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Title: Unravelling the impacts of western-style diets on brain, gut microbiota and cognition

Author List: Michael D. Kendig, Sarah-Jane Leigh, & Margaret J Morris*

Affiliations: School of Medical Sciences, UNSW Sydney, NSW 2052, Australia

*corresponding author at m.morris@unsw.edu.au

Postal Address: Department of Pharmacology, School of Medical Sciences, UNSW Sydney, NSW 2052, Australia

Running Title: Diet, brain, gut and cognition

Abstract

The steady rise in the prevalence of obesity has been fostered by modern environments that reduce energy expenditure and encourage consumption of 'western'-style diets high in fat and sugar. Obesity has been consistently associated with impairments in executive function and episodic memory, while emerging evidence indicates that high-fat, high-sugar diets can impair aspects of cognition within days, even when provided intermittently. Here we review the detrimental effects of diet and obesity on cognition and the role of inflammatory and circulating factors, compromised blood-brain barrier integrity and gut microbiome changes. We next evaluate evidence for changing risk profiles across life stages (adolescence and ageing) and other populations at risk (e.g. through maternal obesity). Finally, interventions to ameliorate diet-induced cognitive deficits are discussed, including dietary shifts, exercise, and the emerging field of microbiome-targeted therapies. With evidence that poor diet and obesity impair cognition via multiple mechanisms across the human lifespan, the challenge for future research is to identify effective interventions, in addition to diet and exercise, to prevent and ameliorate adverse effects.

Keywords: 3-12

Western-style diet, cognition, obesity, microbiome, inflammation, hippocampus, intermittent access, intergenerational transmission, interventions, ageing, adolescence, exercise.

Highlights

- Cognition can be impaired by obesity and diets high in fat and sugar across species
- Intermittent consumption of poor diets may be sufficient to impair cognition
- Dietary and exercise interventions improve diet-induced cognitive deficits
- Microbiome modifications improve diet-induced cognitive deficits in rodents
- Adolescence, ageing and maternal obesity may represent windows of additional risk

1. INTRODUCTION – THE IMPACT OF PALATABILITY ON FOOD INTAKE AND OBESITY

The prevalence of overweight and obesity has rapidly increased in recent decades, affecting children, adolescents and adults, constituting one of the most serious health issues facing the developed world (WHO, 2000). Obesity increases the risk of several diseases, including type 2 diabetes, colorectal, liver, and several other cancers, neuropsychiatric conditions and cardiovascular disease, leading to premature disability and death (Blüher, 2019). Between 1990 and 2015, high body mass index accounted for 4 million deaths globally (Afshin et al., 2017).

While obesity is a multifaceted condition arising from both genetic and environmental risk factors, its rise in prevalence over the last 50 years is thought to result predominantly from reduced daily physical activity and increased access to a western-style diet (Leigh et al., 2018). Lifestyle changes and easy access to a variety of energy-dense, nutrient-poor, and highly palatable foods have dramatically changed the way people eat. For example, in Australia, over a third of energy intake comes from discretionary (snack) foods that tend to be high in fat, sugar and salt (Hadjikakou, 2017) and less than 10% of the population meet the recommended daily intake of vegetables (Australian Institute of Health and Welfare, 2018). Understanding the effects of reduced diet quality on weight gain and disease risk has thus become a major focus of obesity research.

This review focuses on the effects of western-style diets on both cognition and the gut microbiome, and potential interventions to rescue diet-induced cognitive impairments. Western-style diets are defined as those high in simple carbohydrate (sugars), saturated fat and salt, and low in fibre, complex carbohydrate and micronutrients. Here we review the effects of western-style diets in work in humans and rodents and discuss results from models providing continuous as well as intermittent access. We review underlying mechanisms and outline vulnerable populations based on lifespan and intergenerational factors, such as maternal obesity. While most studies included in this review utilise diets high in both fat and sugar, other work relevant for understanding dietary effects on cognition and the microbiome is discussed as appropriate.

1.1 The cafeteria diet model

To model the variety and palatability of the modern food environment, we and others utilise a cafeteria diet, which involves exposing rodents to a wide range of store-bought foods that are high in fat and sugar, alongside their usual healthy diet (Leigh et al., 2019). In our hands, the cafeteria diet drives hyperphagia, more than doubling energy intake relative to the control diet, leading to increased adiposity, metabolic dysfunction and altered hypothalamic feeding circuitry (Hansen et al., 2004, Shiraev et al., 2009). Early work comparing cafeteria diet to purified high-fat or high-carbohydrate

diets found that rats exposed to cafeteria diet exhibit accelerated weight and adipose gain (Sclafani and Springer, 1976, Rolls et al., 1980). More recent work has shown that relative to purified high-fat diets, cafeteria diets induce greater peripheral inflammation and insulin resistance in rats (Sampey et al., 2011) and increased food intake and accelerated hyperglycaemia and insulin resistance in mice (Higa et al., 2014, Zeeni et al., 2015). Interestingly, one study comparing a purified western-style diet (high in both fat and sugar) with cafeteria diet found that the former produced more pronounced metabolic and inflammatory effects (Bortolin et al., 2018), highlighting the importance of further studies comparing cafeteria diets with purified alternatives.

Another important factor modelled by the cafeteria diet is low micronutrient availability, which is a key feature of western-style diets eaten by humans. A high proportion of adults with obesity exhibit micronutrient deficiencies (Krzizek et al., 2018) which may compound the effects of obesity on a number of health domains. Since most purified high-fat rodent diets are nutritionally balanced despite altered macronutrient content, this aspect of modern eating is not usually incorporated into models of diet-induced obesity and metabolic dysfunction.

2. EFFECTS OF DIET AND OBESITY ON COGNITION

Obesity and overweight is consistently associated with cognitive impairment in large human cohorts (Farruggia and Small, 2019, Attuquayefio and Stevenson, 2015), as well as increased risk of neurodegenerative disease (O'Brien et al., 2017, Dye et al., 2017). Obesity and metabolic dysfunction exacerbate brain injury (Bruce-Keller et al., 2009) and accelerate aging processes in neurons and glia (Mattson and Arumugam, 2018).

Systematic reviews have shown that both executive function (Fitzpatrick et al., 2013, Favieri et al., 2019) and episodic memory (Loprinzi and Frith, 2018) are negatively associated with BMI. A recent review by Farruggia and Small (2019) found that increased adiposity across the human lifespan was associated with impaired cognition independent of metabolic dysfunction, particularly in the domains of memory, intelligence, processing speed, attention, cognitive flexibility and executive function.

Critically, obesity-associated cognitive impairment may interfere with weight loss attempts and exacerbate weight gain. In people undergoing a medically-supervised weight loss program, poor cognitive flexibility and higher impulsivity at baseline were associated with less weight loss over an 8-week period (Galioto et al., 2016). Furthermore, a recent meta-analysis concluded that weight loss programs incorporating cognitive training programs (aimed at improving inhibition) significantly improved weight loss and eating control in obese people (Yang et al., 2019).

There is some evidence from population studies that poor diet may worsen cognition independently of obesity, although this is difficult to parse out in human studies. High caloric intake was shown to double the odds of mild cognitive impairment in non-demented elderly adults in a large cross-sectional study (Geda et al., 2013) and a systematic review concluded that reductions in energy intake are associated with better long-term memory and attention, particularly for people with overweight or obesity (Attuquayefio and Stevenson, 2015).

2.1 Experimental work in humans

Long-term experimental studies of diet and cognition are difficult to implement in people for ethical and logistical reasons. However, several short-term studies have shown effects of diets high in fat and sugar. Holloway and colleagues have shown that 5 (Holloway et al., 2011) and 7 (Edwards et al., 2011) days of a 75% high-fat diet significantly impaired attention and reaction times in healthy young men. A more recent study showed that 6 weeks exposure to a calorie-controlled high-fat diet worsened memory consolidation in young people (Schüler et al., 2018), indicating that overconsumption is not necessary for dietary fat to adversely affect cognition. Furthermore, young healthy adults exposed to a high-energy western-style diet (high in both fat and sugar) for only 4 days exhibited impairments in hippocampal-dependent verbal memory (Attuquayefio et al., 2017) and university students who report high levels of high-fat and high-sugar food intake exhibited worse performance in a verbal paired-associate task (Attuquayefio et al., 2016). Overall, while limited experimental work has been undertaken in people, the evidence to date indicates that even short-term exposures to diets high in fat and/or sugar can impact several cognitive domains.

2.2 Diet, obesity and cognition in preclinical rodent models

Work in rodents supports human findings, showing that diets high in fat or high in both fat and sugar impair hippocampal-dependent forms of cognition in both mice and rats within days of access (McLean et al., 2018, Beilharz et al., 2016b, Beilharz et al., 2014, Kanoski and Davidson, 2010). Although these rapid impairments emerge prior to overt body weight changes, several studies have shown that adiposity is increased within 1-2 weeks of access to energy-dense diets (St-Amand et al., 2020; Vaughn et al., 2017). Conversely, diet-induced deficits in place and episodic memory are restored well within a week of removing access to the diet (Tran and Westbrook, 2017, McLean et al., 2018), demonstrating that impairments are sensitive to acute shifts in diet and not simply changes in body weight. However, the short diet durations of these studies (1-2 weeks) may influence the efficacy of diet reversal. Kendig et al. (2018) found that the memory impairment produced by 4 weeks' ad-libitum access to 10% sucrose solution was moderately improved by sucrose removal for 4 weeks, while Wang et al. (2015) observed lasting cognitive impairment in mice over a year after a 15-week

exposure to high-fat diet had ended. Thus, the duration of prior exposure appears to moderate the potential for diet reversal interventions to ameliorate associated cognitive impairment.

A recent meta-analysis concluded that rodent studies using diets high in both fat and sugar produced larger effect sizes on measures of spatial learning and memory than those using fat or sugar alone (Abbott et al., 2019), although less work has been undertaken with high-sugar diets, and most have supplemented a healthy diet with access to liquid sugar solutions. One study from our laboratory showed that a diet high in solid sugar also impairs cognition in rats (Beilharz et al., 2016a), but further work assessing the differences between liquid and solid sugar is required.

2.3 Potential mechanisms

Considerable research interest has explored the mechanisms underlying the relationships between diet, adiposity and cognition, with a range of key processes in the central nervous system and periphery identified. Emerging evidence implicates the gut-brain axis, a term encompassing the complex biochemical signalling between the gastrointestinal tract and the central nervous system, as an important modifier of brain health and function. Hormones produced by the gut have been shown to regulate learning and memory (Mandal et al., 2018) and the gut plays an important role in regulating circulating nutrients and metabolites, as well as systemic inflammation, through the gut microbiome. Before discussing the microbiome in detail, below we briefly summarise other potential mechanisms involved in diet-induced cognitive impairment, including changes in circulating hormones, cytokines and nutrients, blood-brain barrier integrity, and neurogenesis. The breadth of these potential mechanisms underscores the challenge of targeting the underlying causes of diet- and obesity-associated cognitive impairment.

Circulating factors and neuroinflammation

One of the key routes by which changes in peripheral organs are communicated to the brain are circulating factors, including hormones, adipokines and cytokines. These factors are at least partially responsible for obesity-associated cognitive impairment, since working memory can be improved in obese mice by infusing plasma from mice fed a low-fat diet (Johnson et al., 2015).

Several circulating factors show some involvement in diet- and obesity-associated cognitive impairment. Leptin, a hormone produced by white adipose tissue and a key regulator of feeding behaviour, has been shown to affect hippocampal-dependent cognition in rodents (Harvey, 2007). However, the human literature is less clear; while leptin replacement in leptin-deficient individuals improves cognition (Paz-Filho et al., 2008), both low and high leptin levels are associated with cognitive impairment in people with functional leptin (Annweiler et al., 2019). Leptin is also involved

in regulating the innate immune system and may exacerbate low-grade peripheral and central inflammatory signalling, which is also known to impair cognition.

Obesity is characterised by the induction of low-grade systemic inflammation, and some of these changes are observable prior to the onset of obesity (Minihane et al., 2015). Increased circulating inflammatory cytokines, namely interleukin-6 (Bradburn et al., 2018) and C-reactive protein (Chen et al., 2014, Vintimilla et al., 2019), are associated with poorer cognitive outcomes in people and are elevated in obese rodents and people.

Peripheral inflammatory changes are thought to precede the increase in pro-inflammatory signalling in human and rodent hypothalamus (Thaler et al., 2012) and other brain regions in obesity. While limited work has examined the role of central inflammation in diet-induced cognitive impairment in humans, evidence from rodent studies indicates that diet-induced cognitive impairment is associated with IL-1b protein (Almeida-Suhett et al., 2017) or gene (Beilharz et al., 2016a) expression in the hippocampus. Furthermore, a number of studies have shown associations between increased microglial activation and diet-induced cognitive impairment in rodents (Almeida-Suhett et al., 2017, Cope et al., 2018).

Finally, excess circulating nutrients may also affect cognition: both hyperlipidaemia and hyperglycaemia are associated with cognitive impairment in people with obesity. The effects of hyperglycaemia are closely related to the development of metabolic syndrome and type 2 diabetes, which affect cognition independently of poor diet and obesity and have been reviewed elsewhere (Strachan et al., 2011, Farruggia and Small, 2019). Circulating triglycerides, which increase with exposure to diets high in fat, are able to cross the blood-brain barrier in both humans and rodents, and at high levels induce central leptin and insulin resistance in rodents (Banks et al., 2018). Lowering triglycerides in obese (Farr et al., 2008) and healthy (Banks et al., 2018) mice improves cognition, and a small study of aged people without dementia found that plasma triglyceride levels were negatively associated with executive function (Parthasarathy et al., 2017).

In summary, several circulating factors have been associated with cognitive impairment in poor diet and obesity. While triglycerides, cytokines and leptin have all been shown to modify cognitive performance when increased experimentally in rodents, it is likely that these signals interact with chronic poor diet and obesity to impair cognition.

Blood-brain barrier

The brain is encased in a highly specialised blood-brain barrier that regulates the blood-to-brain passage of circulating factors. Obesity is associated with increased blood-brain barrier permeability

in people and rodents (Rhea et al., 2017), and this is observable in rats following at least 10 weeks' exposure to a high-fat high-sugar diet (Rutkowsky et al., 2018, Kanoski et al., 2010). It should be noted that several studies have reported impairments in cognition following shorter diet exposures in the absence of blood-brain barrier changes (Rijnsburger et al., 2017, Hargrave et al., 2016a). While these results suggest that blood brain barrier dysfunction is unlikely to underlie acute diet-induced cognitive impairment in rodents, work in mice has shown reductions in GLUT1 protein expression in vascular endothelial cells of the blood-brain barrier within 3-7 days of exposure to a high-fat diet (Jais et al., 2016). Thus further work is required to clarify the time course of diet-induced changes to tight junction proteins and glucose uptake regulators within the BBB, and evaluate effects on cognition. Finally, given that obesity is also associated with cerebral hypoperfusion in multiple brain regions, including the hippocampus (Amen et al., 2020), it will be important to interrogate whether these changes underlie obesity-associated cognitive impairments.

Hippocampal BDNF

Altered levels of brain-derived neurotrophic factor (BDNF) and reduced neurogenesis have been observed in the hippocampus in rodent models of diet-induced obesity (Hargrave et al., 2016b). Further, circulating BDNF was found to mediate the relationship between visceral adiposity and executive function in a small middle-aged human cohort (Kaur et al., 2016). BDNF is a key modulator of long-term potentiation and synaptic plasticity (Lu et al., 2014), two mechanisms critical for learning and memory. Reductions in hippocampal BDNF have been reported following exposures to high-fat and high-sugar diets of at least 2 months (Molteni et al., 2002, Molteni et al., 2004), although these changes may be mediated by increased pro-inflammatory cytokine expression (Barrientos et al., 2004). Of note, altered BDNF expression has not been observed at shorter diet exposures (Beilharz et al., 2014). Therefore, it is likely that changes in BDNF, as for blood-brain barrier integrity, do not play a central role in early diet-induced cognitive impairment.

3. ROLE OF THE GUT MICROBIOME IN DIET-INDUCED COGNITIVE IMPAIRMENT

The gut microbiome, through its effects on enteric and vagal signalling, immune function, and neuroactive metabolite production, has been implicated in diet- and obesity-associated cognitive impairment. Gut microbiome composition is largely determined by diet, and carbohydrate quality and quantity are key in shaping the bacterial community and their metabolic activity. Microbiome composition shifts within days of changing dietary intake in humans (David et al., 2014, Wu et al., 2011) and mice (Carmody et al., 2015). Thus, acute shifts in microbiome composition may be relevant to diet-induced cognitive impairment, which is observed within days of starting a poor diet (Beilharz et al., 2014, Tran and Westbrook, 2017, McLean et al., 2018). Since diet is such an important regulator

of the gut microbiome, it is important to use models that capture modern eating habits. In this regard rodent studies using purified diets, which involve a single food type with fixed macronutrient composition (typically 40-60% calories from fat) may hold less relevance than cafeteria-style (Leigh et al., 2019) or junk-food (Bayol et al., 2007) diets, which provide access to a variety of palatable foods commonly eaten by humans that are high in fat and sugar.

3.1 Gut microbiome and obesity

In obesity, the microbiome is characterised by reduced microbial species richness (Le Chatelier et al., 2013) – the estimated number of species within the host – alongside some reports of altered Firmicutes:Bacteroidetes ratios in mice (Ley et al., 2005, Turnbaugh et al., 2008) and humans (Ley et al., 2006). Data from studies applying faecal microbiome transfer (FMT) have suggested that microbiome compositional changes may directly induce obesity and metabolic dysfunction. For example, in human twin pairs discordant for obesity, FMT from the obese twin into germ free mice increased fat mass, with no effect of FMT from their lean counterpart (Ridaura et al., 2013). Transfer of the microbiome of diet-induced obese mice was shown to exacerbate weight gain in previously obese and lean naïve mice (Thaiss et al., 2016). While these results suggest that direct manipulation of the microbiome may hold promise to improve metabolic disease, two double-blind placebo-controlled RCTs have found no evidence that oral FMT from lean human donors improves body weight loss or metabolic outcomes in people with obesity (Allegretti et al., 2019, Yu et al., 2020). Further, caution is warranted when extrapolating causality from studies transferring the microbiota from humans into rats (Walter et al. 2020). In summary, both short-term diet and long-term obesity impact the gut microbiota: dietary changes rapidly affect microbiome composition while established obesity is associated with reduced microbial species diversity. Further investigation into the efficacy of FMT in people for weight loss and other markers of metabolic health is needed.

3.2 Gut microbiome and cognition

A number of studies have shown that manipulating the microbiome affects behaviour, with evidence that anxiety-like behaviours and central BDNF are altered by antibiotic (Bercik et al., 2010) or probiotic (Bravo et al., 2011) treatments, and differ between germ-free and conventionally-raised mice (Neufeld et al., 2011). Further, there is increasing evidence for a role of the microbiome in mood (Valles-Colomer et al., 2019) and neurodevelopmental (Hsiao et al., 2013) disorders. There is intriguing evidence for sex differences in the relationship between gut microbiome composition and the brain, as summarised in recent reviews (Jašarević, Morrison & Bale, 2016). A recent mouse study found that 14-week access to a high-fat, high-sugar diet reduced hypothalamic astrocyte density in females (but

not males), and increased hypothalamic microgliosis and gut microbiome alpha diversity in males (but not females) (Daly et al., 2020).

The relationship between the gut microbiome and cognition is less well-established, although there is growing observational data showing associations between microbiome composition and human conditions involving cognitive dysfunction, including Alzheimer's disease (Mahmoudian Dehkordi et al., 2019) and hepatic encephalopathy (Collins et al., 2012), as well as normal age-related cognitive decline (Manderino et al., 2017). Recent studies have begun to elucidate how changes in microbiome composition may influence cognition in people with overweight or obesity. One small study conducted in obese but otherwise healthy individuals reported that the relative abundance of *Burkholderiaceae*, *Coriobacteriaceae* and *Corynebacteriaceae* families were positively associated with cognitive performance (Palomo-Buitrago et al., 2019). Another study reported that obesity-associated impairments in short-term memory (digit span task) and working memory (California Verbal Learning Test) were positive associated with bacteria in the Firmicutes phylum, negatively associated with bacteria in Bacteroides and Proteobacteria phyla, and negatively associated with functions involved in one-carbon metabolism (Arnoriaga-Rodriguez et al., 2020).

There is stronger evidence for associations between diet-induced microbiome changes and cognition from rodent studies. Mice showed significantly improved working and reference memory when fed a healthy diet supplemented 1:1 with lean ground beef, and their behavioural performance was associated with microbiome changes (Li et al., 2009). Another study reported that impaired cognitive flexibility was negatively and positively associated with Clostridiales and Bacteroidales relative abundances, respectively, in mice fed a high-sucrose diet (Magnusson et al., 2015). We subsequently showed that novel place recognition memory was significantly associated with abundance of several bacterial species in rats fed purified energy-matched diets high in sugar, saturated fat and polyunsaturated fat (Beilharz et al., 2016a). Preliminary evidence thus suggests that gut microbiome composition is a key determinant of cognitive performance in rodent models of obesogenic diet exposure.

4. INTERMITTENT CONSUMPTION OF UNHEALTHY DIETS

Population level analyses show that diet composition changes dramatically from weekdays to weekends, with a spike in energy intake and poorer diet quality (An, 2016, de Castro, 1991). The prevalence of disordered eating behaviours, such as binge-eating and extreme dieting, increased dramatically in Australia from 1998-2008 (Mitchison et al., 2012), while NHANES data show a steady rise in chronic dieting and weight cycling in both obese and non-obese populations (Montani et al.,

2015). Thus, intermittent consumption of poor diets may reflect the dietary habits of a substantial proportion of the population, whether in clinical conditions or as part of day-to-day variation in diet.

Studies in rodents have begun to characterise the long-term effects of intermittent consumption of unhealthy diets. Mice alternating between low- and high-fat diets in 4-week cycles gained fat mass but exhibited comparable lifespan to mice continuously fed low-fat diet, and outlived mice continuously fed high-fat diet (List et al., 2013). Thaiss et al. (2016) demonstrated that the obesity and metabolic derangement produced by a single 4-week cycle of HFD intake led to lasting gut microbiome changes that enhanced weight regain during subsequent HFD cycles. Another mouse study found that repeated 2-week cycles between low- and high-fat diets increased fat mass and impaired glucose tolerance to a similar extent to continuous high-fat diet access (Simonds et al., 2018).

Several studies from our laboratory have explored the metabolic and cognitive effects of diet cycling on a shorter, weekly interval. Martire et al. (2015) compared rats fed continuous chow or cafeteria-style diets to a group cycled between 3 days of CAF diet and 4 days of chow per week. This cycled group over-ate cafeteria diet relative to continuous cafeteria diet-fed rats, under-ate chow relative to continuous chow rats, and gained an intermediate amount of body weight. Intriguingly, cycling and continuous cafeteria diet exposure produced near-identical changes to the gut microbiota, with strong negative associations between diet exposure and flavonoid metabolism pathways (Kaakoush et al., 2017).

While extensive work has characterised diet-induced cognitive impairment in rodents continuously exposed to various diets (discussed above), limited research has investigated the effect of diet cycling on cognition. Two recent studies from our group examined spatial and reference memory changes in rats cycled between a healthy chow and unhealthy cafeteria diet. The first showed that male rats given cycling access to cafeteria diet for 5 or 7, but not 3 consecutive days per week, exhibited place recognition memory impairments after 23-25 days of total access (Kendig et al., 2019). Notably, greater adiposity was associated with significantly poorer place memory. The metabolic profile of the 3- and 5-day cycling groups resembled continuous chow and continuous cafeteria groups, respectively. The second study found that cycles of 3 consecutive cafeteria diet days per week did not produce cognitive impairment in adult female rats, despite intermediate changes to their gut microbiome and metabolic phenotype (Leigh et al., 2020a). Place recognition memory impairments were predicted by changes in linear growth and by *a* bacterial operational taxonomic putatively identified as a strain of *Muribaculum intestinale*.

Further work is warranted to identify the factors that promote the protection from cognitive impairment seen following cycling access to cafeteria diet. For example, repeated bouts of healthy

eating in an otherwise unhealthy diet might serve to arrest the onset of low-grade inflammation, slow changes to the composition of the microbiota, or stimulate production of neurotrophic factors that preserve cognition.

5. POPULATIONS AT RISK OF DIET RELATED COGNITIVE IMPACTS

Dietary habits and gut microbiota composition are shaped by dynamic interactions between environmental, geographic and cultural factors. For example, people of different ages and from different geographic locations exhibit unique microbiome profiles in terms of bacterial diversity and dominant phyla (Greenhalgh et al., 2016). In turn, the risks to metabolic and cognitive function posed by unhealthy diets and/or dysregulated microbiome are not static. Evidence points to several key developmental windows that confer particular risk for adverse health outcomes.

5.1 Maternal obesity and childhood

Infant brain development is integrally determined by the health of the mother. The neonatal microbiome is colonised by bacteria transmitted through the placenta, vagina, amniotic fluid and breastfeeding, and is heavily influenced by maternal diet. Children of mothers who report eating a high-fat diet during gestation and lactation exhibit distinct microbiome profiles to those from mothers consuming a low-fat diet, characterised by a reduction in Bacteroides abundance (Chu et al., 2016). Evidence for a relationship between maternal micronutrient intake and child cognitive outcomes is mixed, with a predominance of observational studies (Veena et al., 2016).

By contrast, it is well known that maternal obesity, rather than diet per se, confers increased risk of obesity and metabolic impairment in the child (Godfrey et al., 2017). Evidence from systematic reviews of animal models (Menting et al., 2019) and observational studies in humans (Adane et al., 2016, Veena et al., 2016, Van Lieshout et al., 2011) indicates that cognitive development and psychiatric outcomes are adversely affected by maternal obesity. However, studies often do not measure cognition and psychiatric risk in parents (Van Lieshout, 2013) and effect sizes in humans are estimated to be small (Álvarez-Bueno et al., 2017).

Given the child's microbiome is determined by that of the mother in early life, it will be relevant to assess whether the behavioural effects influenced by maternal obesity are mediated by the microbiota (see Hasebe, Kendig, & Morris, 2021, for review). In our rat model of maternal obesity we demonstrated that maternal microbiome changes induced by obesogenic diet exposure were reflected in their offspring at weaning, and that microbial composition correlated with adiposity measures (Bhagavata Srinivasan et al., 2018). Emerging evidence suggests that dysregulation of

offspring microbiome by maternal diet, alongside other factors, is closely related to cognition: a recent study showed that mice born to obese dams exhibited accelerated body weight gain and cognitive impairment (measured by Y-maze), which was predicted by the abundance of bacteria within Firmicutes, Parabacteroides and Actinobacteria phyla (Sanguinetti et al., 2019).

5.2 Adolescence

Adolescence is a critical developmental window during which the frontal cortex and gut microbiome are still maturing. Several systematic reviews have concluded that obesity in childhood and adolescence is associated with impairments in executive function, attention, working memory and reward-related behaviour (Reinert et al., 2013, Pearce et al., 2018, Liang et al., 2014). Obesity-associated deficits in sub-domains of executive function, such as inhibitory control, may pose particular risk by promoting excess food intake and unhealthy food choices.

Evidence also indicates that dietary habits during adolescence influence cognition. A systematic review of 21 studies found that executive function in children and adolescents was closely tied to dietary quality, associating positively with fruit, vegetable, whole grain and fish intake, and negatively with red meat and sugary beverages (Cohen et al., 2016). Similar results were found in a prospective study of Australian adolescents, where a western-style dietary pattern at age 14 (identified by food frequency questionnaire) was associated with poorer performance on the Groton Maze Learning Test at age 17 (Nyaradi et al., 2014).

While testing long-term effects of poor diets during adolescence is challenging in humans, animal studies allow for cognition to be tested repeatedly over development while restricting unhealthy diet exposure to adolescence. Several studies have shown lasting impairments in hippocampal-dependent forms of cognition following adolescent exposure to diets high in fat and sugar, and that deficits are more pronounced than in adult animals given equivalent exposure (Noble and Kanoski, 2016). A recent study in mice found that adolescent exposure to HFD or CAF altered the abundance of several families of bacteria in the caecal microbiome (*Ruminococcaceae, Lachnospiraceae, Coriobacteriaceae, Alcaligenaceae* and *Erysipelorichaceae*) and upregulated expression of genes regulating short-chain fatty acid signalling, tight junction proteins, and inflammation in the amygdala (Fülling et al., 2020). However, no changes in social recognition, anxiety, fear conditioning and short-term memory tests in adulthood were observed.

5.3 Ageing

Dietary composition is associated with mild cognitive impairment in older populations. A meta-analysis of 12 studies found that greater adherence to a Mediterranean-style diet was associated with

lower rates of normal age-related cognitive decline and a reduced risk of neurodegenerative disease (Lourida et al., 2013). In a 20-year study of Singaporean Chinese adults aged 61-96 at follow up, higher scores on four diet quality measures were associated with a lower risk of developing mild cognitive impairment (Wu et al., 2019). Metabolic markers such as high-density lipoprotein have been linked to cognitive impairment in older populations (Feinkohl et al., 2019). The composition of the gut microbiome and production of bacterial metabolites shifts substantially as we age, perhaps related to shifts in dietary habits and nutrient deficiencies (Salazar et al., 2017), but whether these directly contribute to cognitive function remains to be determined.

The relationship between obesity and dementia has been partially confounded by the weight loss and physical wasting observed prior to onset of clinical dementia symptoms (Knopman et al., 2007). However, a recent analysis of individual data from 39 prospective cohort studies from Europe, USA and Asia found that obesity in midlife increased risk of incident dementia, but reduced this risk in late life (Kivimäki et al., 2018). These findings are concordant with a recent meta-analysis which also found that obesity prior to 65 years increased risk of incident dementia, but was protective in individuals older than 65 years (Pedditzi et al., 2016). Thus, obesity in mid, but not late life is associated with poor cognitive performance, and increased risk of age-related cognitive decline and dementia.

6. OPPORTUNITIES FOR INTERVENTION

Interventions to prevent and rescue the adverse effects of diet-induced obesity include dietary manipulations (intermittent fasting and caloric restriction), exercise regimens, oral pre- and probiotic exposure, and faecal microbiome transfer.

Dietary interventions

Modern environments promote overeating by providing easy access to energy-dense food alongside technology designed to reduce energy expenditure. This combination is unprecedented in our evolution from times when substantial physical and cognitive effort was needed to procure food in scarce and dangerous environments. This evolutionary view holds that while food scarcity drove the development of cognitive abilities to facilitate food procurement, prolonged excess food intake reduces the adaptive value of heightened cognitive abilities and may subsequently reduce cognitive performance (Mattson, 2019).

How then should people eat for optimal health? While many popular diets target specific macronutrients, a recent meta-analysis of 14 weight-loss diets (covering 121 trials and almost 22,000 patients) found similar weight loss effects of diets low in fat, low in carbohydrate, or with moderate intake of all macronutrients (Ge et al., 2020). There is ongoing research into the temporal distribution

of food intake across the day, with mixed evidence from observational studies. For example, Gill & Panda (2015) used an app-based food intake monitoring program to show that half of participants ate for a 15-hr window each day, and that limiting food intake to a 10-11h window facilitated weight loss. By contrast, a meta-analysis of meal frequency studies found that more frequent eating (5+ meals/day) was associated with larger reductions in body fat mass (Schoenfeld et al., 2015). However, this association was driven by a small number of studies with extreme effects.

There is a large literature testing whether intermittent fasting and caloric restriction (CR) regimens can prevent and ameliorate the adverse effects of diet-induced obesity. Caloric restriction (CR) involves a modest reduction in energy intake without malnutrition, and has been shown to benefit lifespan, metabolic and brain health in multiple species since first studied in rats in 1935 (McDonald and Ramsey, 2010). Genes regulating the immune response, circadian rhythms, growth hormone signalling and fat metabolism are among those most profoundly altered by CR (Plank et al., 2012). In mice, exposure to a 20% CR diet for 15 months increased hippocampal neurogenesis and produced sex-specific differences in SIRT1 and mTOR pathways (Wahl et al., 2018). Specifically, CR increased SIRT1 expression and decreased MTOR activation in female but not male mice, and increased PGC1α expression only in males. SIRT1 is highly expressed in hippocampus and hypothalamus, brain regions vulnerable to dietary insult, and regulates cognitive function by altering neural progenitor cell development and axonal and dendritic growth (Ng, Wijaya & Tang, 2015). mTOR signalling is implicated in cognitive function via its effects on synaptic plasticity (Lipton & Sahin, 2014).

While CR regimens involve continuous restriction of daily energy intake, intermittent fasting (IF) interventions restrict food intake on a temporal basis to induce the beneficial effects of fasting. A recent systematic review of 40 studies concluded that IF and CR produce comparable benefits to fat mass, glucose homeostasis and body weight (Seimon et al., 2015). Popular variations of IF include alternate day fasting, 5:2 fasting (two fast days per week) and time-restricted feeding, in which food is eaten within a single window (typically 8-hrs) each day. Time-restricted feeding (TRF) and alternate day fasting are effective in promoting weight loss and improving metabolic health (Jones et al., 2020), with some evidence for benefits to cognitive ability (Anton et al., 2018). Preclinical models of IF mirror several of the benefits observed in people, though effects on systemic inflammatory markers tend to be more varied in humans (Lee et al., 2020).

Importantly, there is evidence that beneficial effects of TRF on metabolic measures are due to restricting the temporal window per se, rather than to secondary consequences of eating less energy overall. Hatori et al. (2012) showed that mice given 8-hr/day access to a purified HFD were protected from the metabolic derangement and dysregulation of circadian rhythms seen in mice fed the diet

continuously, despite comparable energy intake. Delahaye et al. (2018) found that a 6-hr/day TRF schedule protected against HFD-induced weight gain in mice, but that insulin resistance was compromised when the 6-hr window was delayed further into the dark cycle, demonstrating that TRF effects interact with innate feeding rhythms.

Effects on cognition

Meta-analytic evidence indicates that weight loss is associated with improved performance in multiple cognitive domains, including memory and attention (Veronese et al., 2017). Overweight people undergoing a 3-month CR intervention demonstrated improvements in memory that correlated with reductions in plasma insulin and C-reactive protein (Witte et al., 2009). Intriguingly, the benefits to cognition may be contingent upon being in an acute negative energy balance. Prehn et al. (2017) showed that obese women exhibited an increase in hippocampal gray matter volume and corresponding improvements in recognition memory during CR, but that benefits normalised after four weeks of maintaining a lower weight. Comparing the effects of CR and IF on cognitive measures appears an important future research direction.

A recent study showed that a 28-day IF protocol ameliorated a deficit in spatial learning (assessed in the Morris water maze) and increased mitochondrial biogenesis in the hippocampus of db/db mice (Liu et al., 2020). The beneficial effects of IF appeared to be mediated by the gut microbiota, as IF-induced cognitive improvements were not observed in antibiotic-treated mice, but could be reproduced by administration of a range of microbial metabolites, including 5-HT, TUDCA, IPA and short-chain fatty acids (Liu et al., 2020).

Exercise

Regular exercise benefits cognition via a range of neurotrophic effects. A recent systematic review and meta-analysis (333 effect sizes, 36 studies) found that moderate intensity exercise was associated with improved cognition in community-dwelling adults over 50 years of age (Northey et al., 2018). Benefits were evident across multiple cognitive domains (attention, executive function and memory) and in individuals both with and without mild cognitive impairment. In aged mice, a one-month running wheel intervention arrested the age-related decline in hippocampal neurogenesis with corresponding improvements in learning and memory (van Praag et al., 2005). Similarly, a one-year exercise intervention bilaterally increased hippocampal volume and spatial memory in older people (Erickson et al., 2011). In older adults with obesity, aerobic fitness significantly predicts hippocampal volume and cognition (Bugg et al., 2012, Boidin et al., 2020).

The benefits of exercise on cognition may also be mediated by changes to the gut microbiome. Exercise profoundly modulates the composition of the microbiome in a manner that is significantly influenced by weight, but largely independent of the effects of diet (Mailing et al., 2019). A recent longitudinal study demonstrated that a 6-week exercise intervention had divergent effects on microbiome beta diversity in lean versus obese women, and selectively increased short-chain fatty acid levels only in lean women (Allen et al., 2018). Of note, most exercise-induced changes reverted to baseline after a 6-week washout. A mouse study found that HFD exposure and exercise exerted distinct effects on the gut microbiome and behaviour: HFD but not exercise increased anxiety-like behaviour, while exercise but not HFD modestly improved contextual fear conditioning recall (Kang et al., 2014). More work is needed to determine whether shifts in gut microbiota underlie exercise-induced improvements in cognition.

Microbiome modification

Several preclinical studies have investigated the effects of modifying microbiome composition, either through FMT, or administration of antibiotics, prebiotics, probiotics or bacterial products, on cognition.

Faecal transfer

Studies of FMT between conspecifics have illuminated the integral role of the microbiome in host metabolism and results using preclinical models suggest that behavioural phenotypes are transmissible through FMT. Hoban et al. (2018) demonstrated that the reduction in cued fear conditioning observed in germ-free mice was partially restored by FMT from conventionally raised mice. Similarly, mice given FMT from people with major depressive disorder displayed increased depression-like behaviour in the Forced Swim Test (immobility time) relative to those given FMT from controls (Zheng et al., 2016). Only three studies, to our knowledge, have assessed the role of an obese microbiome in cognitive impairment using FMT. Bruce-Keller et al. (2015) showed that lean mice were impaired on a Pavlovian cue-shock memory task following FMT from obese mice. Notably, the hippocampal-dependent component of the task and body weight were unaffected by FMT. Conversely, Yang et al. (2019) found that FMT from adult mice fed a high-fat diet impaired hippocampal-dependent learning and memory (Barnes maze and contextual fear-conditioning tests) in recipient mice fed a chow diet (Yang et al., 2019). Cognitive impairments were observed in the absence of gross motor changes or baseline differences in anxiety-like behaviour. In a recent study by Arnoriaga-Rodiguez et al. (2020), FMT from human donors into lean recipient mice significantly improved novel object recognition and decreased conditioned freezing; however, the improvement in object recognition was specific to mice given FMT from non-obese donors (FMT from donors with

obesity had no effect) (Arnoriaga-Rodriguez et al., 2020). These results highlight the need to clarify whether microbiome transplantation exerts region-specific effects on the brain.

Antibiotics

Oral antibiotic administration has also been shown to influence cognition in preclinical studies. Mice chronically exposed to a broad-spectrum antibiotic cocktail designed to minimise gastrointestinal absorption exhibited impaired object recognition, but not spatial memory (Frohlich et al., 2016) while rats similarly exposed to a broad-spectrum antibiotic cocktail exhibited impaired long-term memory retention in a Morris water maze (Hoban et al., 2016).

Subsequently we have shown that chronic oral administration of minocycline, a bacteriostatic antibiotic and immunomodulator, both prevented and reversed the place recognition deficit produced by cafeteria diet exposure (Leigh et al., 2020b). Using multiple regression models, we identified that cognitive performance in cafeteria-fed rats was accurately predicted by fat mass and the relative abundance of Desulfovibrio Piger. Of note, modest impairments in place recognition were seen in chow rats exposed to minocycline.

Probiotics, prebiotics and bacterial products

Studies have tested whether the effects of diet-induced obesity can be restored by oral supplementation of live species presumed to be depleted (probiotics) or by indigestible fibre compounds that support gut microbiota (prebiotics) (Slavin, 2013). Chunchai et al. (2018) found that the spatial learning and memory impairments produced by 12 weeks of exposure to a high-fat diet were reversed following 12 weeks of daily oral administration of a prebiotic, probiotic, or a combination pre/probiotic treatment. All treatments ameliorated the diet-induced changes to the Firmicutes:Bacteroidetes ratio, hippocampal plasticity and apoptosis markers, microglial morphology, mitochondrial function, and glucose tolerance. Notably, probiotic exposure did not alter body weight or fat mass gain, suggesting that improvements to brain and behaviour were independent of weight in this group. We (Beilharz et al., 2018) found that oral administration of the probiotic VSL3 prevented hippocampal-dependent place recognition memory deficits produced by a western-style cafeteria diet in rats. Intriguingly, probiotic exposure impaired perirhinal-dependent object recognition. The divergent effects on the two cognitive tasks correlated with separate principal components in distance-based linear modelling.

Intriguing recent evidence suggests that the cognitive effects of probiotics may not require the bacteria to be living and could instead be due to altered bacterial product availability. A recent study showed that heat-killed Lactobacillus brevis SBC8803 improved contextual fear memory when fed to

mice chronically (Ishikawa et al., 2019), while ICV infusions of the short-chain fatty acid propionate impaired learning in the Morris water maze (Mepham et al., 2019). Further work investigating whether specific bacterial products play a role in diet- and obesity-induced cognitive impairments is required.

7. SUMMARY AND FUTURE DIRECTIONS

Dynamic interactions between dietary habits and metabolic health shape cognitive function across the lifespan. Accumulating evidence from studies in rodents and humans indicates that acute and chronic access to western-style diets high in fat and sugar can impair aspects of cognition. Observations of cognitive impairment after acute diet exposures are noteworthy because the effects of eating poorly accrue over far longer periods than can be studied ethically. The widespread consumption of western-style diets suggests that the associated cognitive effects may substantially contribute to global disease burden, underscoring the need for further research into mechanisms and potential treatments. It is now clear that changes to the gut microbiome are key mediators of dietary effects on cognition, with emerging evidence suggesting that intervening at the level of the microbiota may hold promise to prevent or reverse deleterious effects of diets high in fat and/or sugar. Clarifying the precise neural circuitries affected by microbiome-based interventions will be a key next step.

One critical challenge for the field is to better understand how adverse effects of these western-style diets vary according to age and the patterns of their consumption. Two important goals for the field will be to better define the conditions under which the impacts of diet on the brain are reversible (and whether this is moderated by age), and to clarify the effects of intermittent access to western-style diets, which arguably represents the dietary habits of most of the population. Each of these aims can be thoroughly addressed using controlled animal experiments.

The high prevalence of obesity in adults calls for continued study of the mechanisms underlying intergenerational transmission of disease risk. We believe that a combination of behavioural and environmental interventions will be needed to improve dietary habits in the developed world and arrest the increase in metabolic disease and associated cognitive impairment, which is integral to maintaining quality of life into older age.

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