3 subregion not the DG. For example, Silva et al. (2015) fed rats a high-fat diet (69% energy from fat) and found that GFAP was significantly increased in the CA3 subregion after one week but not six-weeks of diet access, whereas there was no evidence of diet-induced changes in GFAP in the DG or CA1 subregion at either time point. Similarly, Wu et al. (2018) demonstrated mice maintained on a high-fat diet (23% energy from fat) for six-weeks exhibited neuronal loss within the DG, CA3, and CA1 subregions, however the neuronal loss in the CA3 was the only one found to be significantly different from control mice.

To the best of our knowledge, only one study has examined the effect of high energy diets on information processing pathways in the hippocampus. Lemos and colleagues (2016) demonstrated that rats maintained on 35% sugar solution for nine-

weeks showed a selective reduction in synaptic plasticity within the TA pathway between the EC and CA1 subregions, without relative changes in the Schaffer collateral pathway that connects the CA3 and CA1 subregions. Lemos et al. also reported that the concentration of adenosine A_1 receptor in hippocampal synaptosomal membranes was increased in both pathways in HS rats compared to control rats, however this was only seen to enhance the efficiency of decreasing synaptic transmission within the Schaffer pathway. Most importantly, however, modifications in the TA pathway but not the Schaffer pathway correlated with spatial memory deficits in a place recognition memory test. This finding demonstrates that the cognitive impairments observed in rodents maintained on high-fat and/or high-sugar diets may be attributable to diet-induced disruptions in particular hippocampal pathways.

Taken together, the available literature suggests that certain hippocampal subregions and/or information signalling pathways may be uniquely vulnerable to the effects of high-fat or high-sugar diet and, consequently, more profoundly disrupted by the intake of these diets. However, the evidence from this body of literature is equivocal; for example, studies using high-fat diets suggest that the impact on hippocampal subregions may differ depending on the concentration of energy derived from fat (e.g. Hernandez et al., 2019 vs Wu et al., 2017) or the length of diet exposure (e.g. Hernandez et al., 2019 vs Silva et al., 2015). Consequently, no conclusion regarding which, if any, hippocampal subregions or information pathways are more sensitive to diet-induced disruption can be drawn. Future studies should examine whether the heterogeneity within the hippocampus results in unique vulnerabilities throughout this structure.

One potential candidate for further examination is the MPP input pathway between the MEC and the hippocampal subregions. The MEC and LEC inputs to the hippocampus are distinct from one another in terms of neurophysiology and function.

One of the most fundamental neurophysiological distinctions is the presence of spatial processing neurons within the MEC, which includes grid cells (Fyhn, Hafting, Witter, Moser, & Moser, 2008), boundary cells, and head direction cells (Sargolini et al., 2006; Solstad, Boccara, Kropff, Moser, & Moser, 2008). Grid cells and head-direction cells are argued to be the neural mechanisms underpinning encoding of distance and direction information, while boundary cells respond to the presence of environmental boundaries (Hartley, Lever, Burgess, & O'Keefe, 2014). Thus, these cells are critical for formation of a spatially-structured cognitive map of space. Furthermore, the MEC is highly connected with brain structures that provide robust spatial and movement-related information, including the subiculum and retrosplenial cortex (Witter & Amaral, 2004). These features of the MEC have led to the hypothesis that the MEC is responsible for path integration computations that generate an internal spatial map that represents the external environment (Knierim et al., 2014). In comparison, the LEC is mostly devoid of spatially tuned neurons and produces weak spatial and self-motion signals (Deshmukh & Knierim, 2011), leading to the hypothesis that the LEC processes information about non-spatial information such as local landmarks and item identity (Knierem et al., 2014). Thus, a deficit in processing of geometric information but not featural information, as previously reported by Tran and Westbrook (2015) and hypothesised to possibly account for the differential diet-induced impairment in place recognition memory and configural processing of context in the present thesis, may be due to diet-induced disruptions in the MEC efferent pathways, with relatively intact LEC efferents.

5.4. Theoretical Implications

The results presented in this thesis demonstrate that brief dietary intake of fat, sugar, or both, impairs hippocampal-dependent spatial memory. These findings

compliment the epidemiological evidence of diet-induced cognitive impairments across the lifespan; this includes poorer hippocampal-dependent recognition memory in children (e.g. Baym et al., 2014), poorer visuospatial ability in children, adolescents, and adults (e.g. Abargouei et al., 2012; Gibson et al., 2013; Nyaradi et al., 2014), and impaired global cognitive function and a more rapid cognitive decline in middle-aged and older adults (e.g. Fortune et al., 2019; Morris, Evans, Bienias, Tangney, & Wilson, 2004; Roberts et al., 2012). Humans that consume high-fat and/or high-sugar diets may also consume fewer essential micronutrients and engage in unhealthy behaviours such as a sedentary lifestyle, which make it difficult to establish a causal relationship of intake of such diets on cognitive impairments. However, the evidence of impairments in place recognition memory following high-fat and/or high-sugar diet consumption observed in the present thesis provides experimental evidence that the correlation between intake of these diets and visuospatial ability across the lifespan may reflect a causal relationship.

The results of the meta-analysis and the experimental research further suggest that detection of cognitive impairments after brief high-fat and/or high-sugar diet exposure may be dependent on task demands. These findings may explain why experimental research in humans has demonstrated that brief consumption of high-fat diet (Edwards et al., 2011b) and high-fat high-sugar diet (Attuquayefio et al., 2017) impairs performance on some, but not all, tasks that assess hippocampal-dependent cognition. For example, Attuquayefio et al. (2017) demonstrated significantly reduced learning and recall in a list learning task after four-days of high-fat high-sugar diet intake, but no effect on learning and recall of a short story. The qualitative difference between the list-learning and story-learning tasks, particularly in terms of the information that is processed during learning (unstructured information in the list learning task vs structured information in the story learning task; Silva et al., 2012; Tremont et al., 2010) result in different cognitive

demands being placed on participants for successful performance. Thus, the cognitive deficits induced by brief high-fat high-sugar diet exposure in humans appear to be detectable under certain testing conditions but not others.

One of the more significant implications of diet-induced cognitive impairments being evident under certain test conditions, but not others, is that it complicates the public health message. It means that people who do experience diet-induced cognitive impairments may be able to function in day-to-day life using alternative strategies, resulting in an under-recognition of the impact of their dietary habits on cognition. Similar to what is observed for medical conditions, under-recognition and under-diagnosis of diet-induced impairments can prevent people from undertaking necessary behavioural changes to improve brain health and function. This under-recognition is particularly problematic when individuals do not experience the detrimental effects that arise with short-term high-fat and/or high-sugar diet consumption, as it is often easier for such behavioural changes to be enacted before unhealthy eating patterns become habitual. Thus, it is important for researchers to identify the types of cognitive tasks that are appropriate for examining the relationship between diet and cognition so that successful assessment and intervention can be undertaken.

5.5. Conclusion

The shift in global food trends towards increased consumption of high-fat and/or high-sugar foods has been accompanied by adverse consequences for physical health, including rising prevalence of NCCDs and high rates of premature mortality. There is also growing evidence that the increased consumption of such foods has an adverse effect on brain health and cognitive function. The present thesis has demonstrated that relatively short-term consumption of high-sugar, high-fat, or high-fat high-sugar diets impair spatial

memory that is dependent on the hippocampus. However, the thesis also provides evidence to suggest that the diet-induced deficit in spatial memory may not extend to hippocampal-dependent configural processing of context information. Due to the inconsistent findings across the Pavlovian conditioning experiments that examined the formation and use of configural representations of context, no definite conclusions about the effect of diet-induced impairments in hippocampal configural processing can be drawn. Nevertheless, a number of future studies that may provide greater clarity around the influence of high-fat and/or high-sugar diets on this function of the hippocampus have been proposed. Most critically, the results of the meta-analysis and experimental studies presented in this thesis suggest that high-fat and/or high-sugar diets do not produce a global cognitive impairment. Rather, the diet-induced impairments appear to be observable under certain experimental conditions, such as the cognitive domain examined, the behavioural assessment task used to assess cognition, and the procedure by which the assessment task is undertaken. This finding has important implications in the context of the public health message for promoting healthy dietary choices in the future.

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Appendix A: Meta-analysis Search Terms and Strategy

A search was conducted on PubMed for the following terms:

High Fat Diet

((((((((((high-fat[Title/Abstract]) AND memory[Title/Abstract]) OR fat[Title/Abstract])
AND diet[Title/Abstract]) AND memory[Title/Abstract]) OR high-
fat[Title/Abstract]) AND cognit*[Title/Abstract]) OR fat[Title/Abstract]) AND
diet[Title/Abstract]) AND cognit*[Title/Abstract]

High Sugar Diet

((((((((high-sugar[Title/Abstract]) AND memory[Title/Abstract]) OR
sugar[Title/Abstract]) AND diet[Title/Abstract]) AND memory[Title/Abstract])
OR high-sugar[Title/Abstract]) AND cognit*[Title/Abstract]) OR
sugar[Title/Abstract]) AND cognit*[Title/Abstract]

High Fat Sugar Diet

(((((((Western diet) AND memory) OR cafeteria diet[Title/Abstract]) AND
memory[Title/Abstract]) OR Western diet[Title/Abstract]) AND
cognit*[Title/Abstract]) OR cafeteria diet[Title/Abstract]) AND
cognit*[Title/Abstract]

A search on Proquest was conducted using the search terms:

High Fat Diet

ab(high-fat) AND ab(memory) OR ab(fat) AND ab(diet) AND ab(memory) OR
ab(high-fat) AND ab(cognit*) OR ab(fat) AND ab(diet) AND ab(cognit*)

High Sugar Diet

ab(high-sugar) AND ab(memory) OR ab(sugar) AND ab(diet) AND ab(memory) OR
ab(high-sugar) AND ab(cognit*) OR ab(sugar) AND ab(diet) AND ab(cognit*)

High Fat Sugar Diet

ab(western diet) AND ab(memory) OR ab(cafeteria diet) AND ab(memory) OR

ab(Western diet) AND ab(cognit*) OR ab(cafeteria diet) AND ab(cognit*)

Appendix B: Objects Used for the Object and Place Recognition Memory Tests

Figure B.1. Front view of the objects used in the object and place recognition memory tests conducted in experiment 1 of chapter 3 and chapter 4.

Figure B.2. Top-down view of the objects used in the object and place recognition memory tests conducted in experiment 1 of chapter 3 and chapter 4.

Appendix C: Addendum to Chapter 2– Results and Discussion of Meta-analysis

Heterogeneity Measures

Results

Assessment of heterogeneity was examined using the I^2 statistic generated by the CMA software. The I^2 describes the percentage of variation across studies included in the meta-analysis that is due to heterogeneity rather than chance (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). Interpretation of the estimates of heterogeneity was undertaken using suggestions provided by the Cochrane Handbook for Systematic Reviews of Interventions (Higgens et al., 2021). The results suggest there may be moderate and statistically significant heterogeneity across studies that examined the effect of consuming a diet high in fat ($I^2 = 49.875$, $p < .001$), refined sugar ($I^2 = 44.719$ $p = .02$), and both fat and refined sugar ($I^2 = 42.567$, $p = .05$). There was evidence that there may be substantial and statistically significant heterogeneity across studies that used the Morris water maze ($I^2 = 52.748$, $P < .001$) to examine the effect of diets high in fat, refined sugar, or both, on hippocampal-dependent spatial learning and memory. However, there was no evidence of statistically significant heterogeneity for the place recognition ($I^2 = 33.420$, $p = .069$), radial arm and radial arm water mazes ($I^2 = 0.000$, $p = .957$), and the spontaneous alteration ($I^2 = 47.866$, $p = .074$) tests.

Discussion

The finding of heterogeneity across studies suggests that there may be a distribution of diet intervention effects, rather than a single-intervention effect. The heterogeneity observed across studies examining the effect of a diet high in fat and/or refined sugar on hippocampal-dependent memory and studies using the Morris water maze test to examine the diet effect is likely due to methodological variation that is present across dietary studies. Such variation is observed for the dietary intervention in

the type and concentration of dietary fat and sugar used and the use of ad libitum or a time-restricted access schedule; for the rodent model used, including the species, strain, age, and sex of the rodent; and the behavioural procedure used for the behavioural task. These sources of methodological variation are discussed in greater detail in the discussion of the meta-analysis. While these differences across studies can be identified, we cannot be certain of the true source of the heterogeneity across studies included in the meta-analysis, and this supports the selection of a random-effects model to analyse the extracted data as a random-effects model assumes that the effects being estimated in the studies is not identical but follow some form of distribution (Higgins et al., 2021). The source of the heterogeneity, as well as the hypothesis that there may be a distribution of diet intervention effects, should be examined in future research through the use of a subgroup analysis or a meta-regression analysis.