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SYMPOSIUM REVIEW

Promoting brain health through exercise and diet in older adults: a physiological perspective

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Philippa A. Jackson completed her PhD at Northumbria University (UK) in 2010; for it she investigated the effects of supplemental omega-3 poly-unsaturated fatty acids on cognition in healthy young adults. She has since then continued at Northumbria University as a Research Fellow focusing on the effects of dietary interventions for promoting cognitive function and cerebral blood flow throughout the lifespan. **Marc J. Poulin** completed a PhD in exercise physiology at the University of Western Ontario (Canada). He then completed a DPhil and postdoctoral fellowship in respiratory and cerebrovascular physiology at Oxford with Peter Robbins as supervisor and mentor. He was recruited to the University of Calgary (Canada) in 2000 and he is now Professor and The Brenda Strafford Foundation Chair in Alzheimer Research. His research focuses on healthy brain ageing. **Vincent Pialoux** completed a PhD in exercise physiology at the University Blaise Pascal (Clermont-Ferrand, France). He was then postdoctoral fellow in respiratory and cerebrovascular physiology at the University of Calgary with Marc Poulin as supervisor. He was recruited to the University of Lyon (France) in 2009 as assistant Professor and he is now Professor and holds an Institut Universitaire de France Chair. His research focusses on the role of oxidative stress on vascular and cerebrovascular diseases and the effects of physical activity on this pathological mechanism. **Kirk Erickson** completed a PhD in cognitive psychology in 2005 at the University of Illinois at Urbana-Champaign under the mentorship of Dr. Arthur Kramer. He then went on to a postdoctoral fellowship at the Beckman Institute for Advanced Science and Technology at the University of Illinois. He was recruited to the University of Pittsburgh in 2008 and is now an Associate Professor of Psychology, Medicine, and is appointed in the Center for the Neural Basis of Cognition and the Center for Neuroscience at the University of Pittsburgh. His research focuses on healthy brain aging with an emphasis on the role of physical activity on brain health. **Dale Corbett** completed a PhD in behavioural neuroscience at Concordia University and post-doctoral studies at McGill. He was a faculty member at Harvard and Memorial University of Newfoundland prior to his recruitment to the University of Ottawa as Professor and Scientific Director & CEO of the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery. His research focuses on recovery of function following stroke. **Gail A. Eskes** completed a PhD in Psychology at the University of California, Berkeley, USA and a postdoctoral fellowship focused on memory and aging at the Rotman Research Institute, Toronto, Canada. She is currently a clinical neuropsychologist and Professor at Dalhousie University, Halifax, Canada and her research focuses on developing evidence-based rehabilitation tools for cognitive deficits due to ageing or brain disorders such as Parkinsons disease or stroke. **Lauren L. Drogos** completed a PhD in psychology at the University of Illinois at Chicago, under the mentorship of Dr. Pauline M. Maki, investigating the effects of vasomotor symptoms on autonomic nervous system activity in midlife women. She is currently working as a postdoctoral fellow at the University of Calgary with Dr. Marc J. Poulin, investigating the effects of exercise on cognitive performance in healthy older adults. Her specific focus is on identifying potential predictors of cognitive decline, such as sleep disturbances or neuroendocrine changes.

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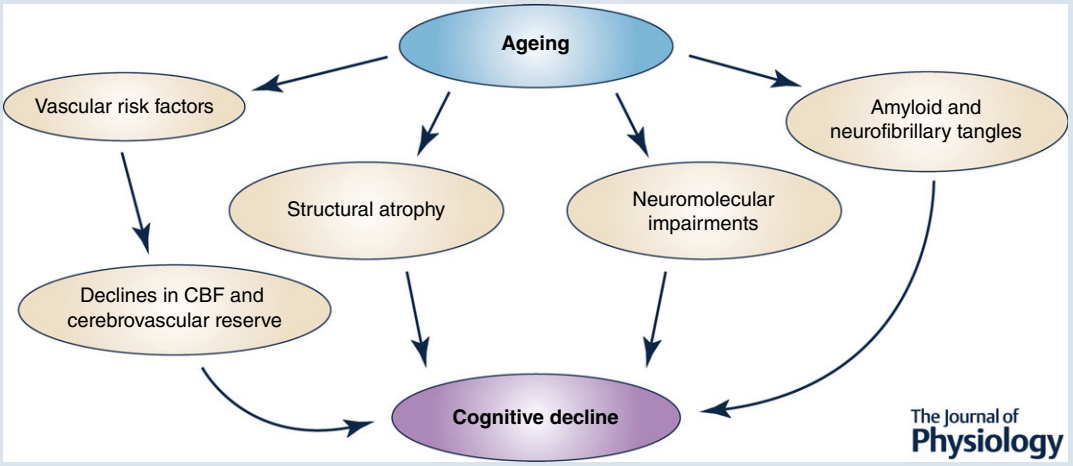

Abstract The rise in incidence of age-related cognitive impairment is a global health concern. Ageing is associated with a number of changes in the brain that, collectively, contribute to the declines in cognitive function observed in older adults. Structurally, the ageing brain atrophies as white and grey matter volumes decrease. Oxidative stress and inflammation promote endothelial dysfunction thereby hampering cerebral perfusion and thus delivery of energy substrates and nutrients. Further, the development of amyloid plaques and neurofibrillary tangles contributes to neuronal loss. Of interest, there are substantial inter-individual differences in the degree to which these physical and functional changes impact upon cognitive function as we grow older. This review describes how engaging in physical activity and cognitive activities and adhering to a Mediterranean style diet promote 'brain health'. From a physiological perspective, we discuss the effects of these modifiable lifestyle behaviours on the brain, and how some recent human trials are beginning to show some promise as to the effectiveness of lifestyle behaviours in combating cognitive impairment. Moreover, we propose that these lifestyle behaviours, through numerous mechanisms, serve to increase brain, cerebrovascular and cognitive reserve, thereby preserving and enhancing cognitive function for longer.

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Abstract figure legend Age-related changes in brain physiology. Ageing is associated with a number of structural, vascular and neuromolecular changes in the brain which contribute to impaired cognitive function. Modifiable lifestyle factors including physical activity, cognitive activity and a Mediterranean-style diet may attenuate the progression of these changes and protect against cognitive decline.

Abbreviations AD, Alzheimer's disease; BDNF, brain derived neutrophic factor; CA, cognitive activity; CBF, cerebral blood flow; CVR, cerebrovascular resistance; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MABP, mean arterial blood pressure; NO, nitric oxide; PA, physical activity; PUFA, polyunsaturated fatty acid; VCI, vascular cognitive impairment.

Introduction

The ageing of the 'baby boom' population and the high costs of providing health care for cognitively impaired individuals make it imperative to develop interventions to delay and/or blunt the age-related development of cognitive impairment. Indeed, without effective intervention or treatment, the prevalence of dementia worldwide could exceed 135 million individuals by the year 2050 (Prince *et al.* 2013). Declining cognitive function occurs with increasing age, but the inter-individual trajectory of this decline varies widely and can be accounted for by a combination of genetic, physiological, environmental and behavioural factors, some of

the latter of which are modifiable. Indeed, while the brain deteriorates and degrades with engagement in unhealthy behaviours, it can be enhanced by participation in healthy behaviours. As such, it has been shown that a sedentary lifestyle and 'Western' style dietary pattern characterised by high intake of red meat, saturated fat and refined carbohydrates increase the risk for cognitive impairment as well as a wide variety of chronic diseases. On the other hand, physical activity and following a Mediterranean style dietary pattern are two such lifestyle behaviours known to promote and support the brain's structural integrity and function, namely 'brain health'.

The positive relationship between brain health and cognitive function in older adults can be described within the context of reserve. Broadly defined, reserve is the capacity of the brain to maintain function in the face of acute injury (e.g. head trauma and ischaemia) or degenerative damage (e.g. ageing), and can be divided into biological, cerebrovascular and cognitive reserve. Biological or brain reserve refers to the structural integrity of the brain and is typically assessed by measuring brain volumes (Stern, 2009). Cerebrovascular reserve is the capacity of the blood vessels of the brain to maintain blood flow in response to chemical, mechanical or neural stimuli (Davenport *et al.* 2012), whilst cognitive reserve relates to a capacity for compensatory brain function in order to maintain cognitive performance (Stern, 2009). The present review will discuss the effects of dietary and physical activity lifestyle behaviours on brain physiology and how they may contribute to increasing reserve and cognitive function. In addition, enhancing brain health and cognitive function via increased cognitive activity and its interaction with physical activity will also be discussed.

Physical activity

Studies in animals and humans show that physical exercise has direct effects on brain health by altering mechanisms of neuronal plasticity involved with learning and memory (Cotman & Berchtold, 2002; Cotman *et al.* 2007). Exercise may prevent age-related deterioration of cognitive and brain function and reduce age-related brain atrophy (Voss *et al.* 2013). For example, both prospective and retrospective observational studies have shown a lower incidence of cognitive impairment, depression and dementia in people who maintained regular physical activity (PA) (Lautenschlager *et al.* 2008; Sofi *et al.* 2011). Similarly, rodents given regular access to running wheels are less impaired than their sedentary counterparts on memory tests that involve the hippocampus (van Praag *et al.* 1999). In rodents, running also increases neurogenesis in the hippocampal dentate gyrus and induces angiogenesis in the cortex and other brain regions (Swain *et al.* 2003; Creer *et al.* 2010) thereby improving oxygen and glucose delivery. In humans, the majority of research examining the effects of PA and fitness on the brain has been conducted in older cognitively normal populations and has predominantly focused on the size and function of the hippocampus. The hippocampus is an important structure in the context of ageing as it plays a dominant role in declarative memory functions and faster rates of hippocampal atrophy are linked to more rapid conversion to Alzheimer's disease (AD). Consistent with animal research, higher cardiorespiratory fitness levels in cognitively normal adults were associated with better performance on a spatial memory task and greater volume of the hippocampus (Erickson *et al.* 2009). This effect remained significant even after controlling for variance associated with age, sex, education and intracranial volume. Interestingly, this effect has now been replicated in children (Chaddock *et al.* 2010), in adolescents (Herting & Nagel, 2012) and in adults with early stage dementia (Honea *et al.* 2009).

Prospective longitudinal studies have also found that engaging in greater amounts of PA is associated with elevated hippocampal and prefrontal cortex volume later in life. For example, in one study of 299 cognitively normal adults, a greater amount of self-reported walking was associated with a greater grey matter volume 9 years later in several regions, including the hippocampus. Further, greater grey matter volume was predictive of a reduced risk of developing cognitive impairment 4 years later (Erickson *et al.* 2010). This and results from other studies (Rovio *et al.* 2010) suggest that participation in greater amounts of PA may have long-term consequences for maintaining grey matter volume into late adulthood. To test the hypothesis that engaging in exercise could increase the size of the hippocampus, 120 inactive older adults were randomized to either 12 months of moderate intensity brisk walking or to a non-aerobic stretching and toning control condition (Erickson *et al.* 2011). Both groups received site-based exercise 3 times per week for 30–45 min. After 12 months of exercise, the brisk walking group showed a significant increase in the size of the hippocampus while the control group showed a slight decline. Further, changes in the size of the hippocampus were correlated with increases in fitness levels, improvements in spatial memory, and increased levels of brain derived neutrophic factor (BDNF) (also see Niemann *et al.* 2014; ten Brinke *et al.* 2015). This study suggests that engagement in regular amounts of moderate intensity activity is sufficient for increasing the size of the hippocampus.

Other studies have also linked exercise and fitness to the connectivity of the hippocampus and prefrontal cortex. For example, greater fitness and exercise were associated with an increase in grey matter volume in the prefrontal cortex (Colcombe *et al.* 2006; Weinstein *et al.* 2012) and greater grey matter volume statistically mediated the association between fitness and cognitive performance (Weinstein *et al.* 2012). Similarly, exercise and fitness have

been linked to greater intrinsic brain connectivity between the hippocampus and prefrontal cortex as measured by both seed-based and graph theory approaches (Burdette *et al.* 2010; Voss *et al.* 2010). Although other brain areas like the basal ganglia have been linked to fitness (Verstynen *et al.* 2012), the prefrontal cortex and hippocampus are regions most consistently observed across studies (Erickson *et al.* 2014).

In addition to enhancing the structural integrity of the brain, PA has also been shown to contribute to brain health via modulation of vascular function and inflammation. The pathology of vascular brain lesions develops in a similar manner to that of atherosclerosis, as increased inflammation and oxidative stress are evident in both conditions (Casserly & Topol, 2004). Recent translational investigations performed in high risk ageing patients and in corresponding animal models suggest a link between populations with high-risk cardiovascular factors and neurodegenerative diseases. In the context of ageing, the brain is highly susceptible to reactive oxygen species (ROS)-induced damage due to its high rate of oxidative metabolism and relatively low levels of antioxidant enzymes (Coyle & Puttfarcken, 1993). In addition, risk factors for atherosclerosis could be involved in the development of inflammatory conditions in the brain, and ultimately lead to ischaemic or haemorrhagic stroke (Dutta *et al.* 2012). It was indeed suggested that blood–brain barrier permeability (Hafezi-Moghadam *et al.* 2007) and macrophage infiltration – two pathological features in atherosclerosis – which affect brain vessel function during the ageing process are specifically associated with a cholesterol-rich diet (Casserly & Topol, 2004). On the other hand, regular physical training has been shown to reduce these risk factors by upregulating antioxidant enzymatic systems and anti-inflammatory processes, which may slow down the usual increase in oxidative stress and inflammation during ageing and therefore potential neurovascular and neurodegenerative diseases (Garcia-Mesa *et al.* 2015).

Chronic exercise training has been also shown to reduce most of the physiological processes involved in the pathogenesis of cardiovascular diseases including oxidative stress, vascular adhesion, impairment of nitric oxide metabolism (Szostak & Laurant, 2011) and inflammation (Lesniewski *et al.* 2011). Exercise is also connected with improvement in general metabolic conditions such as lipid dysfunction and insulin resistance. As shown by Pellegrin *et al.* (2009), the beneficial effects of exercise training on atherosclerosis have been established in ApoE$^{-/-}$ mice. ApoE$^{-/-}$ mice are known to spontaneously develop atherosclerotic lesions and this phenomenon is amplified when the animals are under fat diet (Meir & Leitersdorf, 2004). Since ApoE plays a central role in the brain response to injury and neurodegeneration, this model has also proven its relevance in fields related to neuroinflammation, Alzheimer's disease and dementia (Poirier, 2000).

In addition, the beneficial effects of exercise on oxidative stress and inflammation in the brain and aorta were also determined using a mouse model of atherosclerosis associated with ageing (Chirico *et al.* 2012). It was demonstrated that the occurrence of vascular brain and aortic damage (blood–brain barrier permeability, presence of micro-haemorrhage and accumulation of macrophages measured by both MRI and histology) in an ageing model of atherosclerosis (60-week-old ApoE$^{-/-}$ mice under high fat–high cholesterol diet) was partially reversed by 12 weeks of exercise training. In parallel, exercise training decreased oxidative stress and inflammation directly in the brain and in the aorta. Interestingly, cultures of bone marrow-derived macrophages of these mice also suggested that oxidative stress can modulate the macrophage pro- or anti-inflammatory behaviour. Overall, this study suggests that regular PA may improve neurovascular health by reducing inflammation and oxidative stress.

In humans, the correlation between fitness, oxidative stress, nitric oxide production, mean arterial blood pressure (MABP) and cerebrovascular resistance (CVR) in a small cohort ($n = 42$) of postmenopausal women was examined (Pialoux *et al.* 2009). A greater level of oxidative stress was associated with higher MABP value, and CVR was reported. In contrast, lower levels of end-products of nitric oxide metabolism were associated with higher MABP and CVR. Interestingly, postmenopausal women with higher fitness levels had higher antioxidant enzyme activity and lower levels of oxidative stress, which was associated with better cardio- and cerebrovascular outcomes (i.e. lower MABP and CVR). This study demonstrated that, after menopause, fitness level and regular PA mediate against oxidative stress by maintaining antioxidant enzyme efficiency and also that oxidative stress and NO production modulate CVR in this population.

The structural and physiological brain changes resulting from exercise might also translate to improved behavioural, emotional and cognitive performance. Consistent with this hypothesis, a meta-analysis of 18 randomised exercise interventions found that exercise was an effective approach to improve cognitive function in older adults (Colcombe & Kramer, 2003). Similar meta-analytic results have been reported showing smaller but significant effects across the adult lifespan (e.g. Smith *et al.* 2010), but other recent studies and meta-analyses have reported negative findings on the consistency and robustness of the effects of PA on cognitive outcomes in older adults at risk for mobility disability (Sink *et al.* 2015) and the effects of exercise on cognitive function in older adults without known cognitive impairments (Young *et al.* 2015). Clearly there is an immediate need to better

understand the effects of exercise on brain function and physiology with the brain's behavioural sequelae.

In summary, all available evidence suggests that participation in regular amounts of moderate intensity exercise may improve brain health throughout the life-span and reduce the risk for neurological and psychiatric conditions. However, we still have a very poor understanding of how and if exercise influences cognition in humans. One proposal is that PA increases brain reserve. The aforementioned studies conducted by Erickson *et al.* (2014), which demonstrated simultaneous increases in hippocampal volume and performance on memory tasks following an exercise intervention, would certainly support the concept of increased brain reserve as a mediating factor in the relationship between PA and cognition in older adults (see Fig. 1). In addition, there is emerging evidence that habitual PA (Brown *et al.* 2010; Bailey *et al.* 2013; Guiney *et al.* 2015), aerobic fitness (i.e. maximal oxygen uptake) (Brown *et al.* 2010; J. N. Barnes *et al.* 2013), and aerobic exercise training (Vicente-Campos *et al.* 2012) are associated with increases in cerebrovascular reserve (as measured by cerebrovascular reactivity to hypercapnia. However, not all studies report a beneficial effect of life-long exercise training on age-related changes in cerebral haemodynamics (Zhu *et al.* 2013). Further, higher cerebrovascular reactivity has been shown to be positively associated with executive function in young adults (Guiney *et al.* 2015) and overall cognitive functioning (including domains of executive function and processing speed) in older adults (Brown *et al.* 2010; Davenport *et al.* 2012). Moreover, as reported above, PA enhances vascular function by resolving endothelial dysfunction and reducing the oxidative stress and inflammation that may underpin this relationship. Davenport *et al.* (2012) also recently suggested that cerebrovascular reserve promotes neuro- and synaptogenesis via increased BDNF and NO production, which may serve to preserve or even improve cognitive function. In an attempt to progress our understanding of this complex relationship, the interaction between PA, cerebrovascular reserve and cognition is currently being investigated in a large prospective study (Tyndall *et al.* 2013).

Cognitive activity

Data from observational and longitudinal and cross sectional studies have overwhelmingly suggested that regular cognitive activity (CA) may convey benefits similar to those achieved by PA. Specifically, they have suggested that people who engage in more cognitively stimulating leisure (Crowe *et al.* 2003), social (Karp *et al.* 2006; Sorman *et al.* 2014) and job (Smart *et al.* 2014) activities are at a reduced risk for cognitive decline (Wilson *et al.* 2005; Hogan *et al.* 2012; Mitchell *et al.* 2012). CA has usually been measured by self-reported frequency of participating in daily activities deemed to be cognitively, but not physically, stimulating, e.g. reading, playing games, crossword puzzles, etc. (Wilson *et al.* 2003; Eskes *et al.* 2010). Retrospective studies have examined the influence of leisure time activities on the risk of developing dementia. The Nun Study found that nuns whose diaries

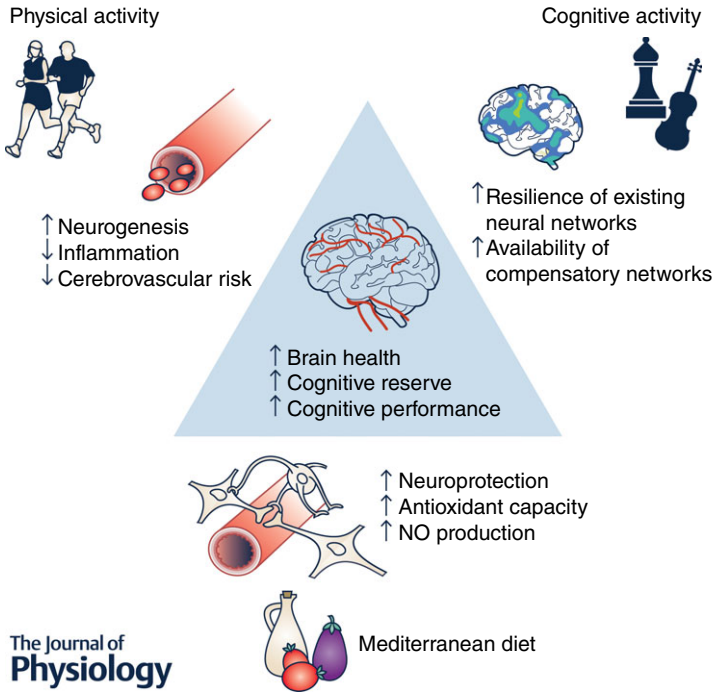

Figure 1. Promoting brain health via a triad of healthy lifestyle behaviours
Proposed associations and potential underlying mechanisms between physical activity, cognitive activity and a Mediterranean-style dietary pattern and increased physical and cognitive performance. The mechanisms underpinning the relationship between cognitive activity and cognitive function may be similar to those of physical activity and potentially include increased resting cerebral blood flow, synaptogenesis and neurogenesis. NO, nitric oxide.

revealed greater time spent in reading, writing and other intellectual activities had a lower incidence of AD than their less academic counterparts (Iacono *et al.* 2009). Further, a retrospective study of the contributions of cognitive and physical activity on cognitive function in a sedentary group of post-menopausal women also showed that greater frequency of different activities (not time) was also predictive of cognitive function (overall cognitive performance, attention and executive function), suggesting the importance of variety of stimulation (Eskes *et al.* 2010). Prospective studies also conclude that increased time spent reading, playing board games, and doing puzzles is associated with a reduction in dementia as diagnosed by neurological and neuropsychological exam, even when patients with possible preclinical dementia are excluded (Verghese *et al.* 2003).

Interventions aimed at increasing cognitive activities have shown consistently positive results in older adults engaging in structured cognitive training programmes, with a meta-analysis reporting a moderate effect of cognitive training on subsequent performance (Willis *et al.* 2006; Papp *et al.* 2009). Overall, these trials have suggested that engaging in cognitively stimulating activities increases cognitive functioning – measured using standardised neuropsychological tests – and potentially decreases dementia risk. However, most cognitive training interventions are challenged to show generalisability across other cognitive domains or tasks (Papp *et al.* 2009), although some studies have reported long term benefits on untrained activity and cognitive domains (Ball *et al.* 2010; Wolinsky *et al.* 2010). The Cochrane review of cognitive training interventions in healthy older adults and those with mild cognitive impairment has concluded that cognitive training does have beneficial effects of cognitive performance, specific to the tasks that individuals were trained on (Martin *et al.* 2011). The greatest benefits were on immediate and delayed verbal memory performance; however no benefit was seen on cognitive performance when cognitive training was compared with an active control group.

Cognitive interventions that focus on real-world skills and lifestyle engagement have had greater success in improving functional outcomes in older adults. Participants in one study were assigned to receive a 14-week intervention including social interaction and learning quilting, digital photography or both skills (Park *et al.* 2014). Participants were also expected to engage with the study community for a minimum of 15 hours per week. After participation in this intervention, episodic memory performance was improved in the participants who engaged in the cognitively demanding tasks. A follow-up to this study found that engaging older adults in a similar intervention learning how to operate a tablet computer also improved memory and processing speed (Chan *et al.* 2015). Likewise, a structured community-based volunteer intervention enhanced executive function and figural memory performance, and increased associated prefrontal cortex activation in an at-risk population (Carlson *et al.* 2008; Carlson *et al.* 2009).

Combined cognitive and physical activity interventions. Increasing evidence indicates that the causes of neuro-degeneration and ischaemic cell death are multi-factorial (Iadecola & Anrather, 2011). Indeed, the brain responds to vascular insults by marshalling a wide array of self-protective mechanisms (Iadecola & Anrather, 2011) that stands in marked contrast to the single-target approach used to treat AD, stroke and other neurological disorders. Consequently, a series of studies (Langdon & Corbett, 2012; Langdon *et al.* 2013, 2014) that combined a PA intervention with a CA intervention were conducted in rodents to determine if this combined approach was more effective in enhancing cognitive function than either intervention alone. In the first of these studies rats were exposed to running wheels (PA) for 2 h per day, 5 days a week or to different versions of a Hebb–Williams maze (CA) for an identical time period or the combination of PA and CA. Results showed that only the combined group exhibited improved cognition as reflected by a reduction in the number of working memory errors and improved choice accuracy in an eight-arm radial arm maze. Increasing the amount of PA from 2 h to 4 h did not enhance cognition. Indeed, only the combined PA–CA group displayed improved learning and memory (Langdon & Corbett, 2012). Subsequently, this 'cognitive rehabilitation' paradigm was used in an animal model of vascular cognitive impairment (VCI) to simulate human disease co-morbidities, which consisted of chronic bilateral carotid artery occlusion of the carotid arteries in middle-aged rats maintained on a diet high in fat and sugar (Langdon *et al.* 2013). In this study, VCI rats showed progressive impairment in spatial learning in the Morris water maze with repeated testing over 24 weeks following carotid artery occlusion. In VCI rats exposed to the PA–CA intervention, the cognitive impairments were significantly reduced. Interestingly, the untreated VCI rats had significant hypertrophy in the CA1 area of the hippocampus that was reduced (or prevented) by the PA–CA treatment. Whether the hippocampal CA1 hypertrophy represents a pathological state preceding cell death or instead an intrinsic repair response is not clear, but a similar form of CA1 hypertrophy was found in asymptomatic autopsy brains in the Nun study (Iacono *et al.* 2009). Finally, a note of caution must be expressed because the PA–CA intervention used to enhance cognitive performance in young, intact male rats (Langdon *et al.* 2013) and to blunt the cognitive impairments in a middle-aged, male rat model of VCI did not provide cognitive benefit in a cohort

of ovariectomised, middle-aged female rats (Langdon *et al.* 2014). The reasons why the cognitive rehabilitation paradigm was effective in male but not female rats is unclear but it may relate to reduced levels of BDNF as a result of ageing and ovariectomy (Langdon *et al.* 2014). Thus a greater 'dose' of exercise may be required to achieve the same levels of BDNF and cognitive performance in female as in male rats, which is in agreement with the aforementioned findings of Pialoux *et al.* (2009) in post-menopausal women.

In humans, a 16 week intervention including unsupervised physical activity, computer based brain training, or both found that older adults (60–85 years) who completed both training types had significantly higher long-term verbal memory compared to the control group (Shah *et al.* 2014). Intervention studies that have included physical activity, cognition and emotional or cultural training have suggested that the combination of physical and cognitive training can improve both cognitive performance and functional outcomes in healthy older adults (Oswald *et al.* 2006; Pieramico *et al.* 2012), although this difference disappears when physical and cognitive activity interventions are compared to an active control group (Lautenschlager & Cox, 2013; D. E. Barnes *et al.* 2013), suggesting that the benefits of social interaction may also be contributing to the positive effects. Indeed, correlational and interventional studies have indicated positive effects of social interaction on cognitive function (e.g. Winocur *et al.* 1987; Krueger *et al.* 2009; Mortimer *et al.* 2012). To test if, and how, these three factors may interact to slow cognitive decline and reduce the risk of dementia there have been some multi-modal interventions including physical activity and cognitive activity. One large longitudinal study has suggested that cognitive, social and physical activity equally contribute to reducing dementia risk in older adults. Individuals who had high engagement in all three areas were at a 37% reduced risk for developing dementia compared with individuals who had low engagement (Karp *et al.* 2006). A combined approach was also adopted in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which included a computer-based cognitive intervention in 1200 individuals who were at risk of cognitive decline (Ngandu *et al.* 2015). Participants who completed the cognitive intervention, in addition to an exercise and diet intervention, had a modest increase in overall cognitive performance when compared to control participants who received general health advice only. Whilst this study has high external generalisability, it is impossible to disentangle the cognitive benefit associated with cognitive training from the diet and exercise interventions.

Overall these data suggest that engaging with stimulating cognitive activities also has a role in preventing cognitive decline, possibly by increasing cognitive reserve (see Fig. 1). In support of this, it has been demonstrated that CA is positively associated with resting cerebral blood flow (CBF) and increased neural efficiency, both of which correlate well with cognitive function in normal ageing and clinical impairment (Stern, 2009). Moreover, it appears that using a combination approach whereby exercise combined with CA is used to either aid stroke recovery or enhance cognitive function in healthy older adults appears to improve cognitive performance more than PA or CA alone.

Diet

Along with physical and cognitive activity, engaging with a healthy diet is a third modifiable lifestyle factor that has been linked to overall brain health and attenuated cognitive decline. One diet in particular, the Mediterranean Diet (MeDi), characterised by high intake of fruits, vegetables, cereals, fish, nuts and olive oil, has received particular attention in the literature. The benefits of adherence to this type of diet have been evidenced in both epidemiological studies and clinical trials and include reduced risk for developing cancer, metabolic syndrome and vascular disease as well as lower incidence of dementia and AD (Lourida *et al.* 2013). Results from the Prevención con Dieta Mediterránea (PREDIMED) study showed that risk of stroke – a major risk factor for cognitive impairment – was reduced by 46% during the 4.8 year follow-up period (median follow-up time) in participants who followed a Mediterranean style dietary pattern including 30 g of mixed nuts (7.5 g hazelnuts, 7.5 g almonds, 15 g walnuts). In addition, in a subsample of the participants that were tested for neuropsychological function, higher intakes of olive oil, coffee, walnuts and wine were associated with better global cognition and memory function, with walnuts in particular linked to better working memory function (Pribis & Shukitt-Hale, 2014). The specific effects of some of the component parts of the MeDi such as polyunsaturated fatty acids (PUFAs) and polyphenols on indicators of brain health appear to underpin these positive findings.

Increased consumption of the omega-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), found predominantly in oily fish, is associated with attenuated cognitive decline and incidence of dementia or AD (Fotuhi *et al.* 2009). Recent MRI studies have indicated that higher circulating levels of omega-3 PUFAs are associated with reduced white matter damage and grey matter atrophy, outcomes which were also shown to improve along with executive function following a 6 month dietary intervention (2.2 g day^{-1} EPA+DHA) in healthy 50–75 year olds (Witte *et al.* 2014). Underpinning these effects are the many actions of DHA and EPA in the brain. DHA in particular is uniquely accumulated in central nervous system tissue and its presence beneficially

impacts upon plasma membrane function, synaptic transmission and cellular signalling (Yehuda *et al.* 1999). *In vitro* studies have also revealed a number of neuroprotective properties of DHA and EPA that may improve brain health including attenuation of inflammatory responses by either suppressing pro-inflammatory pathways and upregulating pro-resolving mediators such as neuroprotectin D1, or modulating mitochondrial function and reducing oxidative stress (Denis *et al.* 2015). There is also evidence from animal and human studies to suggest that dietary supplementation with omega-3 PUFAs improves regional CBF, which may contribute to the preservation of both brain structure and function (Tsukada *et al.* 2000; Jackson *et al.* 2012). Adult hippocampal neurogenesis declines with age but appears to be stimulated with omega-3 supplementation in aged rodents with concurrent improvements in cognitive function (Dyall *et al.* 2010; Cutuli *et al.* 2014). Supplementation studies in healthy adults have been less conclusive, however, with two recent meta-analyses reporting that supplementation with omega-3 PUFAs has a beneficial effect on episodic memory in samples characterised as suffering from mild memory complaints (Yurko-Mauro *et al.* 2015), and a marginal effect of supplementation on working memory in samples that have low baseline omega-3 PUFA status (Cooper *et al.* 2015). Therefore, despite compelling cross-sectional data, these studies suggest either a cognitive or physiological deficit must be present before beneficial effects of relatively short-term dietary interventions (6 months) are observed. Alternatively, it could be that greater consideration should be given to provision of both EPA and DHA in high quantities (Witte *et al.* 2014), which may explain the null effects on cognition of a recent 5 year omega-3 PUFA supplementation study in older adults who were at risk for developing age-related macular degeneration (Chew *et al.* 2015), a possibility that requires further exploration.

Polyphenols are phytochemical micronutrients that are ubiquitous in the diet and are predominantly found in fruits and vegetables, as well as coffee, tea, soy, red wine and chocolate. Despite their diversity, many of the beneficial physiological effects resulting from their consumption are common to many polyphenolic compounds and include promoting vascular function, reducing inflammation, combating oxidative stress and enhancing neuroprotection, all of which contribute to the maintenance of brain health during ageing. For example, the effects of cocoa flavan-3-ols (flavanols) have been well characterised in the literature; at the epidemiological level their consumption is associated with lower blood pressure and increased peripheral blood flow and inversely related to incidence of cardiovascular disease in late adulthood (Haskell & Watson, 2013). Studies in young adults have demonstrated improved cognitive function during demanding tasks following an acute dose of 520 mg cocoa flavanols (Scholey *et al.* 2010), and in older adults following an 8 week dietary intervention with both high (993 mg day^{-1}) and intermediate (520 mg day^{-1}) doses (Mastroiacovo *et al.* 2015), although null effects have also been reported (e.g. Pase *et al.* 2013). These effects may be attributable to a number of mechanisms including improved insulin sensitivity (Mastroiacovo *et al.* 2015), increased CBF (Haskell-Ramsay *et al.* 2015) and improved functioning of the dentate gyrus (Brickman *et al.* 2014).

The phytoalexin resveratrol found in the skin of red grapes and hence red wine also shows potential for preserving brain health. *In vivo* studies have revealed an impressive list of effects of this polyphenol, which has been shown to possess anti-inflammatory, antiviral and antioxidant properties, to protect against the development of cancer and cardiovascular disease, to improve insulin sensitivity and even to increase longevity (Kennedy & Wightman, 2011). In addition, resveratrol offers neuroprotection by increasing CBF and perfusion and attenuating amyloid-β-plaque formation in a transgenic mouse model of AD (Karuppagounder *et al.* 2009; Kennedy *et al.* 2010). Whilst increased CBF following an acute dose of resveratrol (250 mg) in healthy young adults has been repeatedly observed (Kennedy *et al.* 2010; Wightman *et al.* 2014), to date no effect on cognition in humans has been reported. This may be due in part to the cognitive testing paradigms that have been employed, or the bioavailability of the parent compound, or it may simply be that the cognitive effects of resveratrol may only be observed in populations where cognitive function is already impaired. To date, however, studies assessing the effect of resveratrol on cognition in older adults with cognitive impairment have yet to be conducted.

Berry fruits are another example of food high in polyphenols shown to contribute towards brain health and preserve cognitive function in ageing. Impressively, a large epidemiological study concluded that high consumption of berry fruits such as blueberries, strawberries and blackberries – rich in anthocyanin polyphenols – actually delayed cognitive ageing by 2.5 years (Devore *et al.* 2012). The effects of blueberries have been most widely studied, the anthocyanin compounds of which have been shown to cross the blood–brain barrier. In the brains of aged rodents, blueberry supplementation appears to reduce nuclear transcription factor κB, a marker of oxidative stress and inflammation; enhance activation of the cAMP response element binding protein, which is pivotal for maintaining neuronal plasticity; and increase BDNF, which supports neuronal survival and neurogenesis (Pribis & Shukitt-Hale, 2014). Further, these changes in the brain correlate well with memory performance in these supplemented animals. The study of the effects of anthocyanins in humans is limited to a couple of small

scale studies; however, the results of these show promise for improving learning, and episodic and spatial memory in older adults with mild cognitive impairment (Pribis & Shukitt-Hale, 2014).

Other, less well-researched dietary components are also showing promise for promoting brain health. Of these, there has been rapidly growing interest in dietary nitrate, found in high concentrations in red beetroot as well as lettuce and spinach. Dietary nitrate is reduced to nitric oxide *in vivo*, a cellular signalling molecule that promotes endothelial function, a depletion of which is observed in ageing and may contribute to cerebral hypoperfusion commonly associated with cognitive decline (Lidder & Webb, 2013). Beetroot, either in juice or supplement form, has been shown to attenuate oxidative stress and inflammation *in vitro* and in rodent models, and positive effects on endothelial function in humans have also been observed (Clifford *et al.* 2015). Interestingly, two recent intervention studies have shown differing effects of acute beetroot juice consumption on CBF in the pre-frontal cortex in older and younger adults with increased perfusion in this area being observed in older adults at rest (Presley *et al.* 2011), whilst reductions in local CBF during completion of cognitive tasks was observed in younger adults (Thompson *et al.* 2014). In the case of the latter, concurrent improvement on one of the cognitive tasks was observed, which the authors suggest as potentially indicative of a positive effect of dietary nitrate on neural efficiency. Whether the observed increased cerebral perfusion in older adults is associated with similar improvements in cognitive performance remains to be seen. Therefore, larger, longer intervention studies are required, with a specific focus on the effect of beetroot in older populations.

All the available evidence suggests that following a Mediterranean style diet is beneficial for preserving brain health and hence function during ageing. The individual effects of some of the active components of this diet with regard to brain function are the topic of intense current investigation. Although not consistently translated into observable effects in humans, *in vitro* and *in vivo* work indicates that each of these has numerous positive actions that serve to enhance cerebral circulation and offer neuroprotection, which may work to increase both brain and cerebrovascular reserve and thus maintain cognitive function (see Fig. 1). It must be said, however, that the effectiveness of a dietary strategy to combat decline, improve current functioning or even as an adjunctive treatment to pharmacological approaches in combating neurodegenerative diseases associated with ageing is still greatly under-researched. Further, if these dietary components are indeed effective in attenuating brain ageing, whether there is a criterial period of intervention remains to be addressed. Lastly, whilst the specific action and effectiveness of these dietary components is of academic interest – especially given that the dosages provided in the studies discussed here are not always achievable by dietary means alone – the diet as a whole, which includes other fats, proteins and micronutrients, must be considered and the possibility of interactions and synergies explored. The type of long-term large-scale studies that are required to adequately illuminate these issues are resource intensive and thus uncommon in the literature. In this way, the *in vitro* and animal studies will continue to complement more practicable human trials in order to advance our understanding of the effects of diet on the ageing brain.

Conclusions

The evidence described here suggests that the older adult brain retains its capacity for plasticity and that a triad of healthy behaviours may be key to taking advantage of this fundamental neural property. We propose that reserve is built up through engaging with physical and cognitive activities and adhering to a diet rich in healthy fats and plant phytochemicals so that the clinical manifestations of ageing and neurodegenerative disease are kept at bay for longer. Adopting a brain health-promoting lifestyle may even improve current cognition function as well as attenuate decline in addition to preventing the development of other age-related diseases, although this is not universally reported. Interestingly, particularly promising effects on cognitive performance are found when physical and cognitive activities are combined; a three-pronged approach including a MeDi intervention has yet to be developed and may prove to be even more beneficial. Therefore, the design of future studies should allow for a comparison of the effects of singular and combined approaches.

Finally, there are still many unanswered questions. The majority of human research in this area has focused on the effects of these lifestyle interventions in healthy older adults; their effectiveness as a potential adjunctive treatment to traditional therapies for cognitive impairment is currently not established, although animal models continue to show promise. In addition, it is also unknown whether there exists a window of opportunity during which implementing these behaviours yields the best results in terms of functional outcome and at which point the downward trajectory of cognitive function can be influenced no further. Moreover, other, less well understood modifiable lifestyle factors such as sleep may also promote brain health in similar ways as described here, which is a current emerging area of interest. In 2013, the G8 Dementia Summit Declaration revealed the worldwide annual cost of dementia associated care as US$604 billion. Moreover, the cost of care is expected to increase as the prevalence of dementia increases beyond the current capacity of many health care systems

across the globe. Therefore, cost-effective approaches to combating cognitive impairment are imperative and additional research is needed to determine effective and sustainable ways of increasing these promising healthy behaviours at the community level.

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Additional information

Competing interests

None declared.

Author contributions

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