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Title	Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions
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Publication date	2018
Original Citation	Miquel, S., Champ, C., Day, J., Aarts, E., Bahr, B. A., Bakker, M., Bánáti, D., Calabrese, V., Cederholm, T., Cryan, J., Dye, L., Farrimond, J. A., Korosi, A., Layé, S., Maudsley, S., Milenkovic, D., Mohajeri, M. H., Sijben, J., Solomon, A., Spencer, J. P. E., Thuret, S., Vanden Berghe, W., Vauzour, D., Vellas, B., Wesnes, K., Willatts, P., Wittenberg, R. and Geurts, L. (2018) 'Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions', Ageing Research Reviews, 42, pp. 40-55. doi: 10.1016/j.arr.2017.12.004
Type of publication	Review
Link to publisher's version	https://www.sciencedirect.com/science/article/pii/S1568163717302064 - 10.1016/j.arr.2017.12.004
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Download date	2026-11-03 14:35:14
Item downloaded from	https://hdl.handle.net/10468/6326



University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Ageing Research Reviews 42 (2018) 40–55

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Poor cognitive ageing: Vulnerabilities, mechanisms and the impact of nutritional interventions

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ARTICLE INFO

Keywords:
Cognition
Preventive diet
Cognitive decline
Neuroprotection

ABSTRACT

Background: Ageing is a highly complex process marked by a temporal cascade of events, which promote alterations in the normal functioning of an individual organism. The triggers of normal brain ageing are not well understood, even less so the factors which initiate and steer the neuronal degeneration, which underpin disorders such as dementia. A wealth of data on how nutrients and diets may support cognitive function and

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https://doi.org/10.1016/j.arr.2017.12.004
Received 8 August 2017; Received in revised form 8 December 2017; Accepted 8 December 2017
Available online 15 December 2017
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Neuro-inflammation
Plant-food bioactives

preserve brain health are available, yet the molecular mechanisms underlying their biological action in both normal ageing, age-related cognitive decline, and in the development of neurodegenerative disorders have not been clearly elucidated.

Objectives: This review aims to summarise the current state of knowledge of vulnerabilities that predispose towards dysfunctional brain ageing, highlight potential protective mechanisms, and discuss dietary interventions that may be used as therapies. A special focus of this paper is on the impact of nutrition on neuroprotection and the underlying molecular mechanisms, and this focus reflects the discussions held during the 2nd workshop 'Nutrition for the Ageing Brain: Functional Aspects and Mechanisms' in Copenhagen in June 2016. The present review is the most recent in a series produced by the Nutrition and Mental Performance Task Force under the auspice of the International Life Sciences Institute Europe (ILSI Europe).

Conclusion: Coupling studies of cognitive ageing with studies investigating the effect of nutrition and dietary interventions as strategies targeting specific mechanisms, such as neurogenesis, protein clearance, inflammation, and non-coding and microRNAs is of high value. Future research on the impact of nutrition on cognitive ageing will need to adopt a longitudinal approach and multimodal nutritional interventions will likely need to be imposed in early-life to observe significant impact in older age.

1. Introduction

By 2030, the number of people aged 60 years or over is predicted to grow by 56% from 901 million to 1.4 billion (United Nations Department of Economic and Social Affairs, 2015). By 2050, the likelihood of developing neurodegenerative diseases, such as Alzheimer's or vascular dementia (VD) will increase by 45% (Alzheimer's, 2015). As a result, all nations will need to divert an increasing proportion of their healthcare funding to treat and manage dementia and other age-related cognitive diseases. It is predicted that by 2050, increases in the ageing population will present significant economic and social challenges and the burden for healthcare systems and on society will become enormous. The current cost of dementia alone is €725 billion worldwide and is expected to reach €1,7 trillion by 2030 (Alzheimer's Disease International and International, 2015). The costs of dementia care are very substantial, and a large proportion of the costs also fall to unpaid carers. The value concerning loss of quality of life of people with dementia needs to be considered in addition to the costs of care.

To address this major global challenge, research funding and effort has increasingly focused on the mechanisms associated with brain ageing and cognitive decline. The number of publications studying cognitive decline is currently around 16,000, and this growing body of research is increasing rapidly, as scientists and governments seek to identify solutions to the coming challenges.

There is overwhelming evidence that major aspects of cognitive function decline from early adulthood onwards, even in cognitively healthy individuals (Salthouse, 2010; Salthouse, 2012a,b). This decline starts during the third decade of life, affects many dimensions of cognitive function, and occurs in all individuals (Salthouse, 2010). There are two major stages to healthy brain ageing, first maturation and development to adulthood, and second the maintenance of function from adulthood to old age (Salthouse, 2010; Salthouse, 2012a,b). Cognitive function tends to improve over the first 18 years of life, peak during the next few years, and then deteriorate steadily thereafter (Salthouse, 2010; Salthouse, 2012a,b). In the absence of adequate nutrition or in the presence of a variety of disease states, cognitive function in 'healthy' individuals will be detrimentally perturbed during their lifetime. Most people will encounter disease at some stage of their life, with the majority of diseases associated with some form of negative consequences for cognitive function (Wesnes, 2006). However, evidence is accumulating that cognitive decline during normal ageing can be attenuated by a wide variety of factors, such as improved nutrition, appropriate dietary supplementation, increased physical exercise, and the performance of mental exercises (Barberger-Gateau, 2014; Ferreira et al., 2015; Gupta, 2016; Makin, 2016; McGilvray, 2016).

In 2016, the ILSI Europe's Nutrition and Mental Performance Task Force organised the 2nd workshop in a series on 'Nutrition for the Ageing Brain'. To capture the value of this workshop, the aim of this paper is to review the vulnerabilities associated with poor cognitive ageing, highlight potential protective mechanisms and how dietary interventions can be a strategy to target some of these mechanisms, and address future research priorities to ameliorate the effects of brain ageing. This review focuses on molecular mechanisms including the novel angles covered by the workshop.

2. Vulnerabilities associated with poor cognitive ageing

2.1. Early-life stress

Research with humans and animals has demonstrated that the brain is sensitive to stress and is especially vulnerable during early childhood and old age (Benton, 2010; Jane Costello et al., 2007; Maselko et al., 2011; Nelson and Trainor, 2007; Walker et al., 2000). Exposure to early-life stress (ES) is associated with lasting changes in the structure of the adult brain and accelerated cognitive decline. A possible role for epigenetic mechanisms, involving DNA methylation changes has been suggested, although the underlying molecular mechanisms remain largely unknown (Bale, 2015; Blouin et al., 2016; Sheerin et al., 2017; Weaver et al., 2004; Yao et al., 2016). Animal studies impose ES using interventions, such as limited access to nest and bedding material (Molet et al., 2014; Naninck et al., 2015). Such interventions are thought to mimic important aspects of human chronic ES and are considered valuable tools to investigate the mechanisms linking accelerated cognitive decline with ES. So far, the lasting effects of ES on cognition have been attributed mostly to alterations in maternal care and neuroendocrine factors (Naninck et al., 2015; Teicher et al., 2012), while the role of early nutrition has been largely ignored. However, both ES and early-life malnutrition often occur simultaneously, and it may be important to investigate the separate and interactive consequences for cognition (Naninck et al., 2013). If early-life nutrition is involved in mediating ES effects on brain structure and function, it is likely that the lasting effects of ES result from the synergistic action of: 1) the quality and quantity of early nutrition 2) stress hormones and 3) sensory stimuli from the mother (Lucassen et al., 2013). Therefore, it is important to study if (and how) ES alters the nutritional/metabolic environment in both the mother and her offspring. Such an integrated approach provides new opportunities for devising nutritional intervention strategies that prevent enduring effects of ES on mental health. As ES exposure often cannot be prevented, a deeper understanding of all elements involved in early programming of the brain by ES is required to develop novel treatment strategies to protect vulnerable individuals from the lasting effects of ES. The effects of various elements of the early-life environment (e.g. maternal care, neuro-endocrine factors, nutrient availability, and metabolic hormones) are often considered in isolation, despite the intense crosstalk between stress and metabolic programming. However, emerging evidence demonstrates that enriching the diet early in life with essential micronutrients prevents some of the negative consequences of ES, opening new

perspectives for nutritional interventions (Naninck et al., 2017).

2.2. Gut microbiome

Early-life stress in animals results in changes in the microbiome in adulthood (O'Mahony et al., 2009). Specific changes in the stress response are linked to changes in the functioning of the gut-brain axis (Dinan and Cryan, 2013). Furthermore, there is evidence of co-morbidity between gastrointestinal conditions and stress-related psychiatric symptoms (Kennedy et al., 2012).

The gut microbiota influences development and homeostasis in adulthood (Claesson et al., 2012). Unlike healthy adults, the composition of the intestinal microbiota of those aged above 65 shows more inter-individual variation (Biagi et al., 2010; Claesson et al., 2011). The microbiota profiles of ageing individuals have been associated with the degree of retention of a core microbiome, long-term residential care, and age and habitual diet (O'Toole and Jeffery, 2015). The composition of faecal microbiota in the elderly has also been found to correlate with frailty and co-morbidity (Claesson et al., 2012). Specifically, the gut microbiota has been shown to modulate the gut-brain axis, through which it exerts an influence on both cognitive function and plasticity during ageing (Leung et al., 2015).

Differences in the microbiota of young and adult mice fed a control diet have been found to influence social behaviour (Palma et al., 2014). In a series of behavioural experiments, young mice showed significantly elevated exploratory behaviour of a displaced object relative to aged mice, and aged mice explored the open arms of a maze significantly less than young mice. Furthermore, young mice demonstrated significantly greater exploration of a novel mouse compared to aged mice in a social recognition experiment (Desbonnet et al., 2014; Heijtz et al., 2011). Ageing has also been associated with an increase in gut permeability. Oral administration of fluorophores-conjugated macromolecules (i.e. fluorescein isothiocyanate-dextran) in young and aged mice has shown that aged mice have significantly greater gut permeability, especially following restraint stress. Moreover, the presence of proinflammatory cytokines is significantly greater in the plasma of aged mice relative to young mice, thus showing an increased pro-inflammatory profile in ageing (Scott et al., 2017). Work with invertebrates has highlighted the role of the microbiota in directly and indirectly impacting the host genome to promote longevity. For example, worms consuming metformin have an increased lifespan in an AMPK-dependent manner. This relationship is indirectly mediated by the impact of metformin on bacterial folate metabolism (Heintz and Mair, 2014).

Germ-free animals have been used to elucidate the relationship between gut microbiota and pathological ageing. A germ-free mouse model of Alzheimer's disease (AD) was found to show a reduced number of β-amyloid plaques relative to control AD mice with intestinal microbiota. However, the presence of plaques in the germ-free mice increased dramatically following the introduction of microbiota harvested from the control mice (Harach et al., 2015). Germ-free mice models are valuable in illustrating the importance of gut microbiota in the gut-brain relationship. Research has shown that gut microbiota is required for normal stress-hormone signalling, neural function, including increased hippocampal neurogenesis, increased blood-brain barrier permeability, regulating immune function, and anxiety-like and sociability behaviours (Luczynski et al., 2016). Further, postnatal microbial colonisation has been implicated in brain plasticity and the Hypothalamic Pituitary-Adrenal (HPA) stress reaction of germ-free and specific pathogen-free (SPF) mice. Following 1 h of restraint stress, germ-free mice had markedly higher plasma adrenocorticotropic hormone (ACTH) and corticosterone levels relative to SPF mice (Sudo et al., 2004). This HPA response in germ-free mice was partially corrected three weeks following reconstitution of SPF faeces at 9 weeks of age but not at 17 weeks, indicating that microbial colonisation at an early stage of development is needed for the HPA system to become fully susceptible to inhibitory neural modulation. Germ-free mice also had significantly lower levels of brain-derived neurotrophic factor (BDNF) in the cortex and hippocampus to that of SPF mice (Sudo et al., 2004). Similarly, microbial colonisation has been suggested to initiate signalling mechanisms that influence neural circuits, which modulate motor control and anxiety-like behaviours. Specifically, germ-free mice showed greater motor activity and reduced anxiety when compared to SPF mice with a normal gut microbiota (Heijtz et al., 2011). Moreover, as well as displaying reduced anxiety-like behaviour, germ-free mice have also shown increased explorative behaviour in comparison to SPF mice (Neufeld et al., 2011). Interestingly, the microbiome has been found to influence neural circuits in a gender-dependent manner. In male germ-free animals, a significant increase in hippocampal serotonin levels, 5-hydroxyindoleacetic acid, and plasma concentrations of tryptophan were identified relative to conventionally colonised control animals. The elevated serotonin and 5-hydroxyindoleacetic acid concentrations were not influenced by colonisation post-weaning, regardless of tryptophan levels returning to baseline values. As such, the lack of a normal gut microbiome has long-term consequences for central nervous system neurotransmission, which cannot be restored following the introduction of a normal gut microbiome in later life (Clarke et al., 2013). Conversely, there was greater down-regulation of genes related to the immune system (Stilling et al., 2015), which supports the suggestion that germ-free mice have an under-developed immune system (Cebra, 1999). Amygdala transcriptome alterations failed to be completely restored following colonisation with conventional microbiota post-weaning, thus lending further support towards hypotheses involving the existence of critical stages of neuro-development (Stilling et al., 2015). Likewise, both germ-free mice and those colonised post-weaning have been found to have 190 and 15 genes differentially expressed in the prefrontal cortex relative to conventionally colonised mice, respectively; with significant overlap suggesting the absence of microbiota during early development has irreversible consequences for cellular functions. In particular, 19% and 27% of genes found to be up-regulated in both mice types were associated with myelin components or neuronal activity, respectively.

2.3. Non-communicable diseases, such as obesity, type 2 diabetes and glucose regulation

In contrast to some infectious diseases, non-communicable diseases, such as neurodegenerative disease, cancer, obesity, and cardiometabolic disorders do not typically develop rapidly, but rather progress to a pathological state over many years. Obesity is associated with co-morbidities, such as chronic inflammation, impaired glucose tolerance, insulin resistance, and type 2 diabetes mellitus (T2DM), and rates of obesity are increasing. Midlife obesity is a significant risk factor for later life dementia (Sellbom and Gunstad, 2012), and has been found to be associated with cognitive impairment across a range of cognitive domains in a recent systematic review (Prickett et al., 2015). However, in older adults, current obesity levels have been inversely associated with dementia (Fitzpatrick et al., 2009). This could represent an "obesity paradox" in which late life weight loss may precede dementia (Hughes et al., 2009) and occur before a presentation of cognitive impairment. A recent retrospective cohort study of almost 2 million individuals aged over 40 years in the UK reported that being underweight in middle age and old age carries an increased risk of dementia (Qizilbash et al., 2015). However, this is controversial and in contrast to the evidence of an association between obesity and dementia. This finding may therefore reflect the possible tendency to underdiagnose dementia by general practitioners at the time the data was collected, and over or under adjustment for a number of factors, such as competing risk of mortality, selection bias, and bias in the diagnosis of dementia in those with lower BMI/age (Harrison and Shenkin, 2015).

Obesity may impact cognitive function prior to any dementia-related cognitive decline, leading to the suggestion that interventions aimed at promoting weight loss may attenuate late-life cognitive

decline. Midlife obesity is most consistently associated with impaired executive function in older adults, but impairments in language, motor, and memory performance have also been documented (Gunstad et al., 2010). A number of mechanisms have been proposed to account for the association between obesity and impairment of cognitive function. These include inflammation, impaired cerebral metabolism or blood flow, elevated leptin, and neuronal degradation. Inflammatory markers such as C-reactive protein (CRP) are found in the obese, where greater brain atrophy, lower grey matter and total brain volume, and increased white matter hyperintensities have also been observed (Prickett et al., 2015). Other mechanisms suggested to account for obesity-related impairment of cognitive function relate to the co-morbidities, which are common in obese adults and apparent usually from midlife, for example hypertension, dyslipidemia, impaired glucose tolerance, insulin resistance, and T2DM.

The association between diabetes and cognitive impairment was recognised almost a century ago (Miles and Root, 1922). Numerous studies have compared cognitive functioning in diabetic patients with non-diabetic controls (Brands et al., 2005). The majority of these studies detail cognitive impairments, such as decreased performance on attention and memory tasks (Awad et al., 2004; Brands et al., 2004; Lamport et al., 2013; Tun et al., 1990; van den Berg et al., 2009). Performance of complex cognitive tasks appears to be more impaired as a result of diabetes, whereas performance of less demanding tasks seems to be comparable to controls (Tun et al., 1990). This pattern parallels the cognitive changes of normal ageing, where age differences are insignificant on less demanding immediate memory tasks, but more pronounced on secondary or long-term memory tasks (Perlmuter et al., 1984).

Impaired glucose tolerance (IGT) often occurs prior to the development of diabetes and may contribute to cognitive impairments (Lamport et al., 2009). Recent studies have shown that the performance of ostensibly healthy middle-aged women with IGT was impaired in cognitive tasks which predominantly engage the hippocampus (Lamport et al., 2014). Interventions that improve glucose tolerance have also been shown to improve cognitive function (Yamamoto et al., 2009).

Since obesity and subsequent T2DM increases the risk of AD by 65% (relative risk in T2DM is 1.46 (Cheng et al., 2012)), and around 80% of AD patients have problems with glycaemic control, AD has been referred to as Type 3 diabetes (De La Monte and Wands, 2008). It has been proposed that AD is a metabolic disease, mediated by impairments in brain insulin responsiveness, glucose utilisation, and energy metabolism, which leads to increased oxidative stress and inflammation, which worsens insulin resistance (De La Monte and Wands, 2008). Advanced glycation end-products (AGEs) are also elevated in both T2DM and AD. The relative risk of VD in those with T2DM is 2.49 (Cheng et al., 2012), and its development relates to a history of hypertension and disturbances in cerebral blood flow. Metabolic disturbances, such as insulin resistance, hyperlipidaemia, cholesterolaemia, and impaired vascular function (e.g. increased blood pressure and reduced cerebral blood flow), which occur at sub-clinical levels in pre-disease states, may elevate the risk of subsequent cognitive decline and dementia (Hassing et al., 2009). Evidence from MRI studies suggests that asymptomatic cerebrovascular brain injury is common, often occurring in midlife and related to cardiovascular disease risk factors. This implies that interventions that address cerebrovascular risk factors during middle age may be prophylactic for cognitive ageing. One such intervention is bariatric surgery, which has been shown to promote rapid improvements in memory and executive function that persist for several years postoperatively (Spitznagel et al., 2015). This post-operative improvement in memory performance is not seen in individuals with a family history of AD (Alosco et al., 2014), which suggests that genetic vulnerability or family history may attenuate cognitive recovery post-bariatric surgery.

2.4. Environmental factors and epigenetic modulation

Adipocytes release pro-inflammatory adipokines, which can promote the pathological chronic inflammation associated with obesity. Epigenetic ageing can be accelerated by the cumulative addition of chemical DNA methylation marks to the (epi)genome (Quach et al., 2017). As such, an individual's personal lifestyle (stress, diet, pollution, exercise, smoking, alcohol consumption, and sleep deprivation) leaves a trail of chemical epigenetic marks in the genome by means of cumulative (stochastic) DNA methylation, which alters gene expression, leading to a spectrum of disease/health related phenotypes. An unhealthy lifestyle will accelerate an individual's epigenetic age (clock) (Mather et al., 2016; Nevalainen et al., 2017; Quach et al., 2017; Zannas et al., 2015) as compared to their biological age, and promote early onset of complex lifestyle diseases, such as cancer, cardiometabolic diseases, and cognitive decline (Fraga et al., 2005; Wolf et al., 2016). In contrast, a healthy lifestyle will decrease epigenetic age (clock) relative to biological age and delay the onset of lifestyle disease (i.e. healthy years free of disease are added). Epigenetic ageing can be compared to the emptying of an hourglass, where lifestyle determines the speed at which sand moves from the top to the lower compartment (reflecting metabolic inflammatory rate). This may also explain the rather small epigenetic impact of relatively short (6–8 weeks) diet interventions in comparison to the epigenetic impact of chronic disease promoting lifestyle conditions/exposure, which typically are persistent over many years (smoking, stress, pollution, alcohol abuse) (Milenkovic et al., 2014). Moreover, nutrition and exercise interventions trigger highly variable (epigenetic) DNA methylation changes involved in vascular inflammation, cardio-metabolic, cognitive health, and epigenetic age (Quach et al., 2017). Epigenetic variation creates multiple redundant possibilities (homeostasis) to achieve healthy ageing or to develop premature ageing/lifestyle diseases. Inter-individual variation in microbiome composition contributes in different pharmacodynamics of nutritional bioactives (Cortese et al., 2016; Paul et al., 2015; Stilling et al., 2014). Inter-individual epigenetic variation in expression of ADME proteins (involved in absorption, distribution, metabolism, and excretion) further contributes to inter-individual variation through different pharmacodynamics of nutritional bioactives (Fisel et al., 2016; Ingelman-Sundberg and Cascorbi, 2016). Finally, the inter-individual epigenetic nutritional response is also co-determined by genetic single nucleotide polymorphisms (SNPs) in genes associated with methyl (one carbon) donor metabolism, i.e. methylenetetrahydrofolate reductase (Anderson et al., 2012; Declerck et al., 2017; Friso et al., 2002; Quinlivan et al., 2005; Stover, 2009).

3. Potential mechanisms underlying vulnerabilities

3.1. Neurogenesis

The hippocampus is a key brain structure associated with learning, memory, and mood, and is one of the two structures in the adult brain where the formation of new neurons (or neurogenesis) persists throughout life in numerous species, including in human (Eriksson et al., 1998; Ernst et al., 2014; Spalding et al., 2013). The functionality of these adult-born neurons in the adult hippocampus has been linked directly to cognition, learning, and memory (Deng et al., 2010; Eisch and Petrik, 2012). For example, in the adult rodent, hippocampal neurogenesis is crucial for pattern separation abilities (Clelland et al., 2009). Hippocampal neurogenesis decreases with age in rodents, as does pattern separation abilities in humans (and cognition in general). Therefore, neurogenesis could be the target for interventions to prevent or slow down cognitive ageing.

Adult hippocampal neurogenesis can be modulated by the systemic environment (blood) in an age-dependent manner (Murphy and Thuret, 2015). Studies using heterochronic parabiosis, which involves the surgical attachment of young to old organisms so they share a common

vascular system, have revealed that the systemic environment has a profound effect on stem cell function and hippocampal neurogenesis. In particular, specific youthful rejuvenating circulatory factors reverse age-related declines in stem cell function and restore neurogenesis and some associated hippocampal memory tasks, whereas the old milieu contains inhibitory factors that impede stem cell function and neurogenesis when transferred to young animals (Villeda et al., 2014, 2011; Villeda and Wyss-Coray, 2013).

Diet will impact on the composition of the systemic milieu and can similarly modulate stem cell ageing, adult hippocampal neurogenesis, and cognition (Murphy and Thuret, 2015). Therefore, modulation of adult hippocampal neurogenesis by diet emerges as a possible mechanism by which nutrition can impact on cognitive ageing either via the systemic milieu or via the gut-microbiota, as discussed earlier. Given that both age and diet can alter stem cell function and neurogenesis, and that these alterations are facilitated by changes in the levels of circulating factors, these influences should be investigated further. Dietary interventions that potentially could promote healthy ageing by enhancing stem cell function and neurogenesis are discussed further below. There is now a need for dietary human interventions to assess specific neurogenesis-dependent cognitive tasks such as pattern separation.

3.2. Proteostasis and multi-dimensional controllers of ageing

In the early stages of brain ageing, neurons experience an imbalance between protein production and protein clearance, which very likely increases the risk of age-related protein accumulation pathology linked to AD, Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia (FTD), and other dementias (Bahr, 2009; Ross and Poirier, 2004; Wang et al., 2018). AD is the most common multi-proteinopathy, with phosphorylated tau and the Amyloid β42 (Aβ42) peptide suspected as key pathogenic contributors (Glodzik-Sobanska et al., 2009; Grundke-Iqbal et al., 1986). In 50–60% of AD cases, protein accumulations also involve Tar-DNA binding protein-43 (TDP43), a protein linked to FTDs and amyotrophic lateral sclerosis, as well as α-synuclein, which accumulates in PD and related Lewy body diseases. Tau and Aβ42 pathology has been found to propagate across the elderly brain in cognitively normal women and men, and their deposition is associated with distinctive patterns of grey matter loss (Sepulcre et al., 2016). Moreover, the two proteins were found to be associated with aberrant neural activity during memory encoding in cognitively healthy older people, leading to declines in memory performance (Marks et al., 2017). These studies broaden the concepts of cognitive ageing to illustrate that controlling AD-type protein accumulation events during ageing is important for the maintenance of mental performance in late-life.

Strategies are needed to promote proteostasis in older age to control the synthesis, folding, trafficking, and clearance of aggregation-prone proteins in order to reduce occurrences of synaptic compromise and dementia risk. Such strategic avenues will likely need to target multiple pathogenic proteins to offset dementia-related accumulation events, often developing slowly for many years before memory problems arise. Ubiquitously expressed chaperone proteins have been identified that enable cells to cope with protein misfolding events, and the cellular chaperones facilitate native folding and regulate the rates of protein synthesis and clearance (Kalmar and Greensmith, 2017). Chaperone-mediated autophagy degrades many types of proteins delivered to lysosomes and may attenuate proteinopathy and ageing (Loos et al., 2017). Drug targets for proteostasis continue to be identified to: 1) induce chaperone levels and decrease the aggregation of diverse proteins (Jimenez-Sanchez et al., 2015), 2) boost proteasomal protein clearance activity to lower pathogenic tau levels, promote synaptic maintenance, and improve cognitive performance (Farizatto et al., 2017; Myeku et al., 2016), and 3) enhance enzymes of the autophagic-lysosomal pathway to reduce protein accumulation stress and associated synaptic pathology (Bendiske and Bahr, 2003; Butler et al., 2011; Lee et al., 2004). The autophagy-lysosomal system plays a critical role in protein clearance and neuronal homeostasis (Bahr et al., 2012; Bendiske et al., 2002; Bendiske and Bahr, 2003; Mueller-Steiner et al., 2006), affording efficient protein digestion and turnover and contributing to cell health and possibly longevity (Folick et al., 2015). Lysosomal enzymes such as cathepsin B represent therapeutic targets for clearing age-related protein accumulations that lead to synaptic pathology. An additional avenue to offset age-related proteostatic stress has been suggested to be through blocking the extralysosomal enzyme calpain, leading to both induction of autophagy and positive proteasomal regulation (see (Romine et al., 2017)).

The lysosomal protease, cathepsin B, responds to age-related protein accumulation stress (Bahr, 2009; Bendiske and Bahr, 2003), perhaps as a compensatory response that accounts for the gradual nature of disease progression in most AD cases. Cathepsin B has been linked to tau clearance (Farizatto et al., 2017), has been shown to degrade Aβ42 through carboxy-terminal truncation, and to correspondingly reduce Aβ synaptic toxicity and neuropathology in transgenic mouse models and a hippocampal slice model (Bahr et al., 2012; Butler et al., 2011; Mueller-Steiner et al., 2006; Wang et al., 2012). Exercise, which is thought to reduce the risk of AD, heart disease and other disorders, has recently been shown to elevate cathepsin B in monkeys and humans, and the elevated levels also correlate with improved hippocampal-dependent memory (Moon et al., 2016). Taken together, this is consistent with research suggesting that exercise may reduce age-related memory loss and prevent or delay AD. In addition, enhancing lysosomal function has been implicated as a strategy against α-synucleinopathy of PD and Lewy body diseases (Lee et al., 2004). In relation to HD, enhancing cathepsins B and D was found to protect against mutant Huntington toxicity (Liang et al., 2011).

Further research to understand the importance of proteostasis is recommended to identify positive modulators of the systems involved. Positive cathepsin B modulators for reducing the risk of multi-proteinopathy may extend across synthetic and natural compounds. Efficient clearance of age-related protein accumulations may require enhancement of both proteasomal and lysosomal systems, thus future efforts are needed to understand the distinct interactions between the two clearance pathways in the brain (Farizatto et al., 2017) and to assess natural and synthesized agents for distinct and dual modulatory effects. Drugs targeting only one type of pathogenic protein (Aβ42) have failed in recent human trials for AD. However, a more hopeful outlook may be provided by a compound that can target multiple proteins that accumulate abnormally. While the usefulness of transgenic AD models for screening potential therapeutics has been called into question in light of failed clinical trials, this issue reiterates the importance of taking into account the multi-proteinopathy aspect of the disease. Transgenic mice may be missing dozens or even thousands of human proteins to properly replicate human AD, which is something probably vastly different than the disorders produced in mouse models. We may also never be able to adequately model human brain ageing or dementia for precise drug-discovery efforts. For example, in a mouse's short life, it is impossible to reproduce the everyday human stress that can span several decades. Many human genetic factors and protein–protein interactions may be involved in age-related cognitive decline. Targeting multiple aspects of early proteinopathy provides a potential strategy to promote cellular homeostasis and synaptic health for cognitive functions, perhaps through combinations of pro-lysosomal and pro-proteasomal nutrition components. Promoting protein clearance pathways from middle age may be needed to effectively reduce the risk of age-related cognitive impairment and extend the years with good mental performance for optimal benefit.

Ageing is a highly complex, pathophysiological process linking metabolic alterations to the generation of accumulated cellular/tissue damage, and has been shown to underpin a wide variety of disorders associated with neurodegeneration (e.g. AD (Monacelli et al., 2017) and

PD (Reeve et al., 2014), cardiovascular diseases (Ghebre et al., 2016), and metabolic dysfunction (Brewer et al., 2016)). Highly complex processes such as ageing may be regulated by a small group of systems controlling multidimensional protein factors named 'hubs' (Balistreri et al., 2016; Chadwick et al., 2012; Korwitz et al., 2016; Morris, 2013). Hub proteins connect multiple signalling protein 'nodes' within a larger network. This 'higher-level' of network connectivity between hubs greatly enhances the speed and fidelity of molecular coordination between functionally-related proteins/genes that control specific aspects of (patho)physiology in a manner reminiscent of network bridging factors in mathematical small-world network theory (Watts and Strogatz, 1998). Identifying and therapeutically targeting these hubs, before the onset of systemic age-related damage, may represent a novel and highly effective mechanism for treating age-related degeneration. Research has identified the G protein-coupled receptor kinase interacting protein 2 (GIT2) as a potential 'hub' molecule that controls the ageing process by regulating the rate of damage accumulation, in the form of oxidative stress and DNA damage, across the lifespan (Chadwick et al., 2012, 2010; Lu et al., 2015; Martin et al., 2015; Siddiqui et al., 2017). GIT2 acts as a molecular bridge between diverse physiological processes that are interconnected in the ageing process. Therefore, therapeutic control of this keystone factor likely represents an important way forward for the treatment of age-dependent disorders, such as AD and others related to neurodegeneration.

3.3. Oxidative stress, inflammation and mitochondria

The pharmacological manipulation of cellular-stress pathways is emerging as a viable approach to treating certain neurologic diseases such as AD, or psychiatric disorders such as schizophrenia (Calabrese et al., 2016a; Calabrese et al., 2017b). For instance, increased oxidative stress can damage mitochondrial proteins and has been implicated as a contributory factor to AD pathogenesis. To adapt to environmental changes and survive different types of injuries, brain cells have evolved networks of responses that detect and control diverse forms of stress. Consistent with this notion, integrated survival responses exist in the brain, which are under control of redox-dependent genes, called vitagenes, including heat shock proteins (Hsps), sirtuins, thioredoxin, and lipoxin A4 (LXA4) (Calabrese et al., 2011). Vitagenes network is composed, besides those mentioned above, by genes, such as Nrf2-dependent enzymes heme oxygenase and γ-glutamyl cysteine ligase, which sense redox perturbations, including oxidative damage, and actively operate in promoting cell survival under physiopathological conditions (Calabrese et al., 2011). LXA4 as an endogenously produced eicosanoid, which blocks the generations of pro-inflammatory cytokines and toxic compounds including reactive oxygen species (ROS), promotes resolution of inflammation, and acts as an endogenous "breaking signal" in the inflammatory process. Additionally, recent evidence linking the restoration of redox homeostasis by nutritional mushrooms (e.g. *Coriolus versicolor*, *Hericium erinaceus*), suggests potential neuroprotective strategies in brain ageing and neurodegenerative disease aimed at inducing the vitagene defence system mechanism (Trovato et al., 2016a,b).

Recent studies have demonstrated that the inflammasome modulates neuro-inflammatory processes at the initial stage, followed by a secondary cascade of events including oxidative stress (Freeman and Ting, 2016). Inflammasomes are multiprotein complexes assembled in response to infection, cell damage, or environmental stress. The AIM2 inflammasome is activated by cytosolic DNA and in addition, it has recently been demonstrated that mitochondria represent major sources of Damage-Associated Molecular patterns (DAMPs) capable of triggering neuro-inflammatory responses, with resulting apoptosis and pyroptosis (highly inflammatory form of programmed cell death). Inappropriate recognition of cytosolic DNA by AIM2 contributes to the development of a number of autoimmune and inflammatory diseases and neurodegenerative disorders. The pharmacological modulation of exogenous/endogenous stress, as discussed above, may be framed within the context of hormesis, a dose response phenomenon, characterized by low-dose stimulation and high-dose inhibition. Numerous pharmacological agents and chemical stressors, when acting at low doses, are able to upregulate adaptive responses that protect against subsequent noxious stimuli in a broad range of cellular conditions due to normal and pathological ageing processes, as well as damage induced by exogenous agents, such as ionizing radiation and toxic chemicals (Calabrese et al., 2017a; Calabrese et al., 2010; Calabrese et al., 2016b; Pennisi et al., 2017). These hormetic-dose responses are independent of the biological model, cell type, endpoint, and chemical class/physical agents and mechanisms. They are therefore highly generalizable and a fundamental evolutionary strategy. In addition, the phenomenon of pre-conditioning and post-conditioning have also been shown to conform to the quantitative features of the hormetic dose response and are now considered to be manifestations of hormesis (Calabrese et al., 2017a).

3.4. Non-coding RNAs and miRNAs

Coding transcripts responsible for protein expression make up less than three per cent of the human genome. Recently, it has been found that around 80 per cent of the human genome is transcribed into non-coding RNAs, with a substantial amount of these being functionally active RNAs. Non-coding RNAs are divided into 2 groups called small non-coding RNAs (e.g. microRNAs) and long non-coding RNAs (e.g. lncRNAs) (An integrated encyclopedia of DNA elements in the human genome, 2012; Uchida and Dimmeler, 2015). Non-coding RNAs play an important role in regulating a large number of cellular functions and physiological processes. In the brain, they have been shown to play a role in the regulation of different brain functions, such as neural stem cell maintenance, neurogenesis and gliogenesis, brain patterning, synaptic and stress responses, and neural plasticity (Huang et al., 2017). Studies on ageing processes, as well as the characterization of various neurodegenerative diseases using different genetic models (e.g. yeast, fly, mouse, and human systems), have demonstrated the role of these non-coding RNAs on brain function/dysfunction (Szafranski et al., 2015), implicating a variety of RNA-regulatory processes. For example, R-loop formation and RNA accumulation represent mechanisms in brain ageing and neurodegeneration. Long non-coding RNAs have been suggested to regulate depression (Huang et al., 2017). MicroRNAs (miRNAs) are an abundant class of short non-coding RNAs that regulate a variety of cellular processes through the post-transcriptional regulation of gene expression (He and Hannon, 2004). miRNAs have also been shown to regulate processes associated with brain ageing, declining brain function, and neurodegenerative diseases (Karnati et al., 2015). For instance, miRNAs have been identified as critical players in fundamental brain development processes, such as neuronal differentiation, neuronal longevity, and survival. miRNA dysfunction may trigger overt neuronal degeneration and neurodegenerative disease-associated pathways (Szafranski et al., 2015). For example, the level of two proteins, amyloid precursor protein (APP) and membrane-bound proteases β-site APP-cleaving enzyme 1 (BACE1), which contribute to the formation of amyloid plaques in AD, are controlled by miRNAs (Salta and De Strooper, 2012). AD is characterized by the accumulation of amyloid plaques in the brain, consisting of an aggregated form of amyloid β-peptide derived from sequential amyloidogenic processing of the APP by BACE1 and γ-secretase (Toh and Gleeson, 2016). In the adult mouse brain, deletion of Dicer (an enzyme responsible for the final maturation of precursor miRNA (Shukla et al., 2011)), resulted in neurodegeneration and tau pathology (Hébert et al., 2010). In PD, reduced expression of miR-34b and miR-34c has been identified in the affected brain areas including the frontal cortex, cerebellum, substantia nigra, and amygdala. The reduction of these miRNA molecules is thought to cause mitochondrial dysfunction and oxidative stress, as well as the lower expression of DJ1 and Parkin proteins related to both familial and

idiopathic cases (Minones-Moyano et al., 2011). miR-9miR-9* expression is reduced with disease progression of HD (Packer et al., 2008), leading to an increase in REST protein, and consequently suppression of neuronal gene expression that contributes to neuropathology (Junn and Mouradian, 2012). miR-132 was shown to maintain neurite growth by inhibiting its mRNA target, p250GAP (Vo et al., 2005). In mouse models of HD and post-mortem tissue of HD patients, miR-132 was found to be significantly lower, providing support for the abnormal regulation of neurite growth (Dantzer et al., 2008). Furthermore, miRNAs dysfunction has been implicated downstream of some key RNA-binding proteins such as TDP43. As mentioned earlier, TDP43 is linked to dementia and amyotrophic lateral sclerosis. TDP43 may additionally act as a regulator of miRNA biogenesis and function, and this appears as an important pathogenic mechanism in neurodegenerative diseases (Szafranski et al., 2015).

4. Nutritional strategies to modulate mechanisms and vulnerabilities to poor cognitive ageing

The rate and severity of cognitive decline during normal ageing can be attenuated by a wide variety of factors, such as improved nutrition and appropriate dietary supplementation (Swaminathan and Jicha, 2014). Some of those nutrients or dietary interventions involved are detailed below.

4.1. n-3 PUFAs

Prospective observational studies indicate that Mediterranean-like diets (i.e. diets high in fish, olive oil, nuts and vegetables) may postpone the onset of dementia (Martínez-Lapiscina et al., 2013; Scarmeas et al., 2006; Sofi et al., 2008). Omega-3 polyunsaturated fatty acids (n-3 PUFA) may have primary preventive effects on dementia, although mainly positive observational studies are so far not confirmed by intervention studies (Mazereeuw et al., 2012; Morris et al., 2005; van de Rest et al., 2009; Zhang et al., 2016). n-3 PUFA may have secondary preventive effects when given to older subjects with early memory disturbances (Freund-Levi et al., 2006). Nutrition most likely cannot affect AD or other dementia types when the conditions are already established (Burckhardt et al., 2016). Thus, healthy nutrition like Mediterranean-like dietary patterns or n-3 PUFA may be able to prevent or postpone disease processes, but may not be able to reverse the disease process or to dissolve the pathogenic deposited substances in the brain. A n-3 PUFA enriched supplement or oral nutrition support with balanced content of macronutrients for energy as well as of micronutrients like vitamins, minerals, and trace elements may positively affect weight and appetite in patients with mild to moderate AD and other cognitive diseases, and will maintain nutritional status and contribute to better general functionality (Allen et al., 2013; Irving et al., 2009). In animal models of AD, long-term fatty acid supplementation decreases the n-6/n-3 ratio and improves cognitive function, suggesting that the duration of supplementation may be a reason why no effects of n-3 PUFA supplementation could be observed in patients with moderate or advanced AD (Hooijmans et al., 2012). Perspectives for future human studies are thus to clearly define the population that will be subjected to the intervention trial and to include enough participants, as enabling a long enough duration of the intervention (Sydenham et al., 2012).

Experimental studies provide insights into feasible mechanisms for the potential beneficial n-3 PUFA effects on cognitive functions (Chakraborty et al., 2017; Hooijmans et al., 2012). Docosahexaenoic acid (DHA), representing 10–20% of the brain cells lipids, is known to play multi-functional roles in brain health and diseases. DHA and PUFAs regulate several processes within the brain via their mediators, such as neurotransmission, cell survival, and neuroinflammation, and thereby mood and cognition (Bazinet and Laye, 2014; Sun et al., 2017). In animal models, decreased n-3 PUFA alter emotional behaviour and memory, and an inverse relation between fish-derived n-3 PUFA (DHA and eicosapentaenoic acid (EPA)) consumption and prevalence of cognitive decline has been found in humans, with decreased levels of n-3 PUFA in the blood and the brain of aged patients with cognitive impairment (Bazinet and Laye, 2014). Chronic inflammation in the brain together with microglia activation can lead to neuronal damage. Recent evidence indicates that n-3 PUFA and flavonoids play a role in preventing neuroinflammation and modulating age-related memory decline (Vauzour et al., 2015). They act as potent anti-inflammatory bioactives, resolving inflammation through several pathways, i.e. suppressing the activation of microglia through the down-regulation of cytokine expression and the modulation of signalling pathways involved in the resolution of inflammation (Vauzour et al., 2015). n-3 PUFA also harvest protective effects indirectly, through the synthesis of bioactive mediators with pro-resolutive activities such as resolvins (Vauzour et al., 2015). Resolvins (D1 and E1) derived from DHA and EPA are promising therapeutic compounds to target brain inflammation (Rey et al., 2016).

4.2. Amino acids

Tyrosine is a conditionally-essential, large, neutral amino-acid, which is the precursor of the catecholamines (e.g. dopamine and noradrenaline). Tyrosine is naturally present in protein-rich foods, such as meat, fish, dairy products, but also in nuts, seeds, and beans. Oral administration of tyrosine leads to increased catecholamine synthesis, especially dopamine (Growdon and Melamed, 1980; McTavish et al., 1999; Scally et al., 1977). Dopamine is important for cognitive control functions (for a review, see (Cools and D'Esposito, 2011; van Schouwenburg et al., 2010), including working memory and response inhibition. Tyrosine administration increased cognitive control functions in cognitively healthy, young adults, both under stress (Deijen et al., 1999; Deijen and Orlebeke, 1994; Mahoney et al., 2007; Shurtleff et al., 1994; Thomas et al., 1999), which accelerates catecholamine metabolism (Bliss et al., 1968) and in normal circumstances (Colzato et al., 2014, 2013; Steenbergen et al., 2015). Ageing is accompanied by a decline in dopamine signalling (Bäckman et al., 2011, 2006) and associated impairments in cognitive control, such as working memory (Gazzaley et al., 2005; Li and Rieckmann, 2014; Turner and Spreng, 2012) and response inhibition (Bedard et al., 2002; Bloemendaal et al., 2016; Van de Laar et al., 2012). Under which circumstances tyrosine would increase cognitive control functions in cognitively healthy older adults is still to be established. However, it seems likely that tyrosine administration would be especially beneficial in the case of neuroinflammation. Tyrosine is the precursor of L-Dopa in the dopamine synthesis pathway. The synthesis of L-Dopa from tyrosine depends on tyrosine hydroxylase and its cofactor tetrahydrobiopterin (BH4). Reactive Oxygen Species (ROS) that are generated downstream of inflammatory activity can inactivate BH4 (Neurauter et al., 2008), thereby affecting dopamine synthesis. Studies in humans and non-human primates have indeed shown inflammation-associated reductions in dopamine signalling (Felger and Treadway, 2017). Administration of the dopamine precursor L-Dopa reversed the detrimental effect of pro-inflammatory cytokine IFN-α on striatal dopamine release in non-human primates (Felger et al., 2015). Increasing L-Dopa's precursor tyrosine, by dietary supplementation, might similarly be advantageous in reducing the negative effects of inflammation-associated inactivation of BH4 on dopamine synthesis efficiency.

Large neutral amino-acid precursors of neurotransmitters, such as tyrosine and its precursor phenylalanine can also be synthesized by gut microbiota (Clayton, 2012; Gertsman et al., 2015). These microbial-produced precursors might be absorbed through the intestinal epithelium, enter the portal circulation, cross the blood-brain barrier, and influence host catecholamine synthesis (Lyte, 2013). Indeed, a recent study in young adults demonstrated that predicted microbial synthesis of phenylalanine was associated with altered neural reward processing in the ventral striatum (typically dependent on dopamine processing)

(Aarts et al., 2017). Interactions between dietary catecholamine precursors and microbial neurotransmitter precursor synthesis should be taken into account when considering the beneficial effects of dietary phenylalanine and tyrosine in aging.

The essential, large, neutral amino-acid, tryptophan, is the precursor of serotonin (and melatonin). Tryptophan is found in nearly all protein-containing foods. Dietary intake of tryptophan influences serotonin synthesis and release in the brain (Fernstrom, 1983). Serotonin is involved in a variety of neurocognitive functions, including sensorimotor function, learning, and memory (Muller and Jacobs, 2009). Tryptophan administration in young adults has been shown to improve memory (for a review, see van de Rest et al., 2013). Similar to tyrosine, studies of tryptophan administration in cognitively healthy older adults are mostly lacking, even though serotonin signalling also declines with ageing (McEntee and Crook, 1991). Interestingly, the above-mentioned mechanism of ROS-induced inactivation of BH4 is relevant for serotonin synthesis as well, as tryptophan hydroxylase,needed for conversion of tryptophan into 5-Hydroxy-tryptophan (5-HTP), which in turn is converted into serotonin (5-Hydroxy-tryptamine, 5-HT), is dependent on cofactor BH4 also. However, there is another important inflammation-related mechanism associated with tryptophan. Specifically, pro-inflammatory cytokines, such as IFN-γ, IL-1β, and TNF-α catalyse the conversion of tryptophan into kynurenine at the expense of serotonin production, by inducing the expression of indoleamine 2,3-dioxygenase (IDO) (O'Connor et al., 2009a, 2009b). Subsequently, kynurenine is metabolized by microglia into, amongst others, quinolinic acid, a neurotoxic that generates ROS. Indeed, the kynurenine/tryptophan ratio in blood is increased in AD and related to decreased cognitive performance (Widner et al., 2000). Kynurenine can also be converted to kynurenine acid with neuroprotective properties. However, in rats, tryptophan administration increased brain levels of the neurotoxic quinolinic acid to a much greater extent than levels of the neuroprotetive kynurenine acid and even that of serotonin (Freese et al., 1990). Thus, given the potential conversion to kynurenine and quinolinic acid, dietary supplementation of tryptophan should be done with caution. On the other hand, commensal bacteria can catabolize dietary tryptophan to indole, indole-3-aldehyde, and indole-3-propionate, with potential anti-inflammatory effects (for a review, see (Zhang and Davies, 2016)). However, given that the gut microbiome is affected by aging, as discussed above, the beneficial effects of tryptophan consumption in this regard still needs to be elucidated.

4.3. Polyphenols

Polyphenols are micro-constituents of plant-based foods, which are widely distributed in the human diet. The main dietary sources of polyphenol intake are fruits and fruit-derived products (Pérez-Jiménez et al., 2010), which is a main constituent of the Mediterranean-style diet. Adherence to a Mediterranean diet is associated with slower cognitive decline, and reduced incidence of dementia and AD (Vauzour et al., 2017). Epidemiological studies suggest an inverse relationship between the intake of different classes of polyphenols and the risk of different age-related diseases, such as cardiovascular diseases, cancer, or metabolic disorders (Vauzour et al., 2010). The potential of these compounds to prevent neurodegenerative disorders is also documented in several animal studies. For example, it has been shown that diets supplemented with blueberry (a fruit rich in anthocyanins) improve the performance of aged animals in spatial working memory tasks (Williams et al., 2008). Several clinical studies have also demonstrated potential beneficial effects of polyphenol-rich fruit on brain function (Khalid et al., 2017; Miller et al., 2017; Valls-Pedret et al., 2012). One study revealed that consumption of flavanone-rich orange juice is beneficial for cognitive function in cognitively healthy older adults with no significant effects on mood or blood pressure (Kean et al., 2015), while consumption of cocoa flavanols beneficially affects cognitive performance and mood during highly effortful cognitive processing (Scholey et al., 2010). This potentially beneficial effect of polyphenol rich-food on brain function may be linked to increased blood flow in the brain (Lamport et al., 2015). Nutritional intervention with high-flavanol drinks for three months has been shown to significantly increase cerebral blood volume in the dentate gyrus area of the hippocampus and significantly enhance performance (reaction time) on a pattern separation task (Brickman et al., 2014). Pattern separation tests, which test the ability to distinguish between previously presented pictures and very similar ones, can be directly related to activity in the dentate gyrus, an area where neurogenesis occurs (Bakker et al., 2008). Therefore, age-related decline in the ability to discriminate closely similar pictures reflects reduced activity in the dentate gyrus (Toner et al., 2009; Wesnes, 2010). Importantly, deficits in this task have been linked to the genotype associated with susceptibility to AD as well as cerebrospinal levels of Aβ42 (Wesnes et al., 2014).

Even though data exists revealing the positive effect of polyphenols on brain and vascular function, the mechanisms of action underlying their beneficial effects appear to be complex and are not fully understood yet (Field et al., 2011; Scholey et al., 2010; Vauzour et al., 2017). A large number of *in vitro* studies exist showing the capacity of polyphenols to modulate not only the expression of genes, but also expression of miRNA and proteins, and induce epigenetic modifications (Claude et al., 2014; Krga et al., 2016; Mandel et al., 2008; Schroeter et al., 2007, 2001; Vauzour et al., 2007). Most of these studies have been performed using native forms of polyphenols (forms found in fruits) at high concentrations. However, the bioavailability of ingested polyphenols is generally low and most often the absorbed forms are not the native compounds (Bohn et al., 2015). The forms present in the circulation that can reach target tissues result from extensive metabolism involving both enzymatic activities of the gut microbiota (Tomas-Barberan et al., 2016; Williamson and Clifford, 2017) and endogenous conjugative enzymes (Espin et al., 2017). Plasma metabolites of polyphenols are mainly either conjugated derivatives, in glucuronidated-, sulphated-, and methylated-forms, or metabolites of microbial origins found at concentrations in nano to few microM ranges. Taken together, knowledge of the molecular and cellular mechanisms of action is incomplete. Further studies are needed to enhance our knowledge of the mechanisms linking these bioactives with health benefits.

4.4. Multi-nutrient interventions

Single nutrient interventions have generally shown no cognitive benefit in mild cognitive impairment (MCI) and AD (Aisen et al., 2008; Dysken et al., 2014; Freund-Levi et al., 2006; Galasko et al., 2012; McMahon et al., 2006; Petersen et al., 2005; Quinn et al., 2010). It is likely that the potency of single nutrients is insufficient to achieve a clinically relevant benefit. A hypothesis-driven specific nutrient combination (called Fortasyn Connect) of uridine, docosahexaenoic acid, eicosapentaenoic acid, choline, phospholipids, folic acid, vitamins B12, B6, C, E, and selenium has been designed to ameliorate synapse loss, synaptic dysfunction, and other pathological pathways affected in AD by addressing distinct nutritional needs believed to be present in these patients (Van Wijk et al., 2014). This specific nutrient combination is based on the notion that cognitive decline in MCI and AD is a result of loss of synapses (de Wilde et al., 2016). Formation of synapses is rate-limited by specific nutrients that are the precursors for the formation of neuronal membranes and act by enhancing the substrate-saturation of the enzymes that catalyze the rate-limiting steps of membrane phospholipid synthesis through the Kennedy Pathway (Wurtman et al., 2009). Beneficial and synergistic effects of the specific nutrient combination of precursors and cofactors of neuronal membrane formation have been demonstrated in several animal models by various groups and on several biological phenomena that are indicative of increased synapse formation and function and other pathological processes that are characteristic of AD, and published in over 30 peer-reviewed publications (Cansev et al., 2015; Janickova et al., 2015; Van Wijk et al.,

2014; Wiesmann et al., 2016; Wurtman et al., 2009). These results suggest that people with AD pathology may benefit from increased intake of these nutrients. Importantly, meta-analyses show that the levels of these nutrients in circulation and in the brain are lower in AD than in non-AD controls (Lopes Da Silva et al., 2014). Collectively, these insights indicate that the nutritional need for these nutrients is higher in AD and led to the development of Souvenaid, a medical food for early AD comprising this specific nutrient combination (Van Wijk et al., 2014). The clinical efficacy of Souvenaid was tested in a clinical trial program, with trials in AD patients at various stages of AD, and on clinical outcomes as well as neuroimaging measures. Studies in drug-naïve mild AD showed that the intervention increased magnetic resonance spectroscopy measures of brain neuronal membrane synthesis (Rijpma et al., 2017) and electroencephalography (EEG) measures of functional connectivity and functional brain network organisation (De Waal et al., 2014; Scheltens et al., 2012); while in prodromal AD, a 2-year Randomised Control Trial (RCT) showed reduced hippocampal atrophy (Soininen et al., 2017). Studies in drug-naïve mild AD showed a significant benefit on memory performance (Rikkert et al., 2015; Scheltens et al., 2012, 2010), the primary endpoint in these RCTs and the most pronounced clinical symptom of early AD. More recently, an independent EU funded 2-year RCT in prodromal AD reported favourable effects on memory and a clinical relevant combined measure of cognition and function (CDR-SB) (Soininen et al., 2017). In conclusion, mechanistic studies on this specific nutrient combination together with the Souvenaid clinical trials in AD show consistent effects on brain function, metabolism, structure, and measures of cognition and function that corroborate the working mechanism of the specific intervention (De Waal et al., 2014; Hartmann et al., 2014; Rijpma et al., 2017; Scheltens et al., 2012, 2010; Soininen et al., 2017). In addition, these studies together support the notion that clinical relevant benefit on brain function in ageing can be achieved by a hypothesis-driven nutrient combination that amplifies the potency of single compounds (von Arnim et al., 2010).

5. Application and impact

5.1. Multi-domain interventions

Epidemiological studies demonstrate that links exist between nutrition, physical activity, and cognitive and social stimulation that help to improve brain health. As prevention has been advocated as an effective way to reduce the burden of AD (Norton et al., 2014), multi-domain interventions seem therefore appropriate to target the multiple factors involved in cognition and ageing. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER, NCT01041989) was a 2-year multicentre randomized controlled trial with 1260 participants aged 60–77 years recruited from previous population-based survey cohorts. The multi-domain intervention included four components: nutritional guidance, physical exercise, cognitive training and social activities, and management of vascular/metabolic risk factors. The control group received regular health advice. The primary outcome after two years was change in cognition (neuropsychological test battery, NTB z-score). FINGER is the first 'proof-of-concept' trial showing that a multi-domain lifestyle intervention had significant beneficial effects on cognition in an at-risk older general population (Ngandu et al., 2015). Significant intervention effects were also found for several secondary outcomes (e.g. dietary habits, body mass index, physical activity, quality of life, and disability). Key determinants of intervention success were: the combination of group activities with individualized, concrete counselling (facilitating both personal and within-group motivation and support for healthy lifestyle changes), knowledgeable staff, providing positive feedback, and inclusion of community support. FINGER showed that a multi-domain lifestyle intervention in at-risk older individuals is feasible and safe. Compliance was high, and participants' experiences were very positive.

Other European multi-domain interventions offer some additional insights. The Prevention of Dementia by Intensive Vascular care (preDIVA) trial tested a 6-year multi-domain vascular intervention including dietary advice in 3526 older individuals (age 70–78 years) from general practices in the Netherlands (Moll van Charante et al., 2016). The control group received usual care. The intervention did not result in a reduced incidence of all-cause dementia in this unselected sample of older people in a general practice setting with high standards of usual care. However, some benefits on dementia incidence were noted in at-risk subgroups (e.g. participants with untreated hypertension at baseline who adhered to the intervention).

The Multi-domain Alzheimer Preventive Trial (MAPT) study was designed to test whether a combination of nutritional counselling, physical exercise, and cognitive stimulation, together with *n*-3 PUFA supplementation, is effective in slowing cognitive decline in frail older adults at risk of cognitive decline (Andrieu et al., 2017; Vellas et al., 2014). The MAPT trial is the first largest and longest multi-domain preventive trial relevant to cognitive decline in older adults with subjective memory complaints, and is easily implementable in the general population. This multi-domain intervention brings some hope regarding long-term effects of a multi-factorial approach to prevent development of impaired cognition (Andrieu et al., 2017; Vellas et al., 2014). Nevertheless, additional trials are needed to confirm these observations.

Findings from the FINGER, preDIVA and MAPT trials thus suggest that preventive interventions may need to be adequately targeted to at-risk populations in order to be most effective. Interventions may also need to be sufficiently intensive for benefits to become apparent. In conclusion, the various research innovations described above will enable trials to be conducted on scales which were not previously possible, with numerous treatment arms to allow optimal combinations of various interventions to be established for multiple groups of individuals having shared genotypes as well as phenotypes. This field has now entered the 'big data' era, which will enable research questions to be addressed that previously were not feasible even to propose.

5.2. Relevance for public health and regulatory implications

The increased ageing population and rise in cognitive decline expectedly impacts public health. Future outcomes relevant for public health include development of health claims related to improvement of cognitive function. For instance a claim on 'DHA and improvement of memory function' was recently approved by EFSA (EFSA Panel on Dietetic Products, 2016). A claim for 'cognitive function' requires evidence for an effect involving several specific domains and outcomes, emphasising the multi-factorial aspect of the ageing process. Furthermore, some EU initiatives highlight the importance of health and nutrition in the centre of attention. Besides the huge socio-economic impact of healthy and most notably, pathological ageing, the increasing relevance of global public health highlights the growing interest in understanding cognitive function and healthy ageing, with nutrition as spearhead.

In respect of pathological ageing, research interest and regulatory requirements are moving towards studies in cognitively healthy individuals, either carrying specific biomarkers of pathological ageing or in those ageing in the absence of disease. This supports the hypothesis that factors such as diet will help maintain healthy ageing and is crucial to help prevent or delay the onset of neurodegenerative disorders (Harvey et al., 2017; Kozauer and Katz, 2013; Roses et al., 2013; Small and Vorgan, 2012; Sperling et al., 2011; Whitehouse, 2014).

6. Conclusion and future directions

The ILSI Europe workshop 'Nutrition for the ageing brain: functional aspects and strategies' and the present paper highlight the value of combining studies of cognitive ageing with well-designed studies

investigating how dietary interventions can be a strategy to target the mechanisms of ageing. However, to advance, future research in this field may need to adopt a longitudinal approach to ensure the effect of early-life stress is adequately measured. Interventions may also need to be imposed prior to the onset of pathological cognitive ageing. Researchers will need to consider factors, such as epigenetic changes or gut microbiome diversity in the ageing process. Innovation in research and the development of new technologies will enable trials to be conducted on scales which have not previously been possible, with numerous treatment arms to allow optimal combinations of various interventions to be established for multiple groups of individuals that have shared genotypes as well as phenotypes.

Longitudinal monitoring of cognition across the lifespan is essential for effective dementia prevention. Integrative approaches are required that are sensitive to the synergistic action of various risk and protective factors and their possible common pathways. One major question for the field is whether these various lifestyle choices all compete for a limited opportunity to enhance cognitive function, or whether the effects could be additive or even synergistic. Individual variations in risk profiles for dementia must also be taken into account, as different lifestyle choices may have different contributions to the overall risk in different people. Cognitive function is a broad topic and it would be advantageous if the research community could agree on which cognitive tests to use as outcome measures. As Matthews et al. (2013) argue, whether prevalence rates will continue to rise, 'will probably depend on whether further improvements in primary prevention and effective health care for disorders that increase the risk of dementia can be achieved, including addressing inequalities' (Matthews et al., 2013).

The aetiologies of dementia and age-related cognitive decline are multi-factorial, therefore, it is likely that multi-dimensional interventions will be required to effectively delay dementia onset. Large-scale dementia prevention studies are essential to address the current gaps in knowledge and accelerate advances through multifactorial approaches. In addition, it is also crucial to widen the scope of our current concept of potential patho-mechanisms that contribute to cognitive decline, both at the level of the central nervous system and also peripheral tissues. A multifaceted approach to identify new viable strategies is vital for the creation of new and effective therapeutics. International collaborations within extensive networks, including partners from both academia and industry, are already starting to be established. Some key issues for future dementia prevention research are: the harmonisation and optimisation of methodologies for multinational and multi-domain prevention trials across the entire spectrum of cognitive impairment and AD, international sharing of expertise and data, rethinking prevention trials (e.g. adaptive designs, inclusion of e-health components, combining non-pharmacological and pharmacological approaches to prevention), and learning from experiences with prevention research in other fields (Geerts et al., 2016).

The longitudinal epigenetic characterisation of population subgroups, which follow a specific diet for many years, may also yield useful information on transient versus persistent epigenetic changes/epigenetic ageing in the presence/absence of specific diets (e.g. vegetarian, Mediterranean, vegan, etc.) and information related to other lifestyle factors (e.g. regularity and intensity of exercise). Such studies should evaluate the separate and interactive effects of factors, such as nutrition and physical exercise on epigenetic modification. Suitable approaches might include the development of mobile phone applications to measure health and diet/physical exercise. Integrated data analysis pipelines should be developed to explore epigenetic biomarkers in saliva, blood, cerebrospinal fluid, and cognitive imaging data.

The ways that changes in the levels of circulating factors (e.g. Insulin Growth Factor 2 (IGF2) or the Growth and Differentiation Factor 11(GDF11)) facilitate age- and diet-induced effects on stem cell function, neurogenesis, and brain function need to be identified and investigated further. Dietary interventions that tip the balance of factors towards a rejuvenating milieu are potentially effective means to promote healthy cognitive ageing by enhancing stem cell function and neurogenesis (Murphy and Thuret, 2015). There is currently a real need for dietary human interventions coupled with *in vitro* assays involving immortalized human stem-cell lines, and neurogenesis-dependent cognitive tasks such as pattern separation, which targets the dentate gyrus (Bakker et al., 2008). Although the dentate gyrus is suggested to regulate neurogenesis, the only information in humans supporting this is based upon blood perfusion using fMRI (Brickman et al., 2014). There are currently no real ways of measuring neurogenesis in human brain tissue and most of the information gathered to date is derived from animal studies.

In the case of polyphenols, it is important to perform clinical trials using well-defined controls to identify a proper role of compounds (such as flavanols) on brain function. Further *in vitro* studies will be necessary, together with pre-clinical studies, to identify as precisely as possible the cellular and molecular mechanisms of action of polyphenols. Future studies should take into account the multiple targets and multiple modes of action of polyphenols. These studies should simultaneously investigate the impact of polyphenols on the of expression of genes, non-coding RNAs, proteins, and other regulators of cell function, such as cell signalling pathways or epigenetic modifications to identify molecular mechanism(s) of action. For *in vitro* studies, circulating forms of polyphenol metabolites at physiologically relevant concentrations should be used.

Future studies should also assess the peripheral and central mechanisms underlying potential age-related differences in tyrosine or tryptophan effects on cognition in placebo-controlled designs, with both young and older adults. When assessing the effects of age, longitudinal designs are preferred, as cross-sectional designs cannot easily control for between-subject differences other than age. Amino-acid administration studies in older adults should also use longer supplementation designs, as effects of auto-regulation of monoamine synthesis might differ for acute administration with high doses versus supplementation with continuous lower doses.

In the case of fatty acids, it is important to take into account the regular baseline fish or *n*-3 PUFA intake, or baseline serum concentrations of DHA as well as EPA. Recent studies demonstrated that higher levels of DHA/EPA may help protect against the development of dementia (Ammann et al., 2017). If the intake or the serum levels are already sufficient, further beneficial effects of fatty acid supplementation is not to be expected. This would be like performing a study on blood pressure medication without knowing the baseline blood pressure and also providing normotensive subjects with the test medication! Most of the clinical trials recruit patients with high DHA/EPA baseline values and it is therefore recommended to include only subjects with low intake of fish or low levels of DHA/EPA in the intervention studies, even though a threshold needs to be defined.

Priorities for future studies are to clearly define the population that will participate in the intervention trial. Proof of concept studies are needed to design proper RCTs with sufficient power. Also, dose aspect is also a disadvantage, as many of the animal studies investigating mechanisms are supra-physiological and not achievable in humans without risk of toxicity, e.g. green tea catechins producing hepatotoxicity at 500 mg/day (Isomura et al., 2016).

Research suggests it is possible to amplify the potency of nutrient intervention by combining nutrients that work synergistically to ensure the neuroprotective potential of nutrition is fully leveraged. The blending of nutrients should be hypothesis driven and based on the specific contribution of each nutrient to the targeted biological pathway (s) that underlie cognitive effects. Therefore, future research should aim to: 1) increase understanding of the role of specific nutrients on biological pathways that are relevant to cognitive ageing, 2) design and validate nutrient combinations to target mechanisms of cognitive ageing, 3) validate multi-nutrient combinations in well-designed clinical studies, and 4) transfer knowledge of the role of nutrition for

cognitive health to recommendations for public health.

Disclosure

The workshop 'Nutrition for the Ageing Brain: Functional Aspects and Strategies' was organized with funds from the ILSI Europe Nutrition and Mental Performance Task Force. Industry members of this task force are listed on the ILSI Europe website at www.ilsi.eu. For further information about ILSI Europe, please email or call +32 2 771 00 14. This review was prepared taken into account the presentations at the workshop mentioned in the abstract and was conducted by an expert group of ILSI Europe. This publication was coordinated by Dr Lucie Geurts, Scientific Project Manager at ILSI Europe. The opinions expressed herein and the conclusions of this article do not necessarily represent either the views of ILSI Europe or those of its member companies. All authors read and approved the final manuscript.

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