



Published in final edited form as:

*Ageing Res Rev.* 2016 November ; 31: 80–92. doi:10.1016/j.arr.2016.06.006.

## Nutritional strategies to optimise cognitive function in the aging brain

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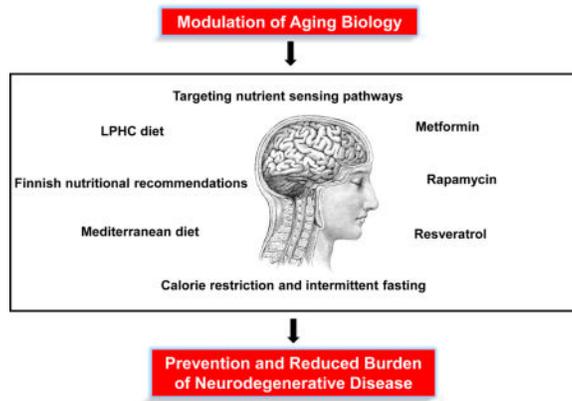
### Abstract

Old age is the greatest risk factor for most neurodegenerative diseases. During recent decades there have been major advances in understanding the biology of aging, and the development of nutritional interventions that delay aging including calorie restriction (CR) and intermittent fasting (IF), and chemicals that influence pathways linking nutrition and aging processes. CR influences brain aging in many animal models and recent findings suggest that dietary interventions can influence brain health and dementia in older humans. The role of individual macronutrients in brain aging also has been studied, with conflicting results about the effects of dietary protein and carbohydrates. A new approach known as the Geometric Framework (GF) has been used to unravel the complex interactions between macronutrients (protein, fat, and carbohydrate) and total energy on outcomes such as aging. These studies have shown that low-protein, high-carbohydrate (LPHC) diets are optimal for lifespan in *ad libitum* fed animals, while total calories have minimal effect once macronutrients are taken into account. One of the primary purposes of this review is to explore the notion that macronutrients may have a more translational potential than CR and IF in humans, and therefore there is a pressing need to use GF to study the impact of diet on brain aging. Furthermore, given the growing recognition of the role of aging biology in dementia, such studies might provide a new approach for dietary interventions for optimizing brain health and preventing dementia in older people.

### Graphical abstract

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Old age is the leading risk factor for neurodegenerative disease. Targeting nutrient sensing pathways through calorie restriction (CR) and intermittent fasting (IF) have proven to be effective treatments to delay ageing, increase healthspan, and postpone the onset of neurodegeneration. Anti-ageing compounds and low-protein, high-carbohydrate (LPHC) diet ratios have improved lifespan but the effects on delaying symptoms of neurodegeneration are still not well understood.



## Keywords

ageing; cognition; geometric framework; macronutrients; intermittent fasting

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**“Don’t dig your grave with your knife and fork.”**

(English Proverb)s

## 1. Introduction

Old age is the major determinant of degenerative diseases of the brain that influence cognition including the various types of dementia (Mowszowski et al., 2010). There has been extensive research into these common diseases with a focus on establishing the etiology and developing therapies for their treatment and prevention (Partridge, 2014). This has generated profound insights into disease-specific cellular pathways, but the discovery of disease-modifying treatments has remained elusive. On the other hand, the relationships between aging biology of the brain and neurodegenerative diseases have been relatively understudied. In recent decades there have been major advances in the understanding of aging biology at the cellular and systemic levels, and the development of strategies that delay aging and the concomitant suite of age-related disorders and pathologies. In particular, there has been a concerted focus on the nutritional interventions that delay aging, especially calorie restriction (CR) and intermittent fasting (IF), and chemicals that act on the pathways that mediate the effects of nutrition on the aging process. More recent focus has been on altering dietary macronutrient ratios (Fat: F; Protein: P; Carbohydrate: C) and assessing the effects on lifespan and healthspan (Solon-Biet et al, 2014). Therefore, there is now the opportunity to consider whether those strategies that delay aging, and in particular macronutrient ratio modulation, might more generally impact brain aging and cognition, and

potentially provide novel approaches to preventing age-related neurodegenerative disorders such as dementia.

## 2. The aging brain

There is a continuum between normal aging and disease in terms of pathological and biochemical changes in many tissues. There are ongoing efforts to differentiate disease from normal brain aging in both qualitative and quantitative terms. Even so, there is general agreement that old age in both animals and humans is associated with changes in brain volume, microscopic morphology, neurotransmitters and various phenotypic measures of cognition and behavior. While such changes may not be severe enough to interfere substantially with activities of daily living, they can reduce performance and increase brain vulnerability to neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Anderton, 2002).

Those features that are usually considered to be associated with aging rather than disease are summarized in Figure 1. In a non-pathological brain, it appears as if the most robust changes that take place are in the medial temporal lobe and prefrontal cortex, with an overall relative decrease in brain volume. The hippocampus and prefrontal cortex experience the most volume loss with age (Anderton, 2002).

It was previously thought that rapid deterioration in the extent of dendritic branching in apical and basilar dendrites takes place in the hippocampus (Brody, 1955). Now it is known that there is hippocampal and frontal cortex dendritic and synaptic stability when comparing middle aged to old subjects (Hanks and Flood, 1991). However, more robust changes take place in the prefrontal cortex, with reduced dendritic branching in the superficial cortical layer (Grill and Riddle, 2002). Given the critical role of dendritic branching patterns in higher cognitive function processes, this might contribute to the reduction in cognitive function that occurs during the aging process (Cubelos and Nieto, 2010).

Aged neurons in the hippocampus and prefrontal cortex have disruptions in calcium homeostasis, which may be secondary to an increased density of calcium channels (Anderton, 2002; Verkhratsky and Toescu, 1998). After depolarization, the neurons utilize potassium channels to repolarize and there is a brief after-hyperpolarization potential (AHP). The AHP in the hippocampus and prefrontal cortex is increased in amplitude in aged organisms, taking the neuron longer to reset to resting potential (Matthews et al., 2009). This coincides with a decrease in levels of brain derived neurotrophic factor (BDNF) which correlates with age-related cognitive deficits (Navarro-Martinez et al., 2015).

With aging, neuron-to-neuron communication in the hippocampus deteriorates which may be due to a dysregulation of genes that are responsible for synaptic protein synthesis (Ryan et al., 2015). This may partially account for cognitive deficits associated with aging. Indeed, a progressive loss of synapses has been observed in some regions of the aging human brain, with this commencing at about twenty years of age (Terry and Katzman, 2001). This is associated with increased inflammation and oxidative stress during later years (Johnson and Johnson, 2015).

It should be noted that similar pathological features are evident in a normal aging brain when compared to a pathological brain (i.e., neurofibrillary tangles, senile plaques); however, these changes occur at a much faster rate in neurodegenerative conditions (Anderton, 1997). Transcriptome changes that take place in the aging human brain are similar to those that occur in the aging mouse brain, suggesting brain aging changes are conserved (Miller et al., 2010).

Age-related molecular and cellular changes in brain cells coincide with behavioral-cognitive changes, which have been observed in humans, monkeys, and rodents. The hippocampus and prefrontal cortex are heavily involved in spatial memory (Chersi and Burgess, 2015), and it is therefore not surprising that an increase in age coincides with a deterioration in spatial and associative memory (Weber et al., 2015). In addition to the hippocampus, the prefrontal cortex is crucially important for working memory, and is critical for high level cognitive and executive function (Stokes, 2015). It has been suggested that the deterioration of these two structures is largely responsible for the decline seen in cognitive function with age (West, 1996).

### 3. Unraveling the relationships among calorie restriction, lifespan, healthspan, and cognitive health

Given there are consistent age-related changes in the brain, the question arises whether strategies that delay aging have any impact on brain aging. To date, the main interventions that delay aging are nutritional. The effects of nutrition on aging, health and lifespan have been recognized since the beginning of recorded history. Ancient philosophers and physicians like Galen, Plato, and Hippocrates realized that particular diets are beneficial for health and can add quality years to life (Schafer, 2005). Moreover it was recognized that restricting food intake can be beneficial for both health span and lifespan. Philippus Paracelsus (1493 – 1541), one of the three fathers of Western medicine, claimed that ‘fasting is the greatest remedy’ while the Venetian, Luigi Conaro (1466–1566) wrote ‘renew yourselves and fast’. The first scientific demonstration of the effects of food restriction on aging was by Clive McCay and colleagues in 1935. In this landmark study, Fischer rats were given fewer calories than their *ad libitum*-fed counterparts in order to delay growth, and they subsequently experienced longer mean and maximum life spans (McCay et al., 1935). This type of nutritional intervention, now called calorie restriction (CR) has been reported to increase lifespan and/or health and healthspan in many species, ranging from yeast to humans and is generally considered to be the primary experimental approach to delay aging in animal models (Everitt, 2010; Fontana and Partridge, 2015; Mercken et al., 2012; Nakagawa et al., 2012; Speakman and Mitchell, 2011).

The mechanisms for the effects of caloric restriction on aging have been extensively studied. The main focus of research has been the nutrient sensing pathways (mTOR, sirtuins, AMPK, IGF1/insulin) which respond to changes in circulating nutrients (amino acids, glucose) or intracellular metabolites that reflect cellular energy supplies (NAD<sup>+</sup>, AMP). These master switches regulate most of the cellular processes linked with aging including mitochondrial function, autophagy, oxidative stress, gene expression, and intracellular metabolism with

downstream tissue-level effects such as inflammation and vascular pathology (Koubova and Guarente, 2003).

There are caveats related to the effects of CR. It has been argued that laboratory diet and conditions allow rodents to become obese (Mattson, 2014), thus accounting for the apparent metabolic benefits of CR. Genetic factors may have an impact on the outcomes of CR. In one meta-analysis (Swindell, 2012) of studies of CR in mice and rats from 1934 to 2011, it was concluded that not only is the effect of CR on lifespan less pronounced in mice compared to rats, but it can also *shorten* the lifespan in particular mouse strains, thus indicating a strong genetic component. Recently, a CR regimen implemented in *Rhesus* macaques at the National Institute on Aging (NIA) improved healthspan but did not improve survival outcomes (Mattison et al., 2012). This contrasted the results of a similar study completed at the Wisconsin National Primate Center where lifespan was increased (Colman et al., 2009). Although these two studies led to controversy surrounding the effectiveness of CR, it is likely that their different dietary components contributed to the results. Importantly, the control group of monkeys in the Wisconsin study was fed *ad libitum*, whereas the control group in the NIA study was fed two portioned meals daily; therefore, the body weights and fat mass of the control Wisconsin monkeys was significantly greater compared to the control NIA monkeys (Mattison et al., 2012).

Due to the positive effects that CR has on healthspan and lifespan, scientists have recently begun to unravel potential mechanisms by which CR positively affects brain health. One of the fundamental theories of how CR contributes to heightened brain function is that the brain may have evolved to function optimally when there is a moderate lack of food and therefore the individual must outwit competitors in the search for nutrients (Mattson, 2015; Mattson, 2002). These challenges produce mild neuronal stress which engages signaling pathways that improve the ability of cells and organs to function optimally, and to resist age-related dysfunction and disease (Mattson, 2010, 2015).

Animal studies have shown that daily CR, intermittent fasting (IF), and alternate day fasting (ADF) not only modify the nutrient sensing pathways in the brain (Figure 2) but also increase synaptic plasticity, neurogenesis and neuroprotection (Fusco and Pani, 2013). CR and IF delay features of aging both on the microscopic and global levels (Pani, 2015). Some of the reported effects of CR and IF on the brain are summarized in Table 1.

CR and IF may enhance synaptic plasticity through an increase in BDNF with downstream effects on neuronal bioenergetics and protein synthesis (Zaptan et al, 2015). BDNF also plays a crucial role in neural precursor cells (NPC) which reside in the dentate gyrus of the hippocampus where they are critical to the formation of new neurons that integrate into the hippocampal circuitry and play roles in spatial pattern separation, a fundamental domain of learning and memory (Marosi and Mattson, 2014; Vivar and van Praag, 2013). It has been shown that IF increases the survival of newly generated neurons in the dentate gyrus of rats (Mattson et al., 2001). Interestingly, it has also been shown that CR increases levels of the nutrient-sensing protein FOXO3 which increases the production of NPC (Renault et al., 2009). It is known that CR decreases levels of circulating IGF-1, which is interesting considering IGF-1 plays important roles in neurogenesis and synaptic plasticity. The

mechanisms. Whilst a beneficial effect of CR on neurogenesis has been demonstrated in rodents, the results are still uncertain in non-human primates and humans.

Neuroprotective effects are also seen through improved mitochondrial respiratory activity (Cerqueira et al., 2012). This is partly due to the up-regulation of PGC1 $\alpha$ , which is a master regulator of mitochondrial respiration and contributes to mitochondrial biogenesis and detoxification (Liang and Ward, 2006). Furthermore, the upregulation of PGC1 $\alpha$  modulates the expression of Nitric Oxide (NO) which has antioxidant and protective properties in the endothelium and may contribute to the preservation of brain microvasculature (Borniquel et al., 2006; Bernier et al. 2016). Additionally, PGC1 $\alpha$  is critical for the maintenance of dendritic spines in the dentate gyrus of the hippocampus, highlighting its importance in memory functions (Cheng et al., 2012). Finally, it does appear that CR preserves hippocampal grey matter volume in Rhesus macaques (Willette et al., 2013) along with the preservation in grey matter volume of subcortical regions (Colman et al., 2009). There have not yet been studies on grey matter preservation with CR in humans.

Of particular interest has been the effect of CR on a family of proteins known as sirtuins that are implicated in healthspan and longevity (Braidy et al., 2015). CR has been shown to increase the activity of sirtuin 1 (SIRT1) thus resulting in lower inflammatory cytokine activity, and enhanced dendritic outgrowth and plasticity (Maalouf et al., 2009; Ng et al., 2015). SIRT1 is of particular interest because it is highly expressed in the hippocampus. Recently it was shown that SIRT1 knockout mice displayed worse cognitive abilities and spatial learning (Michan et al., 2010). SIRT1 also plays a key role in the reduction of brain inflammation. Activation of SIRT1 via resveratrol administration attenuated microglial inflammation in a mouse cell line, possibly through the modulation of several transcription factors including the pro-inflammatory cytokine NF- $\kappa$ B (Li et al., 2015).

Cognitive improvements have been demonstrated in rodents maintained on CR or IF diets. Numerous studies have shown that CR improves spatial, associative, working, and long-term memory in rodents. This has been demonstrated in a range of cognitive-behavioral tests including the Barnes maze, Morris water maze, and novel object recognition tests (Brownlow et al., 2014; Kuhla et al., 2013). CR enhances dendritic spine density in hippocampal dentate granule neurons which is associated with increased levels of BDNF in the hippocampus (Stranahan et al., 2009). Additionally, it was recently shown that 30% CR did improve some aspects of working memory in non-human primates but only on certain tasks (Dal-Pan et al., 2011). In humans the effects of CR on cognition and memory have thus far yielded mixed results. For example, Martin et al. suggested that a 6 month, 25% CR regiment produced no beneficial effect on verbal and visual memory in humans (Martin et al., 2007), whilst Witte et al. showed that a 3 month 30% CR program did improve measures of verbal memory in elderly patients (Witte et al., 2009).

ADF, the most commonly studied type of IF in rodents, has been reported to improve glucose metabolism and cardiovascular risk factors, and can protect cells against oxidative and metabolic stress (Castello et al., 2010; Longo and Mattson, 2014). For example, ADF reduces resting heart rate and blood pressure, increases heart rate variability, and improves cardiovascular stress adaptation in rats (Wan et al., 2003; Mager et al., 2006). In addition,

the hearts of rats and mice maintained on an ADF diet exhibit resistance to ischemia-reperfusion injury in a model of myocardial infarction (Ahmet et al., 2005; Godar et al., 2014). IF also increases the resistance of neurons to dysfunction and degeneration in experimental models of a broad range of neurological disorders including: a focal ischemia-reperfusion model of stroke in rats and mice (Yu and Mattson, 1999; Arumugam et al., 2010); an excitotoxin model of epilepsy in rats (Bruce-Keller et al., 1999); mitochondrial toxin- and genetic mutation-based rat and mouse models of Huntington's disease (Bruce-Keller et al., 1999; Duan et al., 2003); a mouse model of Alzheimer's disease (Halagappa et al., 2007); a mitochondrial toxin- and genetic mutation-based mouse models of Parkinson's disease (Duan and Mattson, 1999; Griffioen et al., 2010); and a rat model of bacterial sepsis-induced neuroinflammation (Vasconcelos et al., 2014). The cellular and molecular mechanisms by which ADF may counteract aging processes and protect against age-related disease are being elucidated and involve stimulation of the production of neurotrophic factors and antioxidant enzymes, enhancement of mitochondrial function and autophagy, and suppression of neuroinflammation (Mattson, 2012). Recent studies of ADF and two days/week fasting in human subjects suggest that IF also improves multiple health indicators in humans (Johnson et al., 2007; Varady and Hellerstein, 2007; Harvie et al., 2010).

#### 4. Macronutrients, aging and the aging brain

There is minimal translational opportunity for daily CR for most humans who have essentially unlimited access to food and cannot sustain the rigors of voluntary CR. While some IF eating patterns are more readily incorporated into modern lifestyles (Mattson et al., 2015), most successful clinical trials have focused on obese or above-average body mass index (BMI) populations (reviewed in Seimon et al., 2015). It is also important to understand the effects of various dietary components on aging and disease risk (Sohal and Forster, 2014). Such studies have tended to focus on altering individual macronutrients in the diet (P; C; and F) although more recent studies have examined the effects of the interactions between macronutrients, i.e., addressing the question of what is the optimum balance of macronutrients for lifespan in *ad libitum* fed animals. It should be noted that without appropriate controls, which are seldom implemented, CR cannot differentiate between the effects of reduced calorie intake versus reduced intake of each of the macronutrients. Additionally, many CR studies are designed to give the animals less food, and therefore are potentially confounded by the effects of IF (Simpson et al., 2015). Intermittent fasting regimes seem to generate similar benefits as CR yet do not necessarily involve reduced calorie intake over longer periods of time because of compensatory periods of overeating. This suggests that IF and even periods of hunger might be important for the effects of CR on aging.

In addition to studies of CR and the aging brain, there has been a considerable amount of research on the effects of micronutrients and pharmaceutical agents on age-related changes cognitive function and dementia in an attempt to find a single therapeutic agent (Barnes et al., 2014; Granzotto and Zatta, 2014; Meramat et al., 2015). However, the role of macronutrients in brain health and aging has more recently been investigated. Many studies have examined the relationship between macronutrients and cognitive function (Table 2). Most of these studies in lower organisms have focused on chronic high-fat diets which

exacerbate cognitive decline with aging (Beilharz et al., 2015). The roles that the macronutrients play in basic aspects of brain health and function have been relatively well established (Figure 3) (Jones et al., 2012; Solfrizzi et al., 2005; Solfrizzi et al., 2003a, b; Yon et al., 2013) and are described below. An understanding of the role of each of the macronutrients on brain function is important when designing a diet with a balance of macronutrients that optimizes brain health. It is not possible to alter the intake of a single macronutrient without influencing the intake of the other two macronutrients or the ratios between the macronutrients so it is likely that the optimum balance of macronutrients for healthy brain aging in an *ad libitum* fed diet will necessitate some trade offs between the beneficial and/or harmful effects of each macronutrient.

#### 4.1 Protein and amino acids

One of the important roles of dietary protein is to provide a supply of amino acids for the production of neurotransmitters, such as catecholamines and serotonin (Bourre, 2006). Of particular interest is the essential amino acid tryptophan, which is a precursor to serotonin, a neurotransmitter involved in mood, information processing and cognitive function. For example, bioavailable tryptophan dietary supplements improved cognition in healthy middle-aged women (Mohajeri et al., 2015). Serotonin cannot cross the blood-brain barrier, however tryptophan crosses via specialized channels and is converted to 5-hydroxytryptophan (5-HTP), which then undergoes further conversion to serotonin (Shabbir et al., 2013). Serotonin levels may decrease with age, possibly contributing to detrimental effects on cognitive function (Bourre, 2006; Melancon et al., 2014). In addition to serotonin other dietary-derived neurotransmitters such as glutamate, aspartate, and taurine are shuttled from surrounding astrocytes to neurons (Gundersen et al., 2015) and potentially could be influenced by dietary amino acids.

#### 4.2 Fats

Dietary fat is an important macronutrient for the brain because it is necessary for the structure of neuronal membranes (Bourre, 2006). All neurons and organelles in the brain are rich in polyunsaturated omega 3 fatty acids (PUFA), which are of dietary origin. Of particular interest have been the omega-3 fatty acids, which make up about 30% of the membrane phospholipid composition in the brain. Whilst the majority of studies on rodents have found detrimental cognitive effects of a long-term high fat diet, a recent study reported that chronic high-fat diet treatment did not affect spatial memory in mice (Kesby et al., 2015). Nonetheless, the omega-3 fatty acid docosahexaenoic acid (DHA) has generated considerable interest due to its role in providing membrane fluidity and synaptic integrity, which in turn can affect cognitive function (Sidhu et al., 2016). It also activates neuronal cascades that affect BDNF and insulin-like growth factor 1 (IGF-1), which further activates signaling cascades at the pre- and post-synaptic levels, thereby affecting long-term potentiation (LTP) and associated memory processes (Gomez-Pinilla, 2008). These effects have been shown in clinical studies, where MRI has confirmed that omega-3 fatty acids can contribute to brain protection during aging (Denis et al., 2015).

### 4.3 Carbohydrates

Adequate carbohydrate consumption is essential for brain function, because glucose is the main energy source for the brain, and the brain requires about 25% of the total glucose energy consumed despite only comprising 2% of total body weight (Sokoloff, 1999). Measures of prefrontal cortex function increase transiently in response to glucose consumption (Kumar et al., 2015). Similarly, in aged rodent models complex cognitive behavioral tasks are rapidly improved post-glucose injection (Gold, 2005). On the other hand, it has been suggested that a chronic excess of glucose consumption can contribute to reduced synaptic plasticity and high levels of inflammation, which may contribute to cognitive deficits (Stefanidis and Watt, 2012). Interestingly, cognitive fatigue is common in older adults, which has been suggested to be partly due to a decline in neuronal glucose utilization with age (Galeffi et al., 2015), possibly as the result of reduced brain sensitivity to insulin (Ryu et al., 2014).

## 5. Anti-aging compounds, the aging brain and dementia

Recently it has been established that a number of compounds can activate or inhibit the nutrient sensing pathways that link diet with aging, and thereby potentially delay aging. Three examples are metformin, rapamycin, and resveratrol. Each of these drugs act via well-established nutrient sensing pathways (Maiese, 2015; Novelle et al., 2015; Pryor and Cabreiro, 2015). For example, the AMPK pathway has received attention as a target for delaying aging because of the availability of the AMPK agonist, metformin (Anisimov, 2013). Metformin has been shown to be a caloric restriction mimetic that prolongs life in various laboratory animals including mice (Martin-Montalvo et al., 2013). Metformin is also widely prescribed for the treatment of type II diabetes. A recent observational study found that diabetics who use metformin have lower mortality than age-matched non-diabetic controls suggesting that its anti-aging effects might also be apparent in humans (Bannister et al., 2014). Metformin has been promoted as a potential anti-dementia treatment based on its metabolic effects. Metformin has been reported to ameliorate cognitive impairment in some mouse models of AD (Li et al., 2012). Observational studies of metformin in diabetic humans, who have a very high risk of dementia as a result of their metabolic dysregulation, have yielded conflicting results with one study showing increased risk of cognitive impairment in diabetics taking metformin (Moore et al., 2013) while other studies have shown reduced risk (Ng et al., 2014). This might reflect different treatment doses, such that overtreatment might also increase the risk of dementia as the result of repeated episodes of hypoglycemia.

Rapamycin inhibits mTOR which plays a central role in signaling downstream pathways that control cell growth and proliferation and is heavily over-activated in certain cancers (Duzgun et al., 2015). Inhibition of mTOR activity with rapamycin is for the treatment of some cancers (Meng and Zheng, 2015) and as an immunosuppressant. Rapamycins increased lifespan in mice, including those mice fed standard diets and commenced on therapy in middle and late life (Harrison et al., 2009; Miller et al., 2011), and its role as a treatment of aging is being tested for feasibility and safety in older humans (Leslie, 2013). Intermittent dosing might be appropriate for long term aging therapy because this should reduce toxicity

(Longo and Fontana, 2011). In AD patients, mTOR signaling is upregulated in the brain and correlates with disease severity (Sun et al., 2014) while down-regulation of mTOR or its inhibition with rapamycin can ameliorate pathology and cognitive impairment in mouse models of AD (Caccamo et al., 2014; Lin et al., 2013; Spilman et al., 2010).

Resveratrol, which is an allosteric activator of SIRT1, has the most beneficial effects under high fat diet conditions, where SIRT1 activity is greatly reduced (Baur et al., 2006; reviewed in Novelle et al. 2015). Some studies in humans have shown improvements in cardiometabolic function with resveratrol (Magyar et al., 2012; Poulsen et al., 2012; Timmers et al., 2012). It has also been shown that resveratrol reverses the phenotype, especially the metabolic changes, in transgenic progeria mice (Labbé et al., 2011) and frailty in old mice (Kane et al., 2016). The role of SIRT1 has also been studied in animal models of AD (Donmez, 2012); for example SIRT1 has recently been shown to mediate effects of metabolic stress on  $\beta$ -secretase (Wang et al., 2013). Overexpression of SIRT1 (Kim et al., 2007; Lalla and Donmez, 2013) and activation of SIRT1 with resveratrol (Porquet et al., 2013; Porquet et al., 2014) can prevent or ameliorate cognitive impairment in experimental models of AD and age-related dementia. Moreover, it was shown that two-year resveratrol supplementation ameliorated neuroinflammation and increased cerebral microvasculature density in Rhesus macaques on a high fat diet (Bernier et al. 2016).

Together these results suggest that rapamycin, resveratrol and metformin, which are agents that delay aging by modulating the nutrient sensing pathways, may also have promise as agents to delay brain aging and forestall the onset of dementia.

## 6. Linking dementia and aging

The observation that dietary and medical interventions that delay aging also delay brain aging and dementia suggests that there is evidence that dementia is part of the aging process, perhaps analogous to sarcopenia and immunosenescence. The prevalence of dementia under the age of 65 years is just 0.1% but this increases 300-fold beyond the age of 85 years, while the majority of people older than 90 years are diagnosed with dementia (Australian Institute of Health and Welfare, 2012; Yang et al., 2013). The powerful influence of aging on the risk of dementia in comparison to other risk factors is demonstrated by the ANU-ADRI scale. Simply living to the age of 85 years confers the same risk for AD as having every other known genetic (i.e., apolipoprotein  $\epsilon$ 4 allele) and environmental risk factor combined (Anstey et al., 2013). Although aging is a risk factor for many diseases (Sierra, 2016), such overwhelming age-dominance is unusual, perhaps shared only with the other as yet untreatable geriatric conditions of sarcopenia and frailty. Therefore, while dementia research has tended to focus on the role of genetic and modifiable risk factors for dementia, it has placed less emphasis on the role of the aging process in the pathogenesis of dementia and the possibility that the aging process is modifiable.

The influence of old age on dementia outweighs all other biomarkers, genes and risk factors (Brayne and Davis, 2012), and the heavily studied amyloid-based biomarkers become less accurate in older people (Mattsson et al., 2012). Numerous clinical trials targeting amyloid have not shown any effect on, and even worsened, cognitive outcomes (Schneider et al.,

2014). This has led some people to question the validity and usefulness of the amyloid cascade hypothesis, which has been the major area of study during the past two decades (Drachman, 2014; Krstic and Knuesel, 2013).

From the clinical perspective it is of note that most chronic disorders that occur in older people – which may have a single etiopathogenesis in younger people – have multifactorial causes on a background of accruing cellular and tissue damage with aging. Thus it is not surprising that Alzheimer's and other forms of dementia share similar trajectories to other disorders and diseases associated with old age in humans. The effects of age on mortality and AD are similar, with a doubling of mortality every 7.5 years from the age of 30, versus a doubling of dementia every 5 years (Raber et al., 2004). Dementia is also closely associated with multi-morbidity and frailty (Oosterveld et al., 2014), which are key clinical manifestations of old age.

Likewise, from the biological perspective it is clear that many of the major cellular and molecular changes of aging (such as characteristic changes in oxidative stress, mitochondrial function, DNA damage, telomere shortening, advanced glycation end products, autophagy) and major systemic changes (microvascular disease, inflammation) have been documented in AD and dementia more broadly (de Cabo and Le Couteur, 2015) (Table 3). All of these processes have been linked individually and separately to dementia. In many cases it has been postulated that they contribute to disease causation.

Although the link between old age and dementia is overwhelming, there have been only a few studies about how the biological changes of aging might influence or even cause dementia. On the other hand, there has been a revolution in understanding the biology of aging in the last decade and this has led to the identification of pharmaceutical, genetic and nutritional interventions that delay aging and multiple age-associated pathologies in a range of species (Fontana et al., 2014). If dementias of all types are multifactorial manifestations of aging and not classical diseases with a discrete pathogenesis, then the therapeutic interventions being developed to act on the aging process could be harnessed and/or exploited for the treatment and prevention of dementia. This opens up a range of novel therapies and drug targets for dementia.

## 7. The Geometric Framework, diet and cognition

Whilst the contribution of individual macronutrients to cognitive fitness has been intensively studied, it is likely that the brain requires a finely tuned balance of macronutrients and micronutrients in order to function properly (Mallidou and Cartie, 2015). It has been shown that changes in diet, even in late life, can have a positive impact on cognition and possibly attenuate dementia (Hardman et al., 2015). An example of this is the Mediterranean dietary pattern. This dietary pattern is mainly followed by people living in the Mediterranean crescent and is largely composed of fresh fish and shellfish, red wine, breads, pasta, fruits, vegetables, and olive oil (Castro-Quezada, Román-Viñas, & Serra-Majem, 2014; Yannakoulia, Kontogianni, & Scarmeas, 2015). People who follow a Mediterranean dietary pattern have improved cognitive function during the transition to old age (Huhn, Kharabian Masouleh, Stumvoll, Villringer, & Witte, 2015; Lourida et al., 2013; Woodside, Gallagher,

Neville, & McKinley, 2014). Another intervention that has been successful in delaying some symptoms of cognitive decline was the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) which combined exercise, cognitive training and diet with defined percentages of fat, carbohydrate and protein, and little sugar (<10%E) (Kivipelto et al., 2013). This multimodal approach was successful in reducing cognitive decline in a cohort of elderly patients (Ngandu et al., 2015). Although these two dietary approaches share some common features such as high intake of fruits, vegetables and wholegrain cereals with limited intake of added sugars, there are also some differences. For example, the FINGER diet is a well-defined diet based on the Finish Nutritional Recommendations and was developed based on a stringent set of specific nutritional guidelines (National Nutrition Council, 2005). On the other hand, the Mediterranean dietary pattern is not as strict in nutritional guidelines and allows for some leniency in food intake (Woodside et al., 2015). Another difference is the source of dietary lipids (rapeseed oil and vegetable margarine in the FINGER diet vs. olive oil and nuts in the Mediterranean diet). Followers of the Mediterranean dietary pattern consume high amounts of legumes which affects the ratio of animal to plant protein as well as the amounts of fibre and phytates in the diet. Contrary to the FINGER diet, moderate consumption of red wine – a moderate source of resveratrol – is recommended in the Mediterranean diet (Huhn et al., 2015).

When looking at the role of macronutrient consumption on aging, one of the main human populations studied in recent years has been the Okinawan people, who enjoy the longest lifespan in the world (Japan Ministry of Health, 2000). There is some evidence that their healthspan and cognitive function is also preserved later in life when compared to other similar populations (Willcox et al., 2014). Whilst there are varying factors involved in this lifespan extension including lifestyle choices and physical activity, perhaps one major factor is their diet, which is 9 percent protein, 85 percent carbohydrate, and very little fat (Reviewed in Le Couteur et al, 2016). Interestingly, these percentages are almost identical to the macronutrient ratios found to increase lifespan and healthspan in mice and insect models, even when compared to CR (Solon-Biet et al, 2014; Le Couteur et al, 2016). These results along with the Mediterranean dietary pattern and the FINGER diet study suggest that many components of the diet (and lifestyle) influence brain aging and that experimental approaches that target individual components of the diet maybe be overly simplistic. It should also be noted that these interventions seem to reduce brain aging as part of a broader outcome which could be termed ‘healthy aging’.

How can the complexity of diet be disentangled experimentally? One approach is the Geometric Framework (GF). GF provides a multidimensional approach that facilitates interpretation of how macronutrients and energy impact on outcomes such as lifespan, age-related phenotypes, and cognitive function (Simpson and Raubenheimer, 2007; Raubenheimer et al. 2016). Responses of individuals, such as cognitive behavior, are phenotypic features that can be superimposed on the experimental nutritional space by plotting these as response surfaces. In a recent study on aging of mice, the GF was used to analyze lifespan and age-related health in animals fed one of 25 diets varying in protein, carbohydrates, fat and total energy content (Solon-Biet et al., 2014). A major conclusion of the latter study is that LPHC diets optimize healthspan and lifespan. LPHC diets were found to inhibit hepatic mTOR, providing a mechanism linking this type of ad libitum diet to

delayed aging. GF was utilized to unravel the complex effects of macronutrients on metabolic health, lifespan (Solon-Biet et al., 2014), immunity (Le Couteur et al., 2015), reproduction (Solon-Biet et al., 2015b) and microcirculation (Cogger et al., 2016). GF methodology is therefore likely to provide insight into how dietary energy and macronutrients influence brain aging and dementia.

## 8. Conclusion

Dietary factors, including energy intake and macronutrient composition, influence brain function, especially during the transition to later life. The study and understanding of aging biology has led to the identification of pharmaceutical and nutritional interventions that delay aging and multiple age-associated pathologies. Therefore, it is plausible that therapeutic interventions that delay the aging process could be used for the treatment and prevention of brain aging and dementia. Whilst the roles of individual macronutrients in the brain have been investigated, interactions among and between macronutrients and micronutrients, with regards to their effects on brain aging are unknown. Diet is complex and this complexity can be disentangled using novel approaches such as the GF, thereby informing future research and nutritional guidelines for the delay of brain aging and dementia.

## Acknowledgments

Funding was provided from the Aging and Alzheimers Research Institute, National Health and Research Council of Australia (NHMRC) grants #571328 and #1084267 and our co-authors in studies cited in this review. RdC and MPM are funded by the Intramural Program of the National Institute on Aging, NIH. SMS-B is supported by the NHMRC Peter Doherty Early Career Fellowship (Grant 1110098).

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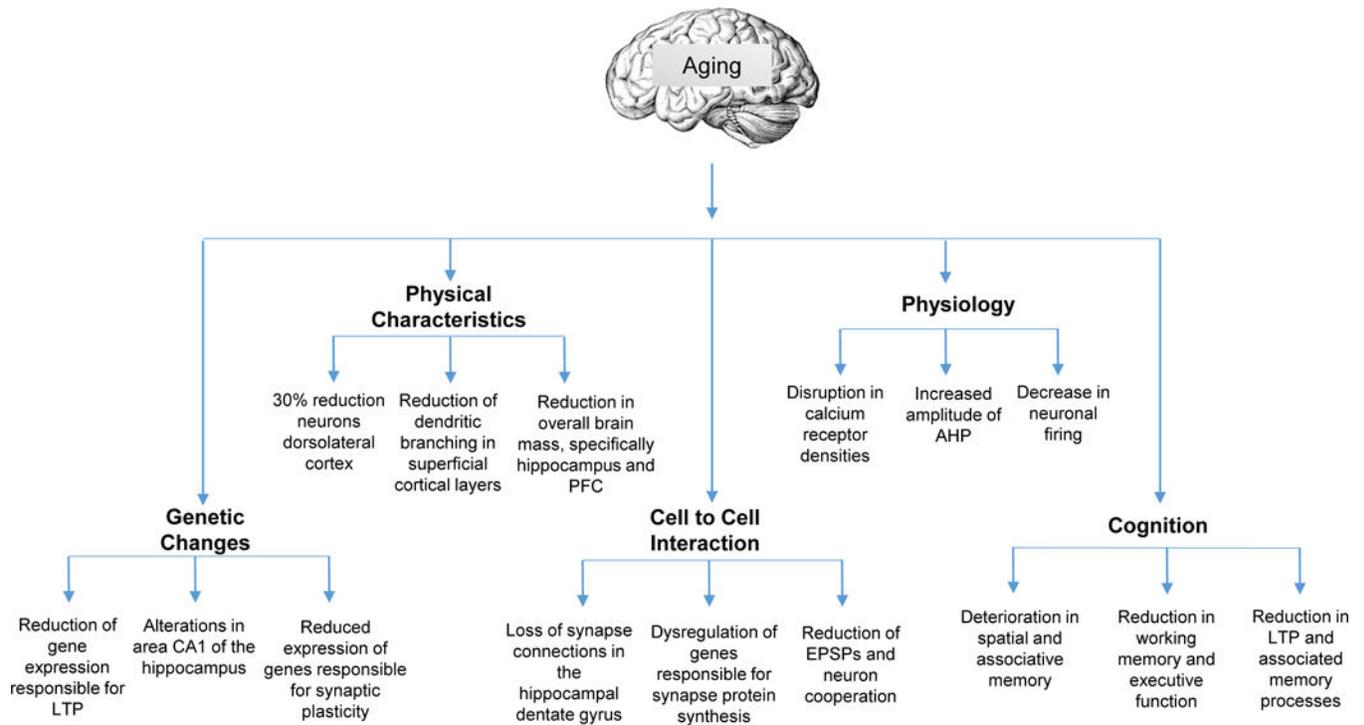
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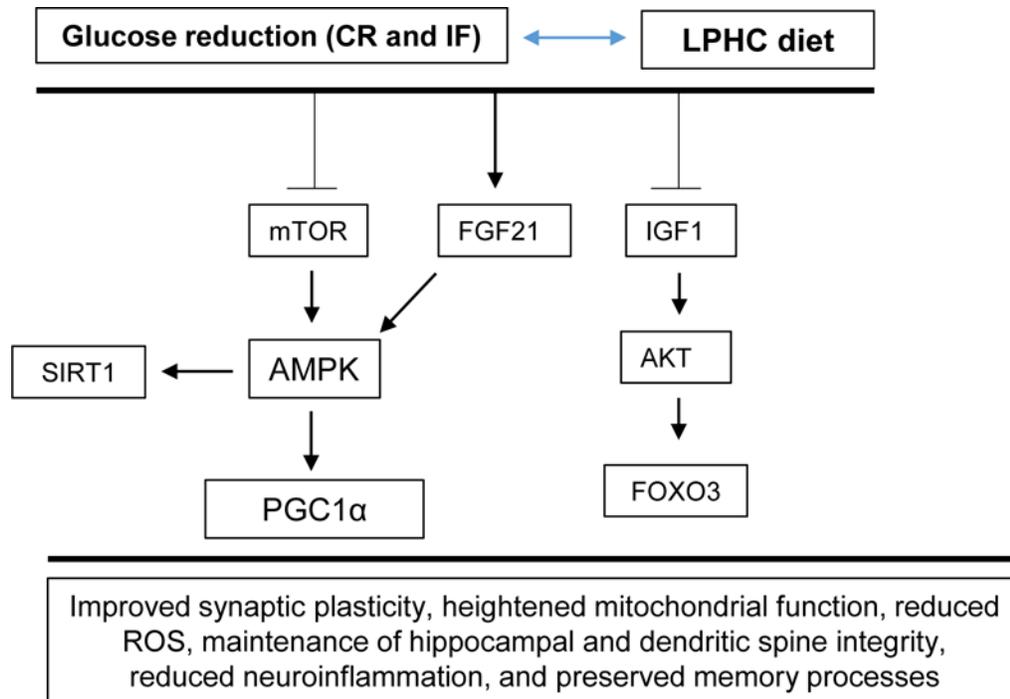
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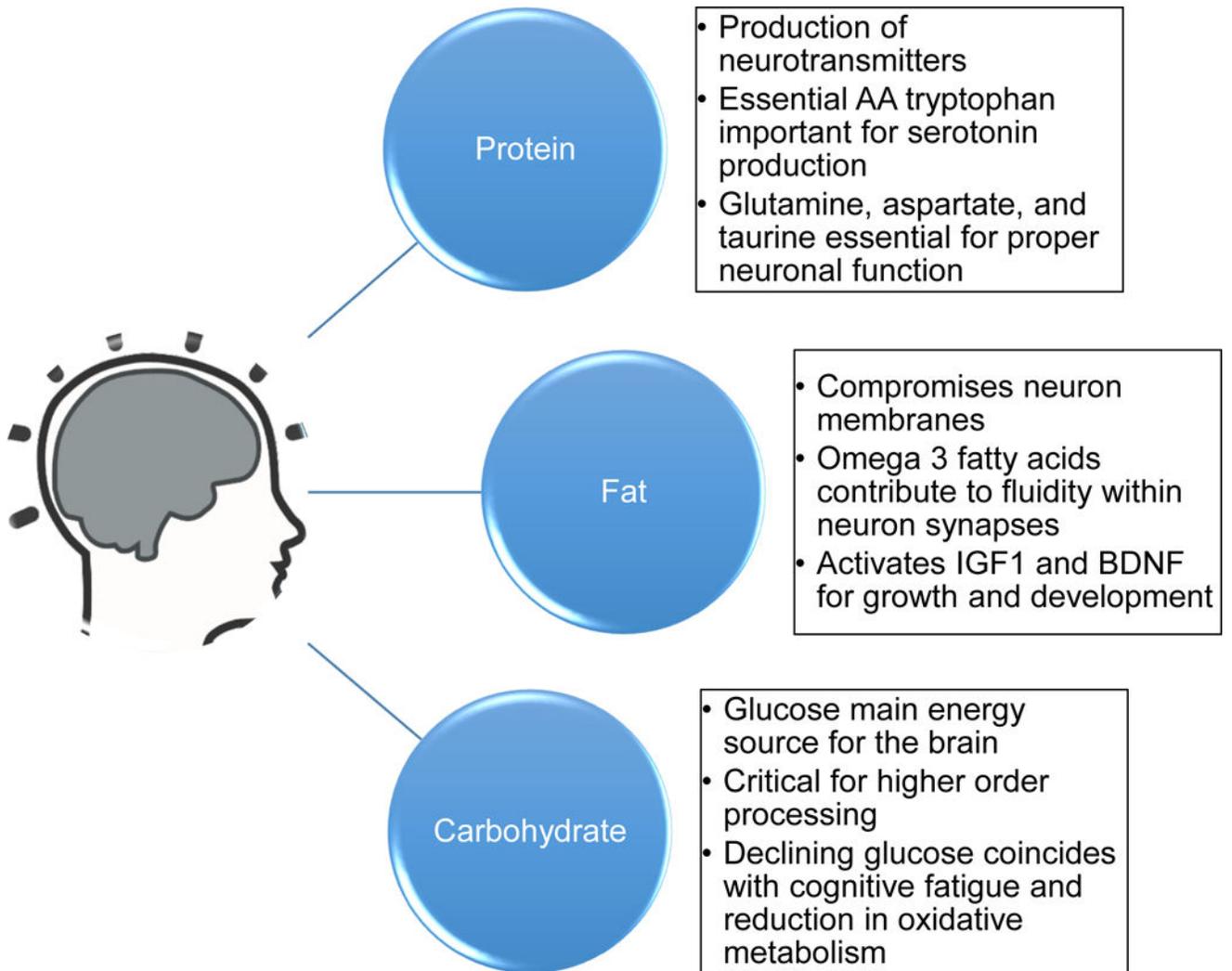
**Figure 1.**

Changes in the brain that occur in aging. Genetic changes, physical characteristics, cell-to-cell interactions, physiological changes, and cognitive differences are included. It has been suggested that these underlying physiological underpinning contribute to the symptoms of cognitive decline. AHP, afterhyperpolarization; EPSPs, excitatory postsynaptic potentials; LTP, long-term potentiation; PFC, prefrontal cortex.



**Figure 2.**

A LPHC diet and its effect on the associated mTOR and related nutrient-sensing pathways. A hypothesis as to how a LPHC diet may affect brain physiology and neuronal function is included. A LPHC diet reduces mTOR activation and increases FGF21 activation, which in turn drives AMPK levels, contributing to the production of beneficial proteins PGC1 $\alpha$  and SIRT1. In parallel, reduced IGF-1 levels heighten the sensitivity of IGF-1 receptors to IGF-1 and contribute to the production of AKT, which drives FOXO3 production, leading to improved insulin sensitivity (Ruderman et al., 2010; Willette et al., 2012; Cheng et al., 2012; Solon-Biet et al., 2015a).



**Figure 3.**

A brief description of the contribution of individual macronutrients to brain health and cognitive function. Whilst the individual contributions have been relatively well-established, what remains elusive is their proper ratios in order to maintain maximal brain fitness in late life.

**Table 1**

Calorie restriction is an effective treatment for many hallmarks of the aging brain, however the effects are still not known or controversial in higher order species.

Aging brain pathology	Species	Calorie restriction effective treatment?	Reference(s)	Notes
Increased mitochondrial Reactive Oxygen Species (ROS)	Rodents Non-human primates Humans	✓ Unknown Unknown	(Hyun et al., 2006)	Only several studies have been published in rodents.
Reduction in neurogenesis	Rodents Non-human primates Humans	✓ Unknown Unknown	(Kaptan et al., 2015)	Although heavily studies in rodents, still unknown in higher-order species perhaps due to a lack of feasible tissue for biochemical analysis.
Slowing of action potentials	Rodents Non-human primates Humans	Unknown Unknown Unknown		The one study in rodents was not cognitive and looked at lumbar motor neurons and corresponding hind-limb muscle activity. The authors concluded no CR effect (Kalmar et al., 2009).
Tangles and plaques	Rodents Non-human primates Humans	✓ Controversial/negative Unknown	(Halagappa et al., 2007) (Sridharan et al., 2013)	Although very few studies exist, there are some promising results in rodents. Presumably the lack of evidence in humans is due to the shortage of tissue for biochemical analysis.
Inflammation	Rodents Non-human primates Humans	✓ ✓ ✓	(Vasconcelos et al., 2014) (Willette et al., 2013) (Johnson et al., 2007)	Perhaps this is the most robust CR effect which has been heavily demonstrated in all three species.
Reduction in spatial, working, and associative memory	Rodents Non-human primates Humans	✓ Limited evidence Controversial	(Brownlow et al., 2014; Kuhla et al., 2013) (Dal-Pan et al., 2011) (Cheatham et al., 2009)	The results are controversial in humans mainly due to the differences in the memory tests and vastly different calorie restriction protocols.

**Table 2**

A selection of clinical trials which looked at individual macronutrient contributions to brain fitness and cognitive function.

Reference and year	Year	Subjects and methods	Nutritional status or intervention	Diet results on cognitive function
(Gibson et al., 2013)	2013	Thirty-eight women, mean age 32.7±5.3 years; BMI 24.9±4.5kg/m <sup>2</sup> . Verbal recognition tasks, delayed matching to sample, and paired associate learning tasks were carried out	Average daily macronutrient intake was assessed via a seven-day food diary. Mean protein (16.3±2.8%); carbohydrate (44.0±5.8%); fat (39.7±6.5%).	Highest fat intake was associated with poorer memory function in all three cognitive tests.
(Holloway et al., 2011)	2011	Sixteen men, mean age 22±1 years. Normal BMI; Double blind, cross over procedure after a 2-week washout period. The Cognitive Drug Research (CDR) computerized assessment battery was performed daily to measure attention, working memory, episodic memory, and self-reported mood and alertness were performed shortly after consumption.	Five days of either a high fat (70%), low carbohydrate (26%) diet or low fat (24%), high (50%) carbohydrate diet.	Cognitive testing showed impaired speed, attention, and mood after consumption of the high fat diet.
(Jones et al., 2012)	2012	Eighteen (5 males, 13 females), mean BMI 21.1kg/m <sup>2</sup> , mean age 19 years. Blind, placebo controlled, wash out, repeated measures design. Tests for spatial working memory, numeric working memory, spatial recall, and immediate word recall were performed shortly after consumption.	Either a 40 g protein in solution, 16 g fat emulsion, 40 g glucose solution, or an inert placebo over four days, with a 5 – 7 day wash out period.	In general, glucose and fat had had the fastest acting effects on memory, whereas protein ingestion had beneficial effects at later time-points. The authors suggested a complex interaction between macronutrients, with each affecting different memory systems.
(Holloway et al., 2011)	2011	Sixteen men, mean age 22±1 year. Normal BMI; Double blind, cross over procedure after a 2-week washout period. The Cognitive Drug Research (CDR) computerized assessment battery was performed daily to measure attention, working memory, episodic memory, and self-reported mood and alertness were performed shortly after consumption.	Five days of either a high fat (70%), low carbohydrate (26%) diet or low fat (24%), high (50%) carbohydrate diet.	Cognitive testing showed impaired speed, attention, and mood after consumption of the high fat diet.
(Jones et al., 2012)	2012	Eighteen (5 males, 13 females), mean BMI 21.1 kg/m <sup>2</sup> , mean age 19 years. Blind, placebo controlled, wash out, repeated measures design. Tests for spatial working memory, numeric working memory, spatial recall, and immediate word recall were performed shortly after consumption.	Either a 40 g protein in solution, 16 g fat emulsion, 40 g glucose solution, or an inert placebo over four days, with a 5 – 7 day wash out period.	In general, glucose and fat had had the fastest acting effects on memory, whereas protein ingestion had beneficial effects at later time-points. The authors suggested a complex interaction between macronutrients, with each affecting different memory systems.
(Roberts et al., 2012)	2012	937 (51% male) participants. Mean BMI 27.7 kg/m <sup>2</sup> . Participants were instructed to record their dietary intake from the past 12 months in a food diary. Cognitive examination took place at 15 month intervals.	As a group, subjects consumed 232 g carbohydrate per day, 78 g protein/day, and 61g fat per day.	High daily carbohydrate percentages were associated with a higher risk of mild cognitive impairment, while higher fat and protein consumption was associated with lower risk of mild cognitive impairment.
(Krikorian et al., 2012)	2012	23 participants (10 men, 13 women) with mild cognitive impairment as per Clinical Dementia Rating (CDR) assessment. Mean age 70.1±6.2 years. Subjects completed a 7-day diet diary prior to intervention. Trial	High carbohydrate (50% of energy) and very low carbohydrate (5–10% of energy) diets with no	Very low percentage of carbohydrate consumption was associated with improved memory performance.

Reference and year	Year	Subjects and methods	Nutritional status or intervention	Diet results on cognitive function
		Making Test Part B and Verbal Paired Associate Learning Test were used to assess executive ability, long term memory, and mood before and after dietary intervention.	restriction on total energy, protein or fat intake.	
(D'Anci et al., 2009)	2009	19 women, aged 22–55 years; repeated measures mixed-factor design. Profile of Mood States (POM) Questionnaire, five computer-based cognitive tasks assessing visuospatial memory, vigilance attention (CPT) with a concurrent secondary task, digit span (forward and backward), and both positive and negative consequences of food preoccupation were performed	Low-carbohydrate (0 g/day 1 <sup>st</sup> week, 5 – 8 g/day 2 <sup>nd</sup> week, 10–16 g/day 3 <sup>rd</sup> week) vs. a low-calorie, macronutrient balanced diet (as per American Dietetic Association)	Low-carbohydrate was associated with less confusion (POMS) and faster response during an attention vigilance task (CPT) than low-calorie, macronutrient balanced dieters.
(Jakobsen et al., 2011)	2011	23 healthy males aged 19–31 years. Randomised, single blinded, parallel intervention study. Addenbrooke Cognitive Examination, Tests for Attentional Performance.	Usual Protein (UP) diet (1.5 g protein/kg BW) for a 1-wk run-pre-intervention then UP or a High Protein (HP) diet (3.0 g protein/kg BW) for 3-wks with controlled intake of food and beverages.	High protein diet improved reaction time.

**Table 3**

Many of the common molecular hallmarks of aging are also present in dementia.

<b>Cellular process</b>	<b>Aging</b>	<b>Dementia reference</b>
Increased oxidative stress	✓(Finkel and Holbrook, 2000)	✓(Wang et al., 2014)
Mitochondrial dysfunction	✓(Balaban et al., 2005)	✓(Ferrer, 2009)
mtDNA mutations	✓(Piko et al., 1988)	✓(Wang et al., 2014)
Shortened telomeres	✓(Honig et al., 2012)	✓(Honig et al., 2012)
Decreased autophagy	✓(Tan et al., 2014)	✓(Tan et al., 2014)
Microvascular abnormalities	✓(Le Couteur and Lakatta, 2010)	✓(Costanza et al., 2012)
Inflammation	✓(Franceschi and Campisi, 2014)	✓(Bettcher and Kramer, 2014)
Advanced glycation endproducts	✓(Baynes, 2001)	✓(Srikanth et al., 2013)

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