CHAPTER

7

Lifestyle and Alzheimer's Disease: The Role of Environmental Factors in Disease Development

Nancy Bartolotti and Orly Lazarov

Department of Anatomy and Cell Biology, College of Medicine, University of Illinois at Chicago, Chicago, IL, United States

OUTLINE

Introduction 198

Epidemiological Studies 201
Cognitive Reserve and Education 201
Brain Reserve 204
Cognitive Reserve 205

The Benefits of Cognitive Complexity Following the Onset of Dementia 207

Physical Activity and Exercise 209

Chemical Exposure and AD Risk 211

Metals 212

Air Pollution and Tobacco Smoke 213

Nutrition and the Microbiome 214
Nutritional Elements that Decrease AD Risk 214
Nutrition and Increased Risk for AD 216
Microbiome 217

Genes, Environment and Alzheimer's Disease.
DOI: http://dx.doi.org/10.1016/B978-0-12-802851-3.00007-3

Sleep and Circadian Rhythm 218
Socialization 219
Conclusion 219
References 220

INTRODUCTION

Environmental factors profoundly influence brain structure and function. Lifestyle elements such as nutrition, physical activity, exposure to chemicals, social interaction, and participation in cognitively demanding activities significantly impact the structure and function of the brain. It is now abundantly clear that this effect is profound to the extent of modulating susceptibility to or inducing neurodegenerative disease. The role of the environment is particularly significant in neurodegenerative diseases that are not clearly caused by a single genetic alteration, such as Late Onset Alzheimer's disease (LOAD). The primary risk factor for LOAD is advanced age. Age-dependent lifestyle changes often include reduced mobility, fewer opportunities for socializing, infrequent participation in cognitively stimulating activities, and poor nutrition. Here we examine evidence that lifestyle and environmental factors affect the risk for the development of AD.

In the early 2000s, several pioneering studies provided the first experimental evidence that environmental factors are disease modulators. These experiments modified the living environment of mouse models of Alzheimer's disease (Ambree et al., 2006; Billings, Green, McGaugh, & LaFerla, 2007; Costa et al., 2007; Herring et al., 2009; Hu et al., 2010; Jankowsky et al., 2005; Lazarov et al., 2005; Levi, Jongen-Relo, Feldon, Roses, & Michaelson, 2003; Nichol, Deeny, Seif, Camaclang, & Cotman, 2009; Nichol et al., 2008; Parachikova, Nichol, & Cotman, 2008; Russo-Neustadt, Beard, & Cotman, 1999; Wolf et al., 2006). Experiments included a paradigm known as environmental enrichment (EE, Figure 7.1), learning tasks, or exercising paradigms. EE typically consists of a larger living space than the standard cage, social interactions, novel objects and nesting materials, as well as running wheels for physical exercise (Figure 7.1). This paradigm enhances many aspects of plasticity in the brain of wild-type mice, as well as improves learning and memory (for recent reviews, see Hirase & Shinohara, 2014; Simpson & Kelly, 2011). Experience of mice expressing familial Alzheimer's disease linked mutant variants (FAD mice) in EE resulted in reduced neuropathology and enhanced neuroplasticity, including enhanced and rescued hippocampal neurogenesis and long term potentiation (LTP), reduced oligomeric Aβ and tau hyperphosphorylation, along with upregulation of critical components of anterograde

FIGURE 7.1 The enriched environment experimental paradigm. In the enriched environment, mice are housed in a large cage with novel stimuli such as tunnels and huts. Running wheels are provided for physical activity. Exposure to an enriched environment such as the one pictured here has been shown to enhance brain plasticity and cognitive function in rodents.

axonal transport (for example, see Hu et al., 2010). Specifically, several studies reported decreased amyloid pathology following EE (Ambree et al., 2006; Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005; Billings et al., 2007; Costa et al., 2007; Arne Herring et al., 2011; Hu et al., 2010; Lazarov et al., 2005; Mirochnic, Wolf, Staufenbiel, & Kempermann, 2009; Nichol et al., 2009; Nichol et al., 2008; Parachikova et al., 2008; Perreau, Adlard, Anderson, & Cotman, 2005; Russo-Neustadt et al., 1999).

Importantly, mice that did not use the environment (e.g., did not run on the running wheel) showed no change in levels of pathology in their brains (Lazarov et al., 2005). In the APPswe/PS1ΔE9 mouse model of AD, EE was shown not only to decrease amyloid-related pathology, but also to increase levels of neprilysin, a protein involved in the degradation of Aβ (Lazarov et al., 2005). In support of that, aging-dependent decline in neprilysin activity (Hellstrom-Lindahl, Ravid, & Nordberg, 2008; Wang, Iwata, Hama, Saido, & Dickson, 2003) can be mitigated by experience of aging mice in EE (Mainardi et al., 2014). Importantly, improvements in learning and memory were observed in FAD mice following EE, even when levels of amyloid deposition were found to be upregulated (Jankowsky et al., 2005), indicating that the protective effect of EE surpasses the detrimental effect of amyloid deposition.

Taken together, these experiments suggest that a complex experience that involves multiple stimuli, such as exercise, novelty, and exploration, dramatically affects brain plasticity and mitigates cognitive dysfunction in mouse models of FAD. Later experiments have unraveled, at least in part, the signaling pathways underlying EE (Berchtold et al., 2005; Billings

et al., 2007; Hu, Long, Pigino, Brady, & Lazarov, 2013; Lazarov et al., 2005; Perreau et al., 2005). Since then, numerous studies have described the effect of environmental components on the development of AD in rodents and humans. We describe and consider the evidence that supports or defers the link between lifestyle and environmental factors and the development of cognitive deficits and AD, and discuss potential mechanisms underlying these effects (for summary see Table 7.1).

TABLE 7.1 Summary of Discussed Environmental Factors and Their Influence on AD Risk

Environmental factor	**Potential mechanism for influencing AD risk ↓ Decreases AD risk ↑ Increases AD risk**	
	Humans	***Rodents***
Cognitive stimulation (Humans: reading, writing, puzzle solving, education, bilingualism. Rodents: environmental enrichment)	↓ Increased brain volume ↓ Increased neuronal density ↓ Increased hippocampal activation ↓ Enhanced connectivity (Cognitive Reserve) ↓ Reduced AD pathology, particularly amyloid pathology	↓ Enhanced neurogenesis ↓ Increased neprilysin activity (increased Aβ clearance) ↓ Reduced GSK3-β activity (reduced tau hyperphosphorylation) ↓ Enhanced plasticity ↓ Enhanced LTP ↓ Reduced AD pathology (Aβ and phosphorylated tau)
Physical activity	↓ Increased hippocampal activity and volume	↓ Increased hippocampal activity and volume ↓ Increased neurotrophins ↓ Reduced myelin degeneration ↓ Reduced AD pathology ↓ Reduced oxidative stress ↓ Increased neurogenesis ↑ Increased amyloid pathology
Pesticides (DDT, chlorpyrifos, rotenone)	↑ Extent of risk and mechanism unclear	↑ Increased APP ↑ Increased Aβ ↑ Increased reactive oxygen species ↑ Degeneration of cholinergic neurons
Metals (copper, lead, and aluminum are increased in AD, selenium and manganese are decreased in AD, zinc is unclear)	↓ Zinc associated with decreased plaque density	↑ Copper decreases neprilysin activity (reduced Aβ clearance) ↓ Zinc reduces copper absorption ↑ Zinc increases APP cleavage and Aβ deposition ↑ Alterations in metal homeostasis may result in a more oxidizing environment in the brain

(*Continued*)

TABLE 7.1 (Continued)

Environmental factor	Potential mechanism for influencing AD risk ⬇ Decreases AD risk ⬆ Increases AD risk	
	Humans	*Rodents*
Pollution	⬆ Increased inflammation ⬆ Increased Aβ and tau pathology ⬆ Increased neurodegeneration ⬆ Increased blood-brain barrier damage	⬆ Increased AD pathology
Good Nutrition (high in antioxidants, fruits, vegetables, cocoa, vitamins, folate, caffeine)	⬇ Reduced oxidative stress via antioxidants ⬇ Reduced AD pathology	⬇ Reduced oxidative stress via antioxidants ⬇ Increased neurotrophins ⬇ Reduced AD pathology ⬇ Increased neprilysin activity ⬇ Reduced GSK3-β activity (reduced tau hyperphosphorylation) ⬇ Increased acetylcholine ⬇ Reduced activity of acetylcholinesterase ⬇ Altered presenilin activity ⬇ Promoting microbiome health
Bad Nutrition (high in animal products, fat, cholesterol, sugar)	⬆ Increased diabetes risk ⬆ Decreased vascular health	⬆ Exacerbate Aβ and tau pathology ⬆ Reduced cholinergic neurons ⬆ Disrupting microbiome health
Sleep	See Chapter 10	See Chapter 10
Socialization	⬇ Cognitive reserve?	

Potential ways by which an environmental factor can affect the development of the disease or the risk—effect on the genetics—APP, PS1, effect on oxidative stress, mitochondria, blood circulation/elimination of toxins, oxygen level, upregulation of neurotrophic factors, upregulation of neurogenesis, synaptic components, etc.

EPIDEMIOLOGICAL STUDIES

Cognitive Reserve and Education

Compelling evidence for the contribution of environmental factors to AD risk comes from studies like the ones performed in American religious orders (Bennett, 2006). In these studies, the cognitive ability of hundreds of individuals was tested regularly throughout life, and the brains

examined following death. Religious orders are a particularly informative observational population since the lifestyles of the members are similarly regulated, thus facilitating a more focused analysis of the effect of a single environmental variable. One factor that was repeatedly found to be associated with risk of AD was the extent of cognitive complexity experienced during life (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005b). For example, the density of ideas in writing samples of nuns during early and midlife was associated with a reduced risk for AD, superior cognitive functioning, and decreased levels of pathological markers for AD (Mortimer, 2012; Riley, Snowdon, Desrosiers, & Markesbery, 2005; Snowdon et al., 1996). The extent of idea density in writing samples may indicate a lifetime of cognitive complexity, in part resulting from higher levels of education (Mitzner & Kemper, 2003). Indeed, in one study of nuns, lower education level was correlated with earlier onset of cognitive impairment (Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2007). Similarly, a recent meta analysis of the literature on education and risk for AD determined that higher education reduced the risk of incidence of AD (Meng & D'Arcy, 2012). Interestingly, even low levels of education appear to exert a protective effect when compared to no formal education (Farfel et al., 2013). Other studies also describe the inverse correlation between education level and severity of cognitive impairments in spite of the presence of AD-related pathology (Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Bennett et al., 2003; Roe, Xiong, Miller, & Morris, 2007).

In addition to education, other environmental factors can offer cognitive complexity during life and confer a benefit to the aging brain. For example, many studies show that lifetime bilinguals have a delayed average onset for AD (Akbaraly et al., 2009; Alladi et al., 2013; Freedman et al., 2014; Rovio et al., 2005; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). For this reason, bilingualism is often now considered an environmental factor (Gold, 2014). Participation in other cognitively demanding activities such as reading, writing, and playing an instrument or games has also been associated with a reduced risk for AD (Sattler, Toro, Schönknecht, & Schröder, 2012; Wilson, Boyle, Yang, James, & Bennett, 2015; Wilson et al., 2002). This observation is still manifest when preclinical depression, which might result in a decreased interest in participating in leisure activities, is accounted for (Verghese et al., 2003). Like religious orders, studies of twins aid in the identification of important environmental factors, since the extent of genetic and environmental variability is smaller. In studies of twins, the twin with greater involvement in leisure activities, or with a more cognitively complex job, had a lower risk for AD (Andel et al., 2005; Crowe et al., 2003; Potter, Helms, Burke, Steffens, & Plassman, 2007). Similarly, in a monozygotic twin study, the twin with greater involvement in cognitive leisure activities had a reduced risk for AD, particularly when the twins were carriers for APOE4, a genetic risk factor for AD (Carlson

et al., 2008). These studies offer compelling evidence that participation in a cognitively complex environment can modulate AD risk independent of genetic contributions to that risk.

Little is known about the mechanism of protection conferred by a lifetime of cognitive activity. Deciphering this mechanism in the human brain is particularly challenging, simply because of the limited ways to detect and measure cellular processes in live individuals. One way to measure the status of AD pathology is by examining the levels of Aβ and tau in the cerebral spinal fluid (CSF), which is thought to be reflective of Aβ and tau pathology in the brain (Wang et al., 2014). Longitudinal studies have shown that greater education results in a slower decline in CSF $A\beta_{42}$ (declining $A\beta_{42}$ in the CSF is indicative of worsening brain pathology), and in postmortem analysis individuals with higher levels of education had lower levels of Aβ in the brain compared to their less educated, but still cognitively intact age-matched counterparts (Lo & Jagust, 2013; Yasuno et al., 2014). In addition, higher levels of self-reported cognitive activity (such as reading and writing) in early life was associated with reduced levels of Pittsburgh Compound B (PiB), a radioactive tracer for amyloid plaques, in later life (Landau et al., 2012). These studies offer evidence that a lifetime of cognitively complex activities may reduce the occurrence of amyloid pathology.

Similarly, in a postmortem analysis, level of education was found to temper the effects of amyloidosis, meaning that individuals with higher education had greater cognitive function when matched to an individual with similar levels of amyloid (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005a). A recent meta analysis of the literature on education and risk for AD determined that the AD pathology was greater than the cognitive performance during life would have otherwise suggested (Meng & D'Arcy, 2012). As in the higher-educated brain, the pathological state of the bilingual brain observed postmortem is often far more severe than the symptoms would have suggested during life, strengthening the argument that an active brain can enhance cognitive functioning even in the presence of AD pathology (Schweizer, Ware, Fischer, Craik, & Bialystok, 2012). Finally, other cognitively stimulating activities performed regularly during life such as reading and playing games have also been shown to be associated with enhanced cognitive function even in the presence of AD pathology in a longitudinal study (Negash et al., 2013).

One interpretation of these findings is that a lifetime of cognitive complexity builds up a "reserve" that allows the brain to better cope with the insults of pathology, requiring a more advanced pathological state before cognitive decline becomes apparent. This reserve may exist in two forms, brain reserve or cognitive reserve. Brain reserve typically refers to greater physical content of the brain, which means that the individual starts with more brain matter before decay begins, so more decay needs to happen

before cognitive symptoms are observed. Cognitive reserve usually refers to increased efficiency or alternate neural pathways that allow for intact cognitive functioning in spite of advanced decay. In this section we will examine the evidence for the protective effects of brain and cognitive reserve on AD risk.

Brain Reserve

Brain reserve hypothetically decreases risk for AD by increasing the quantity of brain tissue, which could mean that a greater extent of degeneration would need to occur before symptoms are manifested (Steffener & Stern, 2012). This could potentially be achieved by greater brain volume or high neuronal density. Greater brain volume has previously been associated with a reduction of AD symptoms (Mori et al., 1997). Individuals with higher education levels have greater gray matter volumes of areas that are typically affected by AD, such as the entorhinal cortex, suggesting that these areas are built up during complex experiences like education and are therefore more resistant to degeneration after onset of AD pathology (Serra et al., 2011). The hippocampus is one of the primary brain structures involved in learning and memory, and lower hippocampal volume has been associated with impaired recall (Mortimer, Gosche, Riley, Markesbery, & Snowdon, 2004). Exercises requiring periods of sustained learning have been associated with persisting changes in gray matter, particularly in the hippocampus (Draganski et al., 2006). Further, individuals who report a lifetime of greater cognitive complexity also have a reduced rate of hippocampal degeneration during aging (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). Older individuals who remain cognitively intact exhibit hippocampal activation similar to that of young individuals, indicating that preserved hippocampal functioning may mean the difference between normal aging and dementia (Persson, Kalpouzos, Nilsson, Ryberg, & Nyberg, 2011). Therefore, a lifetime of cognitive complexity may protect against cognitive decline by preventing hippocampal degeneration and thus preserving function.

Brain reserve can also be theoretically achieved through increasing neuronal or gray matter density. Learning a second language is associated with increased gray matter density (Mechelli et al., 2004). Similarly, participating in musical training is also known to increase gray matter density in areas of the brain important for memory and higher-level cognitive processes (James et al., 2014). These results are meaningful because a higher neuronal density has been linked to a slower cognitive decline, so activities that enhance neuronal density may slow the progression of Alzheimer's symptoms (Wilson, et al., 2013). White matter (myelin) also degenerates during aging, but cognitively active individuals such as lifetime bilinguals maintain their white matter for a longer time (Luk, Bialystok, Craik, & Grady, 2011). Cognitive training has also been shown

to increase myelination, even in older adults, resulting in enhanced connectivity (Engvig et al., 2012; Lövdén et al., 2010; Takeuchi et al., 2010). Additional support for this result comes from experiments in middle age rats, in which EE can increase myelination and improve cognitive performance (Qiu et al., 2012). These studies provide evidence that cognitive complexity can increase the amount and density of brain matter, potentially requiring a greater amount of damage before reaching a point where symptoms of dementia are apparent.

Cognitive Reserve

While cognitive complexity may build up a structural brain reserve, individuals who have experienced a lifetime of cognitive complexity sometimes show extensive brain decay at time of death and yet are still able to remain cognitively intact, suggesting that their brains were somehow better able to deal with the degeneration (Iacono et al., 2009). These observations led to the formulation of the cognitive reserve hypothesis (Stern, 2002). In this hypothesis, a lifetime of cognitive complexity builds up a reserve of alternate neural connections and greater efficiency in brain processing, acting as an architectural and metabolic buffer for the brain, making it less affected by neurodegeneration (Foubert-Samier et al., 2012; Yaakov Stern, 2009). Cognitive reserve may account for why older individuals with higher levels of education are able to perform better at cognitive tasks in spite of comparable reductions in gray matter (Steffener et al., 2014). Similarly, when white matter begins to degenerate during the early stages of AD, experiences associated with greater cognitive complexity such as education and bilingualism may also protect against this degeneration and allow normal functioning to occur for longer before cognitive decline becomes apparent (Brickman et al., 2011; Gold, Johnson, & Powell, 2013; Molinuevo et al., 2014; Schweizer et al., 2012). Indeed, while higher levels of self-reported cognitive activity (such as reading and writing) in early life were associated with reduced levels of PiB, higher levels of self-reported cognitive activity in late life were not significantly associated with lower levels of PiB, suggesting that late life enrichment may not be able to reverse amyloid pathology, but may still improve cognitive function (Landau et al., 2012). In a recent longitudinal study, higher cognitive activity in youth and higher cognitive activity in old age were both independently associated with greater cognitive functioning in old age, regardless of brain pathology, suggesting again that cognitive activity can neutralize the detrimental effects of AD pathology (Wilson, Boyle, et al., 2013). Evidence for cognitive reserve is also observed in mouse models. In the Tg2576 mouse model of AD, exposure to EE prior to the onset of pathology had a lasting effect into aging, mitigating the effects of AD pathology and slowing cognitive decline (Verret et al., 2013).

It has been previously shown that during AD, alternate pathways are recruited in the brain during a task, compared to cognitively intact age-matched controls, indicating that the brain may be trying to redirect processing around pathology-damaged connections (Stern et al., 2000). Multiple studies have shown that a greater cognitive reserve resulted in a protection of cognitive function, even when the extent of amyloid pathology, measured in the CSF and by PiB, would have otherwise predicted cognitive impairments (Dumurgier et al., 2010; Rentz et al., 2010; Roe et al., 2008; Soldan et al., 2013; Sole-Padulles et al., 2011; Yaffe et al., 2011). An individual who has experienced a lifetime of cognitive complexity may have cultivated a system of alternate connections, and may subsequently be in a better position to make functionally relevant alternate connections when pathology begins to damage the brain. Indeed, an analysis of metabolic brain usage in highly educated pre-AD individuals showed higher levels of activation in certain parts of the brain, compared to their poorly educated cohorts, indicating that they were better able to utilize their brain resources and recruit alternate pathways (Morbelli et al., 2013; Perneczky et al., 2006). It has also been hypothesized that bilingual individuals may make more efficient use of their neural resources, allowing them to function normally for a longer period of time (Guzmán-Vélez & Tranel, 2015). Interestingly, the benefits of bilingualism are greater in low-educated populations compared to high-educated populations, suggesting that reserve is limited, and there may be multiple ways to acquire a cognitive reserve (Gollan, Salmon, Montoya, & Galasko, 2011).

Higher education and greater cognitive complexity can also mitigate the increased risk of AD from carrying the APOE4 allele. The APOE gene is one of the genetic factors associated with an increased risk of LOAD. Of the three human isoforms (APOE2, APOE3, and APOE4) carrying one copy of the APOE4 allele increases the lifetime risk of AD from 10–15% to about 20–30%, while carrying two copies of the APOE4 allele increases risk to 50–60% (Genin et al., 2011). In one study, individuals with high levels of cognitive reserve and carrying the APOE4 allele had a comparable AD risk to individuals without a copy of APOE4 (Ferrari et al., 2014). In addition, APOE4 carriers with a high cognitive reserve had a later onset for AD (Ferrari et al., 2013). Prior to the onset of symptoms, APOE4 carriers with a greater cognitive reserve also had reduced PiB uptake, indicating reduced amyloidosis (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Finally, cognitive reserve resulting from high levels of education has been shown to be just as protective in APOE4 carriers as in non-APOE4 carriers (Garibotto et al., 2012). These results suggest that cultivating a cognitive reserve throughout life may be particularly beneficial for individuals at greater genetic risk for AD.

In addition to slowing the onset of cognitive impairment, the cognitive reserve may also delay the conversion from mild-cognitive impairment

(MCI) into AD dementia. One recent study showed that while the initial AD-related decline began around the same time in individuals with either high or low cognitive reserve, the conversion to dementia was delayed by approximately seven years in the high cognitive reserve group (Amieva et al., 2014). In a postmortem analysis, level of education was found to temper the effects of amyloidosis (greater education, greater cognitive function in spite of amyloidosis), but not the effects of neurofibrillary tangles (Bennett et al., 2005a).

The hyperphosphorylation of tau and the formation of neurofibrillary tangles is another hallmark of AD pathology and likely indicates a later and more severe disease state (Sperling et al., 2011). This may suggest that cognitive reserve can offer protection at earlier stages of pathology (Abner et al., 2011; Soldan et al., 2013; Wilson et al., 2004). In line with this idea, it has been shown that while cognitive reserve confers a protective effect at all stages of amyloid pathology, cognitive reserve is less protective when levels of tau and phosphorylated tau are high in the CSF, a phenomenon that may occur in the more advanced stages of the disease (Soldan et al., 2013). However, even when levels of tau and phosphorylated tau are high in the CSF, the time to conversion to dementia is modified by level of education, indicating that even in an advanced pathological state the cognitive reserve may be slowing disease progression (Roe et al., 2011). Interestingly, evidence from mouse models suggests that EE can modify tau pathology. In the 3xTG-AD mouse model of AD, mice that spent time learning a memory task after the onset of pathology exhibited improved memory and reduced severity amyloid and tau pathology, as well as reduced GSK3-β activity, a kinase that may be responsible for the hyperphosphorylation of tau in AD (Billings et al., 2007). Similarly, in the APPswe/PS1ΔE9 mouse model of AD, EE reduced hyperphosphorylated tau in the hippocampus (Hu et al., 2010). Therefore, even though cognitive reserve may be most effective in preventing the onset of AD or mitigating the effects of the earlier stages of pathology, engaging in cognitively complex experiences may still offer some benefit to individuals with a more severe form of AD by slowing the rate of cognitive decline.

THE BENEFITS OF COGNITIVE COMPLEXITY FOLLOWING THE ONSET OF DEMENTIA

Following the onset of dementia, cognitive complexity may still offer some benefit in slowing decline of cognitive functioning and improving quality of life (Liberati, Raffone, & Olivetti Belardinelli, 2012). Participation in cognitively engaging activities can be particularly effective in slowing the progression of cognitive impairment early after the onset of symptoms (Treiber et al., 2011). A review of clinical trials examining the effect

of cognitive stimulation therapy (CST) showed that regular participation in activities such as solving puzzles, playing games, and participating in social activities can improve functioning in people with moderate dementia (Woods, Aguirre, Spector, & Orrell, 2012). CST seems to be particularly beneficial for memory and language-related functioning (Hall, Orrell, Stott, & Spector, 2013). Cognitive training for two months improved memory and increased activation in the hippocampus of persons with MCI (Rosen, Sugiura, Kramer, Whitfield-Gabrieli, & Gabrieli, 2011). CST (via a mneumonic training task) increased activity in the hippocampus of MCI patients during both encoding and retrieval of the memories (Hampstead, Stringer, Stilla, Giddens, & Sathian, 2012). Another review showed that CST could improve memory and general cognition in people with AD (Olazarán et al., 2010). Indeed, CST has been shown to improve cognition, and analysis by fMRI showed changes in the neural circuitry that seem to indicate the AD brain retains some elements of plasticity (Baglio et al., 2015; Belleville et al., 2011). Additional evidence for this plasticity comes from event-related potential (ERP; which measures electrical activity in the brain) studies on individuals with AD who show alterations in ERP response following cognitive training (Spironelli, Bergamaschi, Mondini, Villani, & Angrilli, 2013). These effects seem to be specific to CST, as CST improves memory function even relative to other therapeutic interventions such as occupational therapy (Mapelli, Di Rosa, Nocita, & Sava, 2013). Small clinical trials have shown that CST and involvement in artistic activities stabilized cognition and improved quality of life for both patients and caregivers (Maci et al., 2012; Viola et al., 2011). The benefits of CST appear to be long lasting, and may extend at least as long as 10 years following the therapy (Luttenberger, Hofner, & Graessel, 2012). CST may be particularly beneficial when combined with typical pharmacological interventions used for AD. In combination with a cholinesterase inhibitor, CST resulted in enhanced cognition compared to the drug alone, indicating that cognitive stimulation may be a valuable component of a multiapproach therapy for AD (Matsuda et al., 2010; Onder et al., 2005; Orrell et al., 2014).

CST can be achieved by multiple methods. One possible form of CST is studying a language later in life, which could offer some value as a form of neuroprotection, since this task involves a complex pathway, perhaps more so than other cognitively demanding tasks (Antoniou, Gunasekera, & Wong, 2013). Another way to enhance the effectiveness of CST could be to use music. Patients with AD experience better memory formation when information is sung rather than spoken, indicating a cognitive benefit may exist for musical training (Simmons-Stern, Budson, & Ally, 2010). One challenge for CST for treatment of dementia is that it can be difficult to teach the task. Video game training shows some promise as a means of cognitive stimulation therapy. Research groups are working on making

video games intuitive to learn for people suffering from dementia (Boulay, Benveniste, Boespflug, Jouvelot, & Rigaud, 2011). It may even be possible to provide CST of this kind over the Internet, increasing availability and access (Tarraga et al., 2006). In summary, current evidence suggests that access to cognitively stimulating materials such as puzzles, games, and memory exercises may improve quality of life in the already demented (Bharwani, Parikh, Lawhorne, VanVlymen, & Bharwani, 2012).

PHYSICAL ACTIVITY AND EXERCISE

Physical activity has been proposed as one way to potentially modulate AD risk and progression due to the increase in hippocampal volume and activity in humans, and even in older, healthy humans who are more physically active (Niemann, Godde, & Voelcker-Rehage, 2014; Shah et al., 2014; Varma, Chuang, Harris, Tan, & Carlson, 2015). In rodents too, access to a running wheel has profound effects on areas of the brain commonly affected in AD, such as the hippocampus (for recent review, see Hooghiemstra, Eggermont, Scheltens, van der Flier, & Scherder, 2012). In the 3xTG-AD mouse model of AD, mice that had access to a running wheel had decreased pathology and reduced cognitive impairment (Garcia-Mesa et al., 2011). Also in the 3xTg-AD model following the onset of pathology, access to a running wheel rescued deficits in proteins important for synaptic function normally reduced in this mouse model, such as NR2B PSD-95, synaptophysin, GDNF, and SIRT1 (Revilla et al., 2014). Similar results were observed in the Tg2576 mouse model of AD in which access to a running wheel lessened AD-related brain pathology and improved performance in a memory task (Nichol, Parachikova, & Cotman, 2007; Parachikova et al., 2008; Yuede et al., 2009). In the APPswe/PS1ΔE9 mouse model of AD, physical activity also improved spatial memory and reduced AD-related pathology (Tapia-Rojas, Aranguiz, Varela-Nallar, & Inestrosa, 2015). In a mouse model of APOE4 carriers, access to a running wheel improved performance on a memory task to resemble the performance by mice not carrying APOE4 (Nichol et al., 2009). Voluntary running may also ameliorate tau-related pathology, as experiments in the THY-Tau22 mouse model of AD have shown (Belarbi et al., 2011). However, other evidence suggests that exercise may be less effective as a therapy in more advanced stages of tau-related pathology (Ohia-Nwoko, Montazari, Lau, & Eriksen, 2014). The molecular mechanism behind this benefit is still under investigation, but may include reducing oxidative stress, preventing degeneration, increasing neurogenesis, or enhancing neuroprotective factors and signaling pathways involved in learning and memory (Dao, Zagaar, & Alkadhi, 2014; Herring et al., 2010; Mirochnic et al., 2009). Importantly, the molecular pathways that underlie memory improvements in AD may

be different from those underlying memory improvements in healthy individuals, and further studies will be required to identify the pathways modulated by physical activity in AD specifically (Rao et al., 2015).

However, some evidence suggests that physical activity may not improve AD-related pathology in mouse models. For example, one study found no beneficial effect of wheel running on memory performance in the TgCRND8 mouse model of AD following the onset of pathology, and even observed a worsening of amyloid pathology in the wheel running group (Richter et al., 2008). Another study showed that initiating treadmill running in APP/PS1 mice after the onset of pathology improved memory, but did not improve brain amyloid pathology (Zhao, Liu, Zhang, & Tong, 2015). Treadmill running in the APP/PS1 mouse model did prevent degeneration of myelin in the hippocampus, offering one potential mechanism for the protective effect observed on memory (Chao et al., 2015). Some of the discrepancy in the literature regarding the effect of physical activity on AD may arise from the use of different mouse models of AD, as well as when in the disease course and for how long the wheels are introduced. However, early data in human trials is also conflicting. Preliminary evidence from a cross-sectional study suggested that greater physical activity may reduce risk for AD (Okonkwo et al., 2014). Another report suggests that greater physical activity results in a lower risk for AD (Nikolaos Scarmeas et al., 2009). One clinical trial showed that greater participation in physical activity reduced risk for MCI or AD (Schlosser Covell et al., 2015). However, other studies do not find a correlation between reduced physical activity and dementia risk (Paganini-Hill, Kawas, & Corrada, 2015). Therefore it is not clear whether in humans the effect of physical activity on cognitive performance is as great as the effect of cognitive leisure activities, such as reading and writing (Lautenschlager et al., 2008; Scarmeas, Levy, Tang, Manly, & Stern, 2001).

Although this is not an easy task to address in mice and its translatability may be questionable, this issue is, to some extent, controversial in the mouse too. Thus, some studies in mouse models of FAD have shown that voluntary wheel running does or does not (Nichol et al., 2007; Nichol et al., 2008; Wolf et al., 2006) improve memory or increase markers of brain plasticity such as neurogenesis in a mouse model of AD, whereas total enrichment does enhance memory and plasticity in the same mouse model of AD (Wolf et al., 2006). Similar results were observed in another study, where physical activity was not enough to improve pathology, but cognitive stimulation in addition to physical activity did improve memory function (Cracchiolo et al., 2007). For this reason, physical activity may be most effective when combined with multiple types of leisure activities (Karp et al., 2006). Indeed, physical activity may enhance the effects of cognitive stimulation therapy (Thiel et al., 2012). A recently published clinical trial showed that targeting physical activity, diet, and

cognitive training together could be a promising therapeutic approach for improving cognition in individuals with AD (Ngandu et al., 2015). Other clinical trials investigating the effect of physical activity on AD are currently underway and more work will need to be done to determine the effects of physical activity on AD risk and progression, either alone or in conjunction with other interventions (Hardman, Kennedy, Macpherson, Scholey, & Pipingas, 2015; Yu et al., 2014).

CHEMICAL EXPOSURE AND AD RISK

It is thought that pesticides may have many effects on the brain. Thus, exposure to pesticides may be another environmental factor influencing AD risk (for review see Casida & Durkin, 2013). A challenge when studying the effect of pesticide exposure on the development of AD is that pesticides may cause comorbidities that could perhaps in turn influence the development of AD, or cause death before AD has a chance to develop. Some studies have suggested that exposure to pesticides increases risk for AD (Hayden et al., 2010; Parrón, Requena, Hernández, & Alarcón, 2011; Singh et al., 2013; Tyas et al., 2007). For example, exposure to dichlorodiphenyltrichloroethane (DDT), a ubiquitous mid-twentieth century pesticide, has recently been linked to an increased risk for AD (Richardson et al., 2009). Dichlorodiphenyldichloroethane (DDE; a derivative of DDT) was found to be higher in the serum of individuals with AD, and increased levels of DDE in the serum were correlated with increased levels of DDE in the brain. In addition, DDT concentrations that correlate to levels of what is considered high exposure in humans have been shown to increase the level of APP in cultured neurons, offering a potential mechanistic link to AD risk (Richardson et al., 2014). Although DDT use is infrequent in the United States, it is still used in some countries, and food from these countries is imported to countries not using DDT, making DDT exposure a continuing global concern (Eskenazi et al., 2009). Pesticides other than DDT and DDE are also under investigation. The pesticide chlorpyrifos appears to increase Aβ in the brains of the Tg2576 mouse model of AD (Salazar et al., 2011). Rotenone, a commonly used pesticide and insecticide, may cause degeneration of cholinergic neurons (Ullrich & Humpel, 2009). It has also been suggested that pesticides may be contributing to AD pathology by creating reactive oxygen species in the brain (Leuner et al., 2012). These preliminary experiments indicate that more work should be done to determine the contribution of pesticide exposure to AD risk and disease progression.

Genetic factors may play a critical role in susceptibility to chemically-induced risk for AD and should be considered in future experiments. The presence of the APOE4 allele is thought to worsen the cognitive

impairments due to DDE (Richardson et al., 2014). Two other genes, CYP2D6 and GSTP1, have recently been identified to interact with certain pesticide and metal products, suggesting that individuals with these particular polymorphisms may perhaps be at increased risk for pesticide or metal-induced AD (Singh, Banerjee, Bala, Basu, & Chhillar, 2014).

It is important to note that the data for pesticide exposure on AD risk is still in the early stages and the results are occasionally conflicting (Tanner, Goldman, Ross, & Grate, 2014). For example, some studies do not find an association between organochlorine pesticides and increased AD risk, while other studies suggest an association does exist (Medehouenou et al., 2014; Singh et al., 2013; Tanner et al., 2014). Therefore, it is important to continue to research the role of pesticides in AD to determine which compounds increase risk for AD, especially since pesticides may still be an important part of improving health in developing countries. Longitudinal studies should help assess the effects of pesticide exposure, which otherwise may not be immediately apparent (Baldi et al., 2003).

METALS

In addition to pesticides, exposure to metals in the environment may modulate AD risk. Metals seem to be particularly important in regulating amyloid pathology in AD. For example, copper, lead, and aluminum have been shown to be increased in AD brains, while zinc, selenium, and manganese are decreased (Gonzalez-Dominguez, Garcia-Barrera, & Gomez-Ariza, 2014). High levels of copper in the brain have been linked to AD, and increased copper exposure appears to worsen memory function (Pal, Siotto, Prasad, & Squitti, 2015; Yu et al., 2015). Presenilin has been suggested to play a role in copper uptake from the diet, thus dysfunction of presenilin may lead to defective copper uptake (Southon et al., 2013). Other studies have shown that copper interacts with Aβ and disrupts its homeostasis (Hou & Zagorski, 2006; Singh et al., 2013). In addition, copper decreases the activity of neprilysin, which is important for the degradation of Aβ (Li et al., 2010). One means of exposure to high levels of copper may be through the presence of copper in the soil, and thus food. In that regard, higher levels of copper and iron in the soil have been associated with increased AD severity (Shen, Yu, Zhang, Xie, & Jiang, 2014). It has been suggested that a diet with low copper may be one treatment strategy for the prevention of AD (Squitti, Siotto, & Polimanti, 2014).

Interestingly, in one study mice modeling AD were fed zinc and subsequently showed reduced levels of amyloidosis and copper, suggesting that zinc may prevent absorption of copper from the diet (Harris et al., 2014). Some studies suggest that zinc is deficient in AD, and that supplementing zinc into the diet, along with other nutrients, may ameliorate

symptoms (Loef, von Stillfried, & Walach, 2012). However, in a mouse line modeling APOE4 carriers, additional zinc in the diet worsened performance on a spatial memory task, indicating that additional research on zinc and AD risk is necessary (Flinn, Bozzelli, Adlard, & Railey, 2014). Indeed, some studies have shown that zinc levels tend to be higher in postmortem AD brain, and a positive correlation may exist between levels of amyloid and zinc (Religa et al., 2006). In addition, zinc has been shown to increase APP cleavage and Aβ deposition in the brain of a mouse model of AD (Wang et al., 2010). In a nun study, serum levels of zinc within the normal range were associated with lower plaque density, suggesting that zinc may be an important modulator of APP (Tully, Snowdon, & Markesbery, 1995). Ultimately, imbalance in metals may lead to a more oxidating environment in the brain, which may in turn exacerbate AD symptoms (Stelmashook et al., 2014). Therefore, it may be most critical to maintain an optimal balance of metals in the brain in AD so that metals are present when needed, but not exceeding an optimal level and resulting in an oxidating environment. More research will need to be done to unravel the role of metals in the development of the disease and to determine the dose-dependent effect of metal exposure.

AIR POLLUTION AND TOBACCO SMOKE

Recently, the effects of air pollution (which consists of particulate matter and ozone) on cognitive decline have received increased attention. Individuals who live in an area with high air pollution have been shown to have higher postmortem levels of inflammatory markers and greater levels of $A\beta_{42}$ (Calderon-Garciduenas et al., 2004). It has also been shown that prolonged exposure to air pollution increases risk of AD (Jung, Lin, & Hwang, 2015). Similarly, individuals who are exposed long-term to high pollution levels experience accelerated cognitive decline (Weuve et al., 2012). Alarmingly, one study showed that children raised in areas with high levels of pollution exhibit abnormalities in brain volume and function (Calderón-Garcidueñas, Torres-Jardón, Kulesza, Park, & D'Angiulli, 2014). For example, in a group of accidental death postmortem analysis, nearly half of children from urban areas exhibited plaque and tangle pathology, compared to none of the children growing up in low pollution areas (Calderón-Garcidueñas et al., 2012). Interestingly, consuming dark cocoa decreased endothelin 1 (which is increased following exposure to pollution) in the hippocampus of urban children, suggesting that the negative effects of pollution may be countered by positive nutritional interventions (Calderón-Garcidueñas et al., 2013). In addition to air pollution, exposure to tobacco smoke may increase risk for AD. Individuals who smoke have an increased risk for AD (Anstey, von Sanden, Salim, & O'Kearney, 2007; Cataldo, Prochaska, &

Glantz, 2010). Even second-hand or "environmental" or "passive" smoke exposure may increase the risk for AD (Chen, 2012). In rats, exposure to air with tobacco smoke appeared to increase the aging of the brain and the expression of AD pathology (Ho et al., 2012). The mechanism for the effect of pollution on AD risk is still under investigation, however there is some evidence that pollution may be interfering with the integrity of the blood–brain barrier (Calderón-Garcidueñas et al., 2015). Studies on air pollution and AD risk are still in the early stages, and more studies are warranted for the determination of the effect of air quality on the risk for AD.

NUTRITION AND THE MICROBIOME

Another way the composition of the environment may impact brain function is through nutrition. Certain nutritional factors may alter the oxidative environment of the brain, while others may alter the composition of the endogenous bacteria in the gut, which can have profound repercussions on learning and memory. In this section we review recent literature concerning the effects of diet and AD risk.

Nutritional Elements that Decrease AD Risk

Much of the work on nutrition and AD risk has focused on the effects of individual nutritional elements. For example, one study showed that fruits such as black currants and bilberries lessen AD pathology in the APP/PS1 mouse model of AD (Vepsäläinen et al., 2013). Similarly, addition of pomegranate extract to the diet of another mouse model of AD improved performance on memory tasks (Subash et al., 2015). In a cell culture study, cocoa powder extract was able to promote brain-derived neurotrophic factor (BDNF) signalling, even in the presence of Aβ (Cimini et al., 2013). An extract from green tea, epigallocatechin gallate (EGCG), has been shown to improve memory in a mouse model of AD (Walker et al., 2015). Long-term treatment with resveratol, a nutritional element from red wine, was found to decrease cognitive impairments and AD pathology in a mouse model of AD (Porquet et al., 2013). Resveratol derivatives have been shown to rescue Abeta-induced impairments in LTP (Wang et al., 2014). Taken together, these studies show that individual nutritional elements have the potential to influence AD risk.

The benefits of the foods described above are typically attributed to their antioxidant properties, and indeed, nutrients that act as antioxidants, such as vitamin E, beta carotene, and vitamin C can lower the risk of AD (Li, Shen, & Ji, 2012). However, some nutritional elements may be directly interacting with pathological components. EGCG and curcumin have been shown to have antiamyloidogenic properties, including the ability

to regulate neprilysin activity, likely resulting in greater clearance of Aβ (Hyung et al., 2013; Melzig & Janka, 2003; Wang et al., 2014). Other compounds such as resveratrol may modulate tau pathology by regulating the activity of GSK3-β, an enzyme that can lead to the hyperphosphroylation of tau (Varamini, Sikalidis, & Bradford, 2014). Nutritional elements from apples may also directly interact with the molecular components of AD (Hyson, 2011). Apple juice concentrate has been shown to increase availability of acetylcholine, a neurotransmitter reduced in AD (Chan, Graves, & Shea, 2006). Nutrition can also modulate the activity of presenilin, a protein that is mutated in some forms of familial, early-onset AD. While deficits in folate and vitamin E enhance presenilin activity and increase levels of Aβ, apple juice can reduce this overactivity (Chan & Shea, 2006, 2007, 2009). Interestingly, in a religious order study, those with higher levels of folate in the blood were more likely to be cognitively intact in spite of the presence of AD pathology (Snowdon, Tully, Smith, Riley, & Markesbery, 2000; Wang et al., 2012). Therefore, increasing folate through apple consumption may enhance cognitive function by regulating presenilin activity and rescuing amyloid-induced degeneration. Another nutritional element, caffeine, has also been shown to decrease cognitive impairments and Abeta levels in mouse models of AD (Arendash et al., 2006; Chu et al., 2012; Han, Jia, Li, Yang, & Min, 2013; Laurent et al., 2014). Additional benefits of caffeine include increased absorption of zinc and inhibition of acetylcholinesterase, an enzyme that may be increased in AD and responsible for causing the reduction in acetylcholine (Chang & Ho, 2014; Pohanka & Dobes, 2013).

Although studying individual foods and nutritional elements can be illuminating, it is likely more relevant to study patterns of eating (Eskelinen, Ngandu, Tuomilehto, Soininen, & Kivipelto, 2011). Studies on the Mediterranean diet have indicated that following a diet high in fruits, vegetables, extra virgin olive oil, and low in meat products and sugar are beneficial in lowering the risk of AD and slowing the rate of cognitive decline in humans and in mouse models of AD (Grossi et al., 2013, 2014; Gu, Nieves, Stern, Luchsinger, & Scarmeas, 2010; Lourida et al., 2013; Ozawa et al., 2013; Shah, 2013; Singh et al., 2014; Vassallo & Scerri, 2013). In twin studies, a nonsignificant trend toward decreased risk of AD was observed in the twin with a diet higher in fruits and vegetables (Gustaw-Rothenberg, 2009; Hughes et al., 2010). These observations have led to the development of multinutrient interventions in mouse models of AD, which have been shown to improve learning and memory and decrease AD-related pathology (Jansen et al., 2013; Jansen et al., 2014; van Wijk et al., 2014; Wiesmann et al., 2013).

While a diet consisting primarily of fish and vegetables may decrease risk of AD, these lifestyle factors may instead be indicative of an overall healthier lifestyle that reduces risk for AD. Thus, more targeted research should be done on dietary factors to determine whether they are the

causative factors behind the observed modulation of AD risk (Barberger-Gateau et al., 2007). That may also help resolve some conflicting evidence concerning some dietary interventions. For example, a meta-analysis of antioxidant consumption found that antioxidants do not delay or prevent AD in humans (Crichton, Bryan, & Murphy, 2013; Polidori & Nelles, 2014). A similar result was found in a meta-analysis of the Mediterranean diet (Otaegui-Arrazola, Amiano, Elbusto, Urdaneta, & Martínez-Lage, 2014). Another study even showed that in a mouse model of AD a diet heavy in fish and vegetables exacerbated memory impairments (Parrott, Winocur, Bazinet, Ma, & Greenwood, 2015). Conflicting evidence also exists concerning the risk of high cholesterol on AD. Two 30-year longitudinal studies reached opposite conclusions regarding the risk of high cholesterol as a risk for AD (Mielke et al., 2010; Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009). Therefore, more work should be done on dietary patterns and risk for AD, particularly in the context of other factors known to modify risk for AD. In the meantime, the most recent recommendations for a diet aimed at minimizing risk for AD include reducing consumption of foods high in saturated fats (particularly from dairy and meat); increasing consumption of vegetables and legumes; limiting consumption of metals such as copper, iron, and aluminum; and incorporating regular aerobic exercise (Barnard et al., 2014; Shea & Remington, 2015).

Nutrition and Increased Risk for AD

Dietary foods and patterns that have been shown to reduce risk for AD may also be doing so by counteracting the effects that a poor diet has on increasing risk for AD. Diets high in cholesterol and fat may be particularly problematic. High-fat diets increase risk for Type 2 diabetes and negatively affect cardiovascular health. Diabetes and poor cardiovascular health are factors that may increase risk for AD and indeed, poor vascular health was associated with more severe cognitive decline in a nun study (Reitz & Mayeux, 2014; Snowdon et al., 1997). Diets high in fat have also been shown to worsen behavior impairments and Aβ pathology in a mouse model of AD (Barron, Rosario, Elteriefi, & Pike, 2013). A diet high in cholesterol has been shown to lead to impaired spatial memory, decreased numbers of cholinergic neurons (a neuronal population particularly vulnerable in AD), and increased $A\beta_{42}$ and phosphorylated tau in the brains of rats and in a mouse model of AD (Ehrlich & Humpel, 2012; Park et al., 2013). Indeed, a high-fat diet also increased GSK3-β activity, which correlated with increases in phosphorylated tau in the hippocampus, offering a mechanism for how high-fat diets may be exacerbating AD pathology and cognitive decline (Bhat & Thirumangalakudi, 2013).

It is particularly important to consider high cholesterol diets in the presence of APOE4, since this gene is involved in lipid metabolism (Lim,

Kowgier, Yu, Buchman, & Bennett, 2013). In a mouse model of an APOE4 carrier, high carbohydrate diets led to increased memory impairments and reductions in BDNF (Maioli et al., 2012). Also, while eating fatty fish may decrease the risk for AD in many individuals, the effect is not as pronounced if the person is a carrier of APOE4 (Huang et al., 2005). Clinical studies on fatty acid supplementation in AD are still in early stages and appear to have some beneficial effects, but it will be important to consider the contribution of the APOE4 allele on such interventions (Faxen-Irving et al., 2013; Shinto et al., 2014). Interestingly, while a high-fat diet increased AD pathology in a mouse model of AD, experience in an enriched environment reversed these effects, nicely demonstrating the interaction between environmental components in modulating AD (Maesako, Uemura, Kubota, Kuzuya, Sasaki, Asada, et al., 2012). Similarly, physical exercise was also able to counter the effects of a high-fat diet, possibly by increasing the degradation of Aβ (Maesako, Uemura, Kubota, Kuzuya, Sasaki, Hayashida, et al., 2012). In addition, caffeine can prevent cognitive impairments in mice fed a high-fat diet and increased BDNF in the hippocampus (Moy & McNay, 2013). These experiments again demonstrate that the environment includes many factors that modulate risk for AD, and positive factors such as exercise and cognitive complexity can counteract negative factors such as poor diet.

Microbiome

Another way nutrients from the diet may be impacting the brain is by interacting with the resident gut microbiota. A recent study showed that a diet high in fat resulted in memory impairments in mice, with associated changes in the microbiome (Jorgensen et al., 2014). Interestingly, caffeine, which as we previously discussed can reverse the effects of a high-fat diet, may interact with certain gut microbes, suggesting that a healthy microbiome may mediate some of the effects of caffeine on the treatment of AD (Chang & Ho, 2014).

Recent studies have shown that a healthy microbiome may be a critical part of cognitive functioning. The composition of the microbiota has been shown to modify learning and memory (Li, Dowd, Scurlock, Acosta-Martinez, & Lyte, 2009). Certain strains of microbiota have been shown to improve learning and memory in mice (Matthews & Jenks, 2013). Interestingly, certain microbiota profiles can be correlated with performance on memory tests (Jorgensen et al., 2014). The microbiome has been shown to modify many aspects of brain signaling including GABA, NMDA, and BDNF (for review see Bhattacharjee & Lukiw, 2013). While more work needs to be done on how the microbiome affects alterations in the brain, it is clear that a healthy microbiome contributes to brain health and reduces risk of brain disorders.

The environment, particularly during early life, can shape the microbiome, through stress, diet, antibiotics, or other measures (O'mahony, Hyland, Dinan, & Cryan, 2011). It has been proposed that individuals who suffer from irritable bowl syndrome, likely resulting from a disruption of optimal microbiota functioning, may be at an increased risk for dementia (Daulatzai, 2014). Gut microbiota may also underlie changes in type 2 diabetes, which in turn predispose for AD (Alam, Alam, Kamal, Abuzenadah, & Haque, 2014). Maintaining the integrity of the microbiome may be particularly critical with aging, since increases in oxidative stress that occur during aging have been shown to alter the composition of the microbiome (Duncan & Flint, 2013; Lynch, Jeffery, Cusack, O'Connor, & O'Toole, 2015; Patrignani, Tacconelli, & Bruno, 2014). These aging-related changes in the microbiome could be due to changes in nutrition during aging, but even in controlled mouse studies the microbiome changes with age, as does the efficiency for responding to nutrients (Langille et al., 2014). Another recent hypothesis suggests that aging may favor the growth of a particular type of microbiota that can enhance the inflammation in the central nervous system, contributing to AD pathology (Shoemark & Allen, 2014).

While more work needs to be done, recent studies offer a promising glimpse at the role of probiotics (Desbonnet et al., 2010). In a mouse model in which the microbiome was disrupted and hippocampal deficits were observed, treatment with probiotics rescued the functioning of the hippocampus (Smith et al., 2014). In another study, treatment with probiotics was able to reverse age-related deficits in LTP and increase expression of BDNF (Distrutti et al., 2014). This study is particularly interesting since enhancing BDNF has been proposed as one way to treat AD (Lu, Nagappan, Guan, Nathan, & Wren, 2013). Another study showed that a particular probiotic could restore memory function, as well as inhibit acetylcholinesterase (Xiao et al., 2014). In short, further study on the composition of the microbiome in aging may allow for therapies involving probiotics (Pérez Martínez, Bäuerl, & Collado, 2014). It is also critical that more research is done on the particular strains of beneficial bacteria, and that the public be made aware of the state of the research on probiotics, since not all probiotics may be helpful and some may even be harmful (Slashinski, McCurdy, Achenbaum, Whitney, & McGuire, 2012).

SLEEP AND CIRCADIAN RHYTHM

In a religious order study, sleep disturbances were linked to an increased risk of AD and cognitive decline (Lim et al., 2013; Lim, et al., 2013). In the general population, sleep disturbances have also been linked to an increased risk of AD (Benedict et al., 2014). However, it is not clear if sleep disturbances are causative of AD, or an early symptom of cognitive

dysfunction. For a more detailed discussion of sleep and AD risk, see Chapter 10.

SOCIALIZATION

Social interactions may be another critical environmental element modulating AD risk. One study has shown that low participation in social activities in late life may increase the risk of dementia (Saczynski et al., 2006). Living alone and having fewer social connections may also increase risk (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000). In particular, feelings of loneliness may be the key aspect of low socialization responsible for cognitive decline (Holwerda et al., 2014). In a longitudinal study, individuals who reported feelings of loneliness had double the risk for AD. These individuals also had a faster rate of cognitive decline, in spite of comparable levels of AD pathology (Wilson, Krueger, et al., 2007). Participating in social activities that are considered an integral part of religion, such as regularly attending church, may help to slow cognitive decline, even in AD (Coin et al., 2010; Corsentino, Collins, Sachs-Ericsson, & Blazer, 2009; Hill, Burdette, Angel, Angel, & Series, 2006; Kaufman, Anaki, Binns, & Freedman, 2007; Reyes-Ortiz et al., 2008). One recent longitudinal study showed that attending religious service correlated with a reduced risk for AD (Paganini-Hill et al., 2015). Virtual socialization may also confer a protective effect as one study recently demonstrated that older individuals who regularly use the Internet had better cognitive health (James, Boyle, Yu, & Bennett, 2013). As in the case of cognitive reserve, social connections may help to mitigate the effects of AD pathology (Bennett et al., 2006; Wilson et al., 2005).

CONCLUSION

Here we have discussed the importance of a stimulating, cognitively complex environment in preventing the onset of AD, through the mechanisms of cognitive reserve or through direct interactions with the molecular pathology. We have also considered the contribution of environmental factors such as exposure to pollution and metals on AD risk. From the evidence presented, we can conclude that a cognitively stimulating environment, including higher education, bilingualism, and participation in cognitively challenging leisure activities such as reading, writing, solving puzzles, and playing games can delay the onset of AD. Physical activity may serve as a valuable way to promote brain health and stave off cognitive decline and AD pathology. A diet high in fruits and vegetables and low in meat and sugar may also confer preventative benefits for AD, by

improving overall health and by providing important antioxidants and factors that modulate AD pathology. Finally, environmental manipulations like music training, language learning, video game training, and social interactions can improve quality of life and lessen the severity of cognitive symptoms in individuals with mild and moderate AD, and should be considered as a valuable contribution to a treatment plan with pharmaceutical interventions. Considering multiple environmental factors, such as physical and mental activity, as well as occupational hazards and nutrition may lead to more effective preventative and therapeutic strategies for AD.

References

Abner, E. L., Kryscio, R. J., Schmitt, F. A., Santacruz, K. S., Jicha, G. A., Lin, Y., … Nelson, P. T. (2011). "End-stage" neurofibrillary tangle pathology in preclinical Alzheimer's disease: Fact or fiction? *Journal of Alzheimer's Disease: JAD*, *25*(3), 445–453. http://dx.doi.org/10.3233/JAD-2011-101980.

Akbaraly, T. N., Portet, F., Fustinoni, S., Dartigues, J. F., Artero, S., Rouaud, O., … Berr, C. (2009). Leisure activities and the risk of dementia in the elderly: Results from the Three-City Study. *Neurology*, *73*(11), 854–861.

Alam, M. Z., Alam, Q., Kamal, M. A., Abuzenadah, A. M., & Haque, A. (2014). A possible link of gut microbiota alteration in type 2 diabetes and Alzheimer's disease pathogenic-ity: An update. *CNS & Neurological Disorders Drug Targets*, *13*(3), 383–390.

Alladi, S., Bak, T. H., Duggirala, V., Surampudi, B., Shailaja, M., Shukla, A. K., … Kaul, S. (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology*, *81*(22), 1938–1944.

Ambree, O., Leimer, U., Herring, A., Gortz, N., Sachser, N., Heneka, M. T., … Keyvani, K. (2006). Reduction of amyloid angiopathy and A beta plaque burden after enriched housing in TgCRND8 mice—Involvement of multiple pathways. *American Journal of Pathology*, *169*(2), 544–552. http://dx.doi.org/10.2353/ajpath.2006.051107.

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., … Dartigues, J.-F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. *Brain: A Journal of Neurology*, *137*(Pt 4), 1167–1175.

Andel, R., Crowe, M., Pedersen, N. L., Mortimer, J., Crimmins, E., Johansson, B., et al. (2005). Complexity of work and risk of Alzheimer's disease: A population-based study of Swedish twins. *Journal of Gereontology: Psychological Sciences*, *60*(5), 251–258.

Anstey, K. J., von Sanden, C., Salim, A., & O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. *American Journal of Epidemiology*, *166*(4), 367–378. http://dx.doi.org/10.1093/aje/kwm116.

Antoniou, M., Gunasekera, G. M., & Wong, P. C. M. (2013). Foreign language training as cognitive therapy for age-related cognitive decline: A hypothesis for future research. *Neuroscience and Biobehavioral Reviews*, *37*(10 Pt 2), 2689–2698.

Arendash, G. W., Schleif, W., Rezai-Zadeh, K., Jackson, E. K., Zacharia, L. C., Cracchiolo, J. R., … Tan, J. (2006). Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. *Neuroscience*, *142*(4), 941–952.

Baglio, F., Griffanti, L., Saibene, F. L., Ricci, C., Alberoni, M., Critelli, R., … Farina, E. (2015). Multistimulation group therapy in Alzheimer's disease promotes changes in brain functioning. *Neurorehabilitation and Neural Repair*, *29*(1), 13–24.

Baldi, I., Lebailly, P., Mohammed-Brahim, B., Letenneur, L., Dartigues, J. F., & Brochard, P. (2003). Neurodegenerative diseases and exposure to pesticides in the elderly. *American Journal of Epidemiology*, *157*(5), 409–414.

Barberger-Gateau, P., Raffaitin, C., Letenneur, L., Berr, C., Tzourio, C., Dartigues, J. F., & Alpérovitch, A. (2007). Dietary patterns and risk of dementia: The Three-City cohort study. *Neurology*, *69*(20), 1921–1930.

Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J., de Jager, C. A., Erickson, K. I., & Fraser, G. (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiology of Aging*, *35*(Suppl), S74–S78. 2 SRC – GoogleScholar. http://dx.doi.org/10.1016/j.neurobiolaging.2014.03.033.

Barron, A. M., Rosario, E. R., Elteriefi, R., & Pike, C. J. (2013). Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD mice: Implications for Alzheimer's disease. *PLoS One*, *8*(10), e78554.

Belarbi, K., Burnouf, S., Fernandez-Gomez, F. J., Laurent, C., Lestavel, S., Figeac, M., … Blum, D. (2011). Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiology of Disease*, *43*(2), 486–494. http://dx.doi.org/10.1016/j.nbd.2011.04.022.

Belleville, S., Clément, F., Mellah, S., Gilbert, B., Fontaine, F., & Gauthier, S. (2011). Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain: A Journal of Neurology*, *134*(Pt 6), 1623–1634.

Benedict, C., Byberg, L., Cedernaes, J., Hogenkamp, P. S., Giedratis, V., Kilander, L., … Schioth, H. B. (2014). Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(9), 1090–1097.

Bennett, D. A. (2006). Postmortem indices linking risk factors to cognition: Results from the religious order study and the memory and aging project. *Alzheimer Disease and Associated Disorders*, *20*(3 Suppl 2), S63–S68.

Bennett, D. A., Schneider, J. A., Tang, Y. X., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: A longitudinal cohort study. *Lancet Neurology*, *5*(5), 406–412. http://dx.doi:10.1016/S1474-4422(06)70417-3.

Bennett, D. A., Schneider, J. A., Wilson, R. S., Bienias, J. L., & Arnold, S. E. (2005a). Education modifies the association of amyloid but not tangles with cognitive function. *Neurology*, *65*(6), 953–955.

Bennett, D. A., Schneider, J. A., Wilson, R. S., Bienias, J. L., & Arnold, S. E. (2005b). Education modifies the association of amyloid but not tangles with cognitive function. *Neurology*, *65*(6), 953–955. http://dx.doi.org/10.1212/01.wnl.0000176286.17192.69.

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Mendes de Leon, C. F., Arnold, S. E., … Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*, *60*(12), 1909–1915.

Berchtold, N. C., Chinn, G., Chou, M., Kesslak, J. P., & Cotman, C. W. (2005). Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience*, *133*(3), 853–861. http://dx.doi.org/10.1016/j.neuroscience.2005.03.026.

Bharwani, G., Parikh, P. J., Lawhorne, L. W., VanVlymen, E., & Bharwani, M. (2012). Individualized behavior management program for Alzheimer's/dementia residents using behavior-based ergonomic therapies. *American Journal of Alzheimer's Disease and Other Dementias*, *27*(3), 188–195.

Bhat, N. R., & Thirumangalakudi, L. (2013). Increased tau phosphorylation and impaired brain insulin/IGF signaling in mice fed a high fat/high cholesterol diet. *Journal of Alzheimer's Disease: JAD*, *36*(4), 781–789.

Bhattacharjee, S., & Lukiw, W. J. (2013). Alzheimer's disease and the microbiome. *Frontiers in Cellular Neuroscience*, *7*, 153.

Billings, L. M., Green, K. N., McGaugh, J. L., & LaFerla, F. M. (2007). Learning decreases A beta*56 and tau pathology and ameliorates behavioral decline in 3xTg-AD mice. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *27*(4), 751–761.

Boulay, M., Benveniste, S., Boespflug, S., Jouvelot, P., & Rigaud, A.-S. (2011). A pilot usability study of MINWii, a music therapy game for demented patients. *Technology and Health Care: Official Journal of the European Society for Engineering and Medicine*, *19*(4), 233–246.

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J. J., Luchsinger, J. A., Yeung, L.-K., … Stern, Y. (2011). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology of Aging*, *32*(9), 1588–1598.

Calderón-Garcidueñas, L., Kavanaugh, M., Block, M., D'Angiulli, A., Delgado-Chávez, R., Torres-Jardón, R., … Diaz, P. (2012). Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. *Journal of Alzheimer's Disease: JAD*, *28*(1), 93–107.

Calderón-Garcidueñas, L., Mora-Tiscareño, A., Franco-Lira, M., Cross, J. V., Engle, R., Aragón-Flores, M., … D'Angiulli, A. (2013). Flavonol-rich dark cocoa significantly decreases plasma endothelin-1 and improves cognition in urban children. *Frontiers in Pharmacology*, *4*, 104.

Calderon-Garciduenas, L., Reed, W., Maronpot, R. R., Henriquez-Roldan, C., Delgado-Chavez, R., Calderon-Garciduenas, A., … Swenberg, J. A. (2004). Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicologic Pathology*, *32*(6), 650–658. http://dx.doi.org/10.1080/01926230490520232.

Calderón-Garcidueñas, L., Torres-Jardón, R., Kulesza, R. J., Park, S. -B., & D'Angiulli, A. (2014). Air pollution and detrimental effects on children's brain. The need for a multidisciplinary approach to the issue complexity and challenges. *Frontiers in Human Neuroscience*, *8*, 613.

Calderón-Garcidueñas, L., Vojdani, A., Blaurock-Busch, E., Busch, Y., Friedle, A., Franco-Lira, M., … D'Angiulli, A. (2015). Air pollution and children: Neural and tight junction antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. *Journal of Alzheimer's Disease: JAD*, *43*(3), 1039–1058.

Carlson, M. C., Helms, M. J., Steffens, D. C., Burke, J. R., Potter, G. G., & Plassman, B. L. (2008). Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *4*(5), 324–331.

Casida, J. E., & Durkin, K. A. (2013). Neuroactive insecticides: Targets, selectivity, resistance, and secondary effects. *Annual Review of Entomology*, *58*, 99–117.

Cataldo, J. K., Prochaska, J. J., & Glantz, S. A. (2010). Cigarette smoking is a risk factor for Alzheimer's disease: An analysis controlling for tobacco industry affiliation. *Journal of Alzheimer's Disease: JAD*, *19*(2), 465–480. http://dx.doi.org/10.3233/JAD-2010-1240.

Chan, A., Graves, V., & Shea, T. B. (2006). Apple juice concentrate maintains acetylcholine levels following dietary compromise. *Journal of Alzheimer's Disease: JAD*, *9*(3), 287–291.

Chan, A., & Shea, T. B. (2006). Supplementation with apple juice attenuates presenilin-1 overexpression during dietary and genetically-induced oxidative stress. *Journal of Alzheimer's Disease: JAD*, *10*(4), 353–358.

Chan, A., & Shea, T. B. (2007). Folate deprivation increases presenilin expression, gamma-secretase activity, and Abeta levels in murine brain: Potentiation by ApoE deficiency and alleviation by dietary S-adenosyl methionine. *Journal of Neurochemistry*, *102*(3), 753–760.

Chan, A., & Shea, T. B. (2009). Dietary supplementation with apple juice decreases endogenous amyloid-beta levels in murine brain. *Journal of Alzheimer's Disease: JAD*, *16*(1), 167–171.

Chang, K. L., & Ho, P. C. (2014). Gas chromatography time-of-flight mass spectrometry (GC-TOF-MS)-based metabolomics for comparison of caffeinated and decaffeinated coffee and its implications for Alzheimer's disease. *PLoS One*, *9*(8), e104621.

Chao, F., Zhang, L., Luo, Y., Xiao, Q., Lv, F., He, Q., … Tang, Y. (2015). Running exercise reduces myelinated fiber loss in the dentate gyrus of the hippocampus in APP/PS1 transgenic mice. *Current Alzheimer Research*, *12*(4), 377–383.

Chen, R. (2012). Association of environmental tobacco smoke with dementia and Alzheimer's disease among never smokers. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *8*(6), 590–595. http://dx.doi.org/10.1016/j.jalz.2011.09.231.

Chu, Y.-F., Chang, W.-H., Black, R. M., Liu, J.-R., Sompol, P., Chen, Y., … Cheng, I. H. (2012). Crude caffeine reduces memory impairment and amyloid β(1-42) levels in an Alzheimer's mouse model. *Food Chemistry*, *135*(3), 2095–2102.

Cimini, A., Gentile, R., D'Angelo, B., Benedetti, E., Cristiano, L., Avantaggiati, M. L., … Desideri, G. (2013). Cocoa powder triggers neuroprotective and preventive effects in a human Alzheimer's disease model by modulating BDNF signaling pathway. *Journal of Cellular Biochemistry*, *114*(10), 2209–2220.

Coin, A., Perissinotto, E., Najjar, M., Girardi, A., Inelmen, E. M., Enzi, G., … Sergi, G. (2010). Does religiosity protect against cognitive and behavioral decline in Alzheimer's dementia? *Current Alzheimer Research*, *7*(5), 445–452.

Corsentino, E. A., Collins, N., Sachs-Ericsson, N., & Blazer, D. G. (2009). Religious attendance reduces cognitive decline among older women with high levels of depressive symptoms. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, *64*(12), 1283–1289.

Costa, D. A., Craechiolo, J. R., Bachstetter, A. D., Hughes, T. F., Bales, K. R., Paul, S. M., … Potter, H. (2007). Enrichment improves cognition in AD mice by amyloid-related and unrelated mechanisms. *Neurobiology of Aging*, *28*(6), 831–844. http://dx.doi.org/10.1016/j.neurobiolaging.2006.04.009.

Cracchiolo, J. R., Mori, T., Nazian, S. J., Tan, J., Potter, H., & Arendash, G. W. (2007). Enhanced cognitive activity-over and above social or physical activity is required to protect Alzheimer's mice against cognitive impairment, reduce A beta deposition, and increase synaptic immunoreactivity. *Neurobiology of Learning and Memory*, *88*(3), 277–294. http://dx.doi.org/10.1016/J.Nlm.2007.07.007.

Crichton, G. E., Bryan, J., & Murphy, K. J. (2013). Dietary antioxidants, cognitive function and dementia—A systematic review. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *68*(3), 279–292.

Crowe, M., Andel, R., Pedersen, N. L., Johansson, B., Gatz, M., & Series, B. (2003). Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. *Journal of Gerontology: Psychological Sciences*, *58*(5), 249–255.

Dao, A. T., Zagaar, M. A., & Alkadhi, K. A. (2014). Moderate treadmill exercise protects synaptic plasticity of the dentate gyrus and related signaling cascade in a rat model of Alzheimer's disease. *Molecular Neurobiology*, *52*(3), 1067–1076.

Daulatzai, M. A. (2014). Chronic functional bowel syndrome enhances gut-brain axis dysfunction, neuroinflammation, cognitive impairment, and vulnerability to dementia. *Neurochemical Research*, *39*(4), 624–644.

Desbonnet, L., Garrett, L., Clarke, G., Kiely, B., Cryan, J. F., & Dinan, T. G. (2010). Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience*, *170*(4), 1179–1188.

Distrutti, E., O'Reilly, J.-A., McDonald, C., Cipriani, S., Renga, B., Lynch, M. A., & Fiorucci, S. (2014). Modulation of intestinal microbiota by the probiotic VSL#3 resets brain gene expression and ameliorates the age-related deficit in LTP. *PLoS One*, *9*(9), e106503.

Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., Büchel, C., & May, A. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(23), 6314–6317.

Dumurgier, J., Paquet, C., Benisty, S., Kiffel, C., Lidy, C., Mouton-Liger, F., … Hugon, J. (2010). Inverse association between CSF Aβ 42 levels and years of education in mild form of Alzheimer's disease: The cognitive reserve theory. *Neurobiology of Disease*, *40*(2), 456–459.

Duncan, S. H., & Flint, H. J. (2013). Probiotics and prebiotics and health in ageing populations. *Maturitas*, *75*(1), 44–50.

Ehrlich, D., & Humpel, C. (2012). Chronic vascular risk factors (cholesterol, homocysteine, ethanol) impair spatial memory, decline cholinergic neurons and induce blood-brain barrier leakage in rats in vivo. *Journal of the Neurological Sciences*, *322*(1–2), 92–95.

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, Ø., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A longitudinal diffusion tensor imaging study. *Human Brain Mapping*, *33*(10), 2390–2406.

Eskelinen, M. H., Ngandu, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2011). Midlife healthy-diet index and late-life dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders Extra*, *1*(1), 103–112.

Eskenazi, B., Chevrier, J., Rosas, L. G., Anderson, H. A., Bornman, M. S., Bouwman, H., … Stapleton, D. (2009). The Pine River statement: Human health consequences of DDT use. *Environmental Health Perspectives*, *117*(9), 1359–1367.

Farfel, J. M., Nitrini, R., Suemoto, C. K., Grinberg, L. T., Ferretti, R. E. L., Leite, R. E. P., … Brazilian Aging Brain Study Group, (2013). Very low levels of education and cognitive reserve: A clinicopathologic study. *Neurology*, *81*(7), 650–657.

Faxen-Irving, G., Freund-Levi, Y., Eriksdotter-Jonhagen, M., Basun, H., Hjorth, E., Palmblad, J., … Wahlund, L. O. (2013). Effects on transthyretin in plasma and cerebrospinal fluid by DHA-rich n—3 fatty acid supplementation in patients with Alzheimer's disease: The OmegAD study. *Journal of Alzheimer's Disease: JAD*, *36*(1), 1–6. http://dx.doi.org/10.3233/JAD-121828.

Ferrari, C., Nacmias, B., Bagnoli, S., Piaceri, I., Lombardi, G., Pradella, S., … Sorbi, S. (2014). Imaging and cognitive reserve studies predict dementia in presymptomatic Alzheimer's disease subjects. *Neuro-Degenerative Diseases*, *13*(2–3), 157–159. http://dx.doi.org/10.1159/000353690.

Ferrari, C., Xu, W.-L., Wang, H.-X., Winblad, B., Sorbi, S., Qiu, C., & Fratiglioni, L. (2013). How can elderly apolipoprotein E ε4 carriers remain free from dementia? *Neurobiology of Aging*, *34*(1), 13–21.

Flinn, J. M., Bozzelli, P. L., Adlard, P. A., & Railey, A. M. (2014). Spatial memory deficits in a mouse model of late-onset Alzheimer's disease are caused by zinc supplementation and correlate with amyloid-beta levels. *Frontiers in Aging Neuroscience*, *6*, 174.

Foubert-Samier, A., Catheline, G., Amieva, H., Dilharreguy, B., Helmer, C., Allard, M., & Dartigues, J.-F. (2012). Education, occupation, leisure activities, and brain reserve: A population-based study. *Neurobiology of Aging*, *33*(2) 423.e415-425.

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: A community-based longitudinal study. *Lancet*, *355*(9212), 1315–1319.

Freedman, M., Alladi, S., Chertkow, H., Bialystok, E., Craik, F. I. M., Phillips, N. A., … Bak, T. H. (2014). Delaying onset of dementia: Are two languages enough? *Behavioural Neurology*, *2014*, 808137.

Garcia-Mesa, Y., Lopez-Ramos, J. C., Gimenez-Llort, L., Revilla, S., Guerra, R., Gruart, A., … Sanfeliu, C. (2011). Physical exercise protects against Alzheimer's disease in 3xTg-AD mice. *Journal of Alzheimer's Disease: JAD*, *24*(3), 421–454. http://dx.doi.org/10.3233/JAD-2011-101635.

Garibotto, V., Borroni, B., Sorbi, S., Cappa, S. F., Padovani, A., & Perani, D. (2012). Education and occupation provide reserve in both ApoE ε4 carrier and noncarrier patients with probable Alzheimer's disease. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *33*(5), 1037–1042.

Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., … Campion, D. (2011). APOE and Alzheimer disease: A major gene with semi-dominant inheritance. *Molecular Psychiatry*, *16*(9), 903–907. http://dx.doi.org/10.1038/mp.2011.52.

Gold, B. T. (2014). Lifelong bilingualism and neural reserve against Alzheimer's disease: A review of findings and potential mechanisms. *Behavioural Brain Research*, *281C*, 9–15. http://dx.doi.org/10.1016/j.bbr.2014.12.006.

Gold, B. T., Johnson, N. F., & Powell, D. K. (2013). Lifelong bilingualism contributes to cognitive reserve against white matter integrity declines in aging. *Neuropsychologia*, *51*(13), 2841–2846.

Gollan, T. H., Salmon, D. P., Montoya, R. I., & Galasko, D. R. (2011). Degree of bilingualism predicts age of diagnosis of Alzheimer's disease in low-education but not in highly educated Hispanics. *Neuropsychologia*, *49*(14), 3826–3830.

Gonzalez-Dominguez, R., Garcia-Barrera, T., & Gomez-Ariza, J. L. (2014). Homeostasis of metals in the progression of Alzheimer's disease. *Biometals*, *27*(3), 539–549. http://dx.doi.org/10.1007/s10534-014-9728-5.

Grossi, C., Ed Dami, T., Rigacci, S., Stefani, M., Luccarini, I., & Casamenti, F. (2014). Employing Alzheimer disease animal models for translational research: Focus on dietary components. *Neuro-Degenerative Diseases*, *13*(2–3), 131–134. http://dx.doi.org/10.1159/000355461.

Grossi, C., Rigacci, S., Ambrosini, S., Ed Dami, T., Luccarini, I., Traini, C., … Stefani, M. (2013). The polyphenol oleuropein aglycone protects TgCRND8 mice against Ass plaque pathology. *PLoS One*, *8*(8), e71702.http://dx.doi.org/10.1371/journal.pone.0071702.

Gu, Y., Nieves, J. W., Stern, Y., Luchsinger, J. A., & Scarmeas, N. (2010). Food combination and Alzheimer disease risk: A protective diet. *Archives of Neurology*, *67*(6), 699–706.

Gustaw-Rothenberg, K. (2009). Dietary patterns associated with Alzheimer's disease: Population based study. *International Journal of Environmental Research and Public Health*, *6*(4), 1335–1340.

Guzmán-Vélez, E., & Tranel, D. (2015). Does bilingualism contribute to cognitive reserve? Cognitive and neural perspectives. *Neuropsychology*, *29*(1), 139–150.

Hall, L., Orrell, M., Stott, J., & Spector, A. (2013). Cognitive stimulation therapy (CST): Neuropsychological mechanisms of change. *International Psychogeriatrics*, *25*(3), 479–489.

Hampstead, B. M., Stringer, A. Y., Stilla, R. F., Giddens, M., & Sathian, K. (2012). Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. *Hippocampus*, *22*(8), 1652–1658.

Han, K., Jia, N., Li, J., Yang, L., & Min, L.-Q. (2013). Chronic caffeine treatment reverses memory impairment and the expression of brain BNDF and TrkB in the PS1/APP double transgenic mouse model of Alzheimer's disease. *Molecular Medicine Reports*, *8*(3), 737–740.

Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., & Pipingas, A. (2015). A randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: The Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol [ACTRN12614001133628]. *Nutrition Journal*, *14*(1), 53. http://dx.doi.org/10.1186/s12937-015-0042-z.

Harris, C. J., Voss, K., Murchison, C., Ralle, M., Frahler, K., Carter, R., … Quinn, J. F. (2014). Oral zinc reduces amyloid burden in Tg2576 mice. *Journal of Alzheimer's Disease: JAD*, *41*(1), 179–192.

Hayden, K. M., Norton, M. C., Darcey, D., Ostbye, T., Zandi, P. P., Breitner, J. C. S., … Cache County Study Investigators. (2010). Occupational exposure to pesticides increases the risk of incident AD: The Cache County study. *Neurology*, *74*(19), 1524–1530.

Hellstrom-Lindahl, E., Ravid, R., & Nordberg, A. (2008). Age-dependent decline of neprilysin in Alzheimer's disease and normal brain: Inverse correlation with A beta levels. *Neurobiology of Aging*, *29*(2), 210–221. http://dx.doi.org/10.1016/j.neurobiolaging.2006.10.010.

Herring, A., Ambree, O., Tomm, M., Habermann, H., Sachser, N., Paulus, W., & Keyvani, K. (2009). Environmental enrichment enhances cellular plasticity in transgenic mice with Alzheimer-like pathology. *Experimental Neurology*, *216*(1), 184–192. http://dx.doi.org/10.1016/j.expneurol.2008.11.027.

Herring, A., Blome, M., Ambree, O., Sachser, N., Paulus, W., & Keyvani, K. (2010). Reduction of cerebral oxidative stress following environmental enrichment in mice with

Alzheimer-like pathology. *Brain Pathology (Zurich, Switzerland)*, *20*(1), 166–175. http://dx.doi.org/10.1111/j.1750-3639.2008.00257.x.

Herring, A., Lewejohann, L., Panzer, A.-L., Donath, A., Kröll, O., Sachser, N., … Keyvani, K. (2011). Preventive and therapeutic types of environmental enrichment counteract beta amyloid pathology by different molecular mechanisms. *Neurobiology of Disease*, *42*(3), 530–538.

Hill, T. D., Burdette, A. M., Angel, J. L., Angel, R. J., & Series, B. (2006). Religious attendance and cognitive functioning among older Mexican Americans. *Journal of Gerontology: Psychological Sciences*, *61*(1), 3–9.

Hirase, H., & Shinohara, Y. (2014). Transformation of cortical and hippocampal neural circuit by environmental enrichment. *Neuroscience*, *280*, 282–298.

Ho, Y. S., Yang, X., Yeung, S. C., Chiu, K., Lau, C. F., Tsang, A. W., … Chang, R. C. (2012). Cigarette smoking accelerated brain aging and induced pre-Alzheimer-like neuropathology in rats. *PLoS One*, *7*(5), e36752. http://dx.doi.org/10.1371/journal.pone.0036752.

Holwerda, T. J., Deeg, D. J. H., Beekman, A. T. F., van Tilburg, T. G., Stek, M. L., Jonker, C., & Schoevers, R. A. (2014). Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(2), 135–142.

Hooghiemstra, A. M., Eggermont, L. H. P., Scheltens, P., van der Flier, W. M., & Scherder, E. J. A. (2012). Exercise and early-onset Alzheimer's disease: Theoretical considerations. *Dementia and Geriatric Cognitive Disorders Extra*, *2*, 132–145.

Hou, L., & Zagorski, M. G. (2006). NMR reveals anomalous copper(II) binding to the amyloid A beta peptide of Alzheimer's disease. *Journal of the American Chemical Society*, *128*(29), 9260–9261.

Hu, Y. S., Long, N., Pigino, G., Brady, S. T., & Lazarov, O. (2013). Molecular mechanisms of environmental enrichment: Impairments in Akt/GSK3 beta, neurotrophin-3 and CREB signaling. *PLoS One*, *8*(5), e64460. http://dx.doi.org/10.1371/journal.pone.0064460.

Hu, Y. -S., Xu, P., Pigino, G., Brady, S. T., Larson, J., & Lazarov, O. (2010). Complex environment experience rescues impaired neurogenesis, enhances synaptic plasticity, and attenuates neuropathology in familial Alzheimer's disease-linked APPswe/PS1DeltaE9 mice. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *24*(6), 1667–1681.

Huang, T. L., Zandi, P. P., Tucker, K. L., Fitzpatrick, A. L., Kuller, L. H., Fried, L. P., … Carlson, M. C. (2005). Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. *Neurology*, *65*(9), 1409–1414.

Hughes, T. F., Andel, R., Small, B. J., Borenstein, A. R., Mortimer, J. A., Wolk, A., … Gatz, M. (2010). Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *18*(5), 413–420.

Hyson, D. A. (2011). A comprehensive review of apples and apple components and their relationship to human health. *Advances in Nutrition (Bethesda, Md.)*, *2*(5), 408–420.

Hyung, S.-J., DeToma, A. S., Brender, J. R., Lee, S., Vivekanandan, S., Kochi, A., … Lim, M. H. (2013). Insights into antiamyloidogenic properties of the green tea extract (-)-epigallocatechin-3-gallate toward metal-associated amyloid-β species. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(10), 3743–3748.

Iacono, D., Markesbery, W. R., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., & Troncoso, J. C. (2009). The Nun Study: Clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology*, *73*(9), 665–673.

James, B. D., Boyle, P. A., Yu, L., & Bennett, D. A. (2013). Internet use and decision making in community-based older adults. *Frontiers in Psychology*, *4*, 605.

James, C. E., Oechslin, M. S., Van De Ville, D., Hauert, C.-A., Descloux, C., & Lazeyras, F. (2014). Musical training intensity yields opposite effects on grey matter density in cognitive versus sensorimotor networks. *Brain Structure & Function*, *219*(1), 353–366.

Jankowsky, J. L., Melnikova, T., Fadale, D. J., Xu, G. M., Slunt, H. H., Gonzales, V., … Savonenko, A. V. (2005). Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(21), 5217–5224.

Jansen, D., Zerbi, V., Arnoldussen, I. A. C., Wiesmann, M., Rijpma, A., Fang, X. T., … Kiliaan, A. J. (2013). Effects of specific multi-nutrient enriched diets on cerebral metabolism, cognition and neuropathology in AβPPswe-PS1dE9 mice. *PLoS One*, *8*(9), e75393.

Jansen, D., Zerbi, V., Janssen, C. I. F., van Rooij, D., Zinnhardt, B., Dederen, P. J., … Kiliaan, A. J. (2014). Impact of a multi-nutrient diet on cognition, brain metabolism, hemodynamics, and plasticity in apoE4 carrier and apoE knockout mice. *Brain Structure & Function*, *219*(5), 1841–1868.

Jorgensen, B. P., Hansen, J. T., Krych, L., Larsen, C., Klein, A. B., Nielsen, D. S., … Sorensen, D. B. (2014). A possible link between food and mood: Dietary impact on gut microbiota and behavior in BALB/c mice. *PLoS One*, *9*(8), e103398. http://dx.doi.org/10.1371/journal.pone.0103398.

Jung, C.-R., Lin, Y.-T., & Hwang, B.-F. (2015). Ozone, particulate matter, and newly diagnosed Alzheimer's disease: A population-based cohort study in Taiwan. *Journal of Alzheimer's Disease: JAD*, *44*(2), 573–584.

Karp, A., Paillard-Borg, S., Wang, H.-X., Silverstein, M., Winblad, B., & Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders*, *21*(2), 65–73.

Kaufman, Y., Anaki, D., Binns, M., & Freedman, M. (2007). Cognitive decline in Alzheimer disease: Impact of spirituality, religiosity, and QOL. *Neurology*, *68*(18), 1509–1514.

Landau, S. M., Marks, S. M., Mormino, E. C., Rabinovici, G. D., Oh, H., O'Neil, J. P., … Jagust, W. J. (2012). Association of lifetime cognitive engagement and low β-amyloid deposition. *Archives of Neurology*, *69*(5), 623–629.

Langille, M. G., Meehan, C. J., Koenig, J. E., Dhanani, A. S., Rose, R. A., Howlett, S. E., & Beiko, R. G. (2014). Microbial shifts in the aging mouse gut. *Microbiome*, *2*(1), 50.

Laurent, C., Eddarkaoui, S., Derisbourg, M., Leboucher, A., Demeyer, D., Carrier, S., … Blum, D. (2014). Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology. *Neurobiology of Aging*, *35*(9), 2079–2090.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., … Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA*, *300*(9), 1027–1037.

Lazarov, O., Robinson, J., Tang, Y. P., Hairston, I. S., Korade-Mirnics, Z., Lee, V. M., … Sisodia, S. S. (2005). Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell*, *120*(5), 701–713. http://dx.doi.org/10.1016/j.cell.2005.01.015.

Leuner, K., Schütt, T., Kurz, C., Eckert, S. H., Schiller, C., Occhipinti, A., … Müller, W. E. (2012). Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation. *Antioxidants & Redox Signaling*, *16*(12), 1421–1433.

Levi, O., Jongen-Relo, A. L., Feldon, J., Roses, A. D., & Michaelson, D. M. (2003). ApoE4 impairs hippocampal plasticity isoform-specifically and blocks the environmental stimulation of synaptogenesis and memory. *Neurobiology of Disease*, *13*(3), 273–282.

Li, F.-J., Shen, L., & Ji, H.-F. (2012). Dietary intakes of vitamin E, vitamin C, and β-carotene and risk of Alzheimer's disease: A meta-analysis. *Journal of Alzheimer's disease: JAD*, *31*(2), 253–258.

Li, M., Sun, M., Liu, Y., Yu, J., Yang, H., Fan, D., & Chui, D. (2010). Copper downregulates neprilysin activity through modulation of neprilysin degradation. *Journal of Alzheimer's Disease: JAD*, *19*(1), 161–169.

Li, W., Dowd, S. E., Scurlock, B., Acosta-Martinez, V., & Lyte, M. (2009). Memory and learning behavior in mice is temporally associated with diet-induced alterations in gut bacteria. *Physiology & Behavior*, *96*(4–5), 557–567.

Liberati, G., Raffone, A., & Olivetti Belardinelli, M. (2012). Cognitive reserve and its implications for rehabilitation and Alzheimer's disease. *Cognitive Processing*, *13*(1), 1–12.

Lim, A. S. P., Kowgier, M., Yu, L., Buchman, A. S., & Bennett, D. A. (2013). Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*, *36*(7), 1027–1032.

Lim, A. S. P., Yu, L., Kowgier, M., Schneider, J. A., Buchman, A. S., & Bennett, D. A. (2013). Modification of the relationship of the apolipoprotein E ε4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurology*, *70*(12), 1544–1551.

Lim, W. L. F., Lam, S. M., Shui, G., Mondal, A., Ong, D., Duan, X., … Martins, R. N. (2013). Effects of a high-fat, high-cholesterol diet on brain lipid profiles in apolipoprotein E ε3 and ε4 knock-in mice. *Neurobiology of Aging*, *34*(9), 2217–2224.

Lo, R. Y., & Jagust, W. J. (2013). Effect of cognitive reserve markers on Alzheimer pathologic progression. *Alzheimer Disease and Associated Disorders*, *27*(4), 343–350. http://dx.doi.org/10.1097/WAD.0b013e3182900b2b.

Loef, M., von Stillfried, N., & Walach, H. (2012). Zinc diet and Alzheimer's disease: A systematic review. *Nutritional Neuroscience*, *15*(5), 2–12.

Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I. A., Ukoumunne, O. C., & Llewellyn, D. J. (2013). Mediterranean diet, cognitive function, and dementia: A systematic review. *Epidemiology (Cambridge, Mass.)*, *24*(4), 479–489.

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., … Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*, *48*(13), 3878–3883.

Lu, B., Nagappan, G., Guan, X., Nathan, P. J., & Wren, P. (2013). BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nature Reviews Neuroscience*, *14*(6), 401–416.

Luk, G., Bialystok, E., Craik, F. I. M., & Grady, C. L. (2011). Lifelong bilingualism maintains white matter integrity in older adults. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(46), 16808–16813.

Luttenberger, K., Hofner, B., & Graessel, E. (2012). Are the effects of a non-drug multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial. *BMC Neurology*, *12*, 151.

Lynch, D. B., Jeffery, I. B., Cusack, S., O'Connor, E. M., & O'Toole, P. W. (2015). Diet-microbiota-health interactions in older subjects: Implications for healthy aging. *Interdisciplinary Topics in Gerontology*, *40*, 141–154.

Maci, T., Pira, F. L., Quattrocchi, G., Nuovo, S. D., Perciavalle, V., & Zappia, M. (2012). Physical and cognitive stimulation in Alzheimer disease. the GAIA Project: A pilot study. *American Journal of Alzheimer's Disease and Other Dementias*, *27*(2), 107–113.

Maesako, M., Uemura, K., Kubota, M., Kuzuya, A., Sasaki, K., Asada, M., … Kinoshita, A. (2012). Environmental enrichment ameliorated high-fat diet-induced Aβ deposition and memory deficit in APP transgenic mice. *Neurobiology of Aging*, *33*(5) 1011.e1011-1023.

Maesako, M., Uemura, K., Kubota, M., Kuzuya, A., Sasaki, K., Hayashida, N., … Kinoshita, A. (2012). Exercise is more effective than diet control in preventing high fat diet-induced β-amyloid deposition and memory deficit in amyloid precursor protein transgenic mice. *The Journal of Biological Chemistry*, *287*(27), 23024–23033.

Mainardi, M., Di Garbo, A., Caleo, M., Berardi, N., Sale, A., & Maffei, L. (2014). Environmental enrichment strengthens corticocortical interactions and reduces amyloid-beta oligomers in aged mice. *Frontiers in Aging Neuroscience*, *6*, 1. http://dx.doi.org/10.3389/fnagi.2014.00001.

Maioli, S., Puerta, E., Merino-Serrais, P., Fusari, L., Gil-Bea, F., Rimondini, R., & Cedazo-Minguez, A. (2012). Combination of apolipoprotein E4 and high carbohydrate diet reduces hippocampal BDNF and arc levels and impairs memory in young mice. *Journal of Alzheimer's Disease: JAD*, *32*(2), 341–355.

Mapelli, D., Di Rosa, E., Nocita, R., & Sava, D. (2013). Cognitive stimulation in patients with dementia: Randomized controlled trial. *Dementia and Geriatric Cognitive Disorders Extra*, *3*(1), 263–271.

Matsuda, O., Shido, E., Hashikai, A., Shibuya, H., Kouno, M., Hara, C., & Saito, M. (2010). Short-term effect of combined drug therapy and cognitive stimulation therapy on the cognitive function of Alzheimer's disease. *Psychogeriatrics: The Official Journal of the Japanese Psychogeriatric Society*, *10*(4), 167–172.

Matthews, D. M., & Jenks, S. M. (2013). Ingestion of Mycobacterium vaccae decreases anxiety-related behavior and improves learning in mice. *Behavioural Processes*, *96*, 27–35.

Mechelli, A., Crinion, J. T., Noppeney, U., O'Doherty, J., Ashburner, J., Frackowiak, R. S., & Price, C. J. (2004). Neurolinguistics: Structural plasticity in the bilingual brain. *Nature*, *431*(7010), 757.

Medehouenou, T. C. M., Ayotte, P., Carmichael, P.-H., Kröger, E., Verreault, R., Lindsay, J., … Laurin, D. (2014). Plasma polychlorinated biphenyl and organochlorine pesticide concentrations in dementia: The Canadian Study of Health and Aging. *Environment International*, *69*, 141–147.

Melzig, M. F., & Janka, M. (2003). Enhancement of neutral endopeptidase activity in SK-N-SH cells by green tea extract. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *10*(6–7), 494–498.

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. *PLoS One*, *7*(6), e38268. http://dx.doi.org/10.1371/journal.pone.0038268.

Mielke, M. M., Zandi, P. P., Shao, H., Waern, M., Östling, S., Guo, X., … Gustafson, D. R. (2010). The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology*, *75*(21), 1888–1895.

Mirochnic, S., Wolf, S., Staufenbiel, M., & Kempermann, G. (2009). Age effects on the regulation of adult hippocampal neurogenesis by physical activity and environmental enrichment in the APP23 mouse model of Alzheimer disease. *Hippocampus*, *19*(10), 1008–1018. http://dx.doi.org/10.1002/hipo.20560.

Mitzner, T. L., & Kemper, S. (2003). Oral and written language in late adulthood: Findings from the Nun Study. *Experimental Aging Research*, *29*(4), 457–474. http://dx.doi.org/10.1080/03610730303698.

Molinuevo, J. L., Ripolles, P., Simó, M., Lladó, A., Olives, J., Balasa, M., … Rami, L. (2014). White matter changes in preclinical Alzheimer's disease: A magnetic resonance imaging-diffusion tensor imaging study on cognitively normal older people with positive amyloid β protein 42 levels. *Neurobiology of Aging*, *35*(12), 2671–2680.

Morbelli, S., Perneczky, R., Drzezga, A., Frisoni, G. B., Caroli, A., van Berckel, B. N. M., … Nobili, F. (2013). Metabolic networks underlying cognitive reserve in prodromal Alzheimer disease: A European Alzheimer disease consortium project. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *54*(6), 894–902.

Mori, E., Hirono, N., Yamashita, H., Imamura, T., Ikejiri, Y., Ikeda, M., & Kitagaki, H. (1997). *Premorbid brain size as a determinant of reserve capacity against intellectual decline in Alzheimer's disease* (Vol. 154).

Mortimer, J. A. (2012). The Nun Study: Risk factors for pathology and clinical-pathologic correlations. *Current Alzheimer Research*, *9*(6), 621–627.

Mortimer, J. A., Gosche, K. M., Riley, K. P., Markesbery, W. R., & Snowdon, D. A. (2004). Delayed recall, hippocampal volume and Alzheimer neuropathology: Findings from the Nun Study. *Neurology*, *62*(3), 428–432.

Moy, G. A., & McNay, E. C. (2013). Caffeine prevents weight gain and cognitive impairment caused by a high-fat diet while elevating hippocampal BDNF. *Physiology & Behavior*, *109*, 69–74.

Negash, S., Wilson, R. S., Leurgans, S. E., Wolk, D. A., Schneider, J. A., Buchman, A. S., et al. (2013). Resilient brain aging: Characterization of discordance between Alzheimer's disease pathology and cognition. *Current Alzheimer Research*, *10*(8), 844–851.

Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., … Kivipelto, M. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet*, *385*(9984), 2255–2263.

Nichol, K., Deeny, S. P., Seif, J., Camaclang, K., & Cotman, C. W. (2009). Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *5*(4), 287–294. http://dx.doi.org/10.1016/j.jalz.2009.02.006.

Nichol, K. E., Parachikova, A. I., & Cotman, C. W. (2007). Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. *Behavioural Brain Research*, *184*(2), 124–132. http://dx.doi.org/10.1016/j.bbr.2007.06.027.

Nichol, K. E., Poon, W. W., Parachikova, A. I., Cribbs, D. H., Glabe, C. G., & Cotman, C. W. (2008). Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. *Journal of Neuroinflammation*, *5*, 13. http://dx.doi.org/10.1186/1742-2094-5-13.

Niemann, C., Godde, B., & Voelcker-Rehage, C. (2014). Not only cardiovascular, but also coordinative exercise increases hippocampal volume in older adults. *Frontiers in Aging Neuroscience*, *6*, 170. http://dx.doi.org/10.3389/fnagi.2014.00170.

Ohia-Nwoko, O., Montazari, S., Lau, Y. S., & Eriksen, J. L. (2014). Long-term treadmill exercise attenuates tau pathology in P301S tau transgenic mice. *Molecular Neurodegeneration*, *9*, 54. http://dx.doi.org/10.1186/1750-1326-9-54.

Okonkwo, O. C., Schultz, S. A., Oh, J. M., Larson, J., Edwards, D., Cook, D., … Sager, M. A. (2014). Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*, *83*(19), 1753–1760. http://dx.doi.org/10.1212/WNL.0000000000000964.

Olazarán, J., Reisberg, B., Clare, L., Cruz, I., Peña-Casanova, J., Del Ser, T., … Muñiz, R. (2010). Nonpharmacological therapies in Alzheimer's disease: A systematic review of efficacy. *Dementia and Geriatric Cognitive Disorders*, *30*(2), 161–178.

O'mahony, S. M., Hyland, N. P., Dinan, T. G., & Cryan, J. F. (2011). Maternal separation as a model of brain-gut axis dysfunction. *Psychopharmacology*, *214*(1), 71–88. http://dx.doi.org/10.1007/S00213-010-2010-9.

Onder, G., Zanetti, O., Giacobini, E., Frisoni, G. B., Bartorelli, L., Carbone, G., … Bernabei, R. (2005). Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: Randomised controlled trial. *The British Journal of Psychiatry: The Journal of Mental Science*, *187*, 450–455.

Orrell, M., Aguirre, E., Spector, A., Hoare, Z., Woods, R. T., Streater, A., … Russell, I. (2014). Maintenance cognitive stimulation therapy for dementia: Single-blind, multicentre, pragmatic randomised controlled trial. *The British Journal of Psychiatry: The Journal of Mental Science*, *204*(6), 454–461.

Otaegui-Arrazola, A., Amiano, P., Elbusto, A., Urdaneta, E., & Martínez-Lage, P. (2014). Diet, cognition, and Alzheimer's disease: Food for thought. *European Journal of Nutrition*, *53*(1), 1–23.

Ozawa, M., Ninomiya, T., Ohara, T., Doi, Y., Uchida, K., Shirota, T., … Kiyohara, Y. (2013). Dietary patterns and risk of dementia in an elderly Japanese population: The Hisayama Study. *The American Journal of Clinical Nutrition*, *97*(5), 1076–1082.

Paganini-Hill, A., Kawas, C. H., & Corrada, M. M. (2015). Lifestyle factors and dementia in the oldest-old: The 90+ study. *Alzheimer Disease and Associated Disorders*. epub ahead of print.

Pal, A., Siotto, M., Prasad, R., & Squitti, R. (2015). Towards a unified vision of copper involvement in Alzheimer's disease: A review connecting basic, experimental, and clinical research. *Journal of Alzheimer's Disease: JAD*, *44*(2), 343–354.

Parachikova, A., Nichol, K. E., & Cotman, C. W. (2008). Short-term exercise in aged Tg2576 mice alters neuroinflammation and improves cognition. *Neurobiology of Disease*, *30*(1), 121–129. http://dx.doi.org/10.1016/j.nbd.2007.12.008.

Park, S. H., Kim, J. H., Choi, K. H., Jang, Y. J., Bae, S. S., Choi, B. T., & Shin, H. K. (2013). Hypercholesterolemia accelerates amyloid β-induced cognitive deficits. *International Journal of Molecular Medicine*, *31*(3), 577–582.

Parrón, T., Requena, M., Hernández, A. F., & Alarcón, R. (2011). Association between environmental exposure to pesticides and neurodegenerative diseases. *Toxicology and Applied Pharmacology*, *256*(3), 379–385.

Parrott, M. D., Winocur, G., Bazinet, R. P., Ma, D. W. L., & Greenwood, C. E. (2015). Whole-food diet worsened cognitive dysfunction in an Alzheimer's disease mouse model. *Neurobiology of Aging*, *36*(1), 90–99.

Patrignani, P., Tacconelli, S., & Bruno, A. (2014). Gut microbiota, host gene expression, and aging. *Journal of Clinical Gastroenterology*, *48*(Suppl 1), S28–S31. http://dx.doi.org/10.1097/MCG.0000000000000229.

Pérez Martínez, G., Bäuerl, C., & Collado, M. C. (2014). Understanding gut microbiota in elderly's health will enable intervention through probiotics. *Beneficial Microbes*, *5*(3), 235–246.

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Schmid, G., Wohlschläger, A., Kars, S., … Kurz, A. (2006). Schooling mediates brain reserve in Alzheimer's disease: Findings of fluoro-deoxy-glucose-positron emission tomography. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(9), 1060–1063.

Perreau, V. M., Adlard, P. A., Anderson, A. J., & Cotman, C. W. (2005). Exercise-induced gene expression changes in the rat spinal cord. *Gene Expression*, *12*(2), 107–121.

Persson, J., Kalpouzos, G., Nilsson, L.-G., Ryberg, M., & Nyberg, L. (2011). Preserved hippocampus activation in normal aging as revealed by fMRI. *Hippocampus*, *21*(7), 753–766.

Pohanka, M., & Dobes, P. (2013). Caffeine inhibits acetylcholinesterase, but not butyrylcholinesterase. *International Journal of Molecular Sciences*, *14*(5), 9873–9882.

Polidori, M. C., & Nelles, G. (2014). Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease-challenges and perspectives. *Current Pharmaceutical Design*, *20*(18), 3083–3092.

Porquet, D., Casadesús, G., Bayod, S., Vicente, A., Canudas, A. M., Vilaplana, J., … del Valle, J. (2013). Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8. *Age (Dordrecht, Netherlands)*, *35*(5), 1851–1865.

Potter, G. G., Helms, M. J., Burke, J. R., Steffens, D. C., & Plassman, B. L. (2007). Job demands and dementia risk among male twin pairs. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *3*(3), 192–199.

Qiu, X., Huang, C.-X., Lu, W., Yang, S., Li, C., Shi, X.-Y., … Tang, Y. (2012). Effects of a 4 month enriched environment on the hippocampus and the myelinated fibers in the hippocampus of middle-aged rats. *Brain Research*, *1465*, 26–33.

Rao, S. K., Ross, J. M., Harrison, F. E., Bernardo, A., Reiserer, R. S., Reiserer, R. S., … McDonald, M. P. (2015). Differential proteomic and behavioral effects of long-term voluntary exercise in wild-type and APP-overexpressing transgenics. *Neurobiology of Disease*, *78*, 45–55. http://dx.doi.org/10.1016/j.nbd.2015.03.018.

Reitz, C., & Mayeux, R. (2014). Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochemical Pharmacology*, *88*(4), 640–651.

Religa, D., Strozyk, D., Cherny, R. A., Volitakis, I., Haroutunian, V., Winblad, B., … Bush, A. I. (2006). Elevated cortical zinc in Alzheimer disease. *Neurology*, *67*(1), 69–75.

Rentz, D. M., Locascio, J. J., Becker, J. A., Moran, E. K., Eng, E., Buckner, R. L., … Johnson, K. A. (2010). Cognition, reserve, and amyloid deposition in normal aging. *Annals of Neurology*, *67*(3), 353–364.

Revilla, S., Suñol, C., García-Mesa, Y., Giménez-Llort, L., Sanfeliu, C., & Cristòfol, R. (2014). Physical exercise improves synaptic dysfunction and recovers the loss of survival factors in 3xTg-AD mouse brain. *Neuropharmacology*, *81*, 55–63.

Reyes-Ortiz, C. A., Berges, I. M., Raji, M. A., Koenig, H. G., Kuo, Y. F., & Markides, K. S. (2008). Church attendance mediates the association between depressive symptoms and cognitive functioning among older Mexican Americans. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, *63*(5), 480–486.

Richardson, J. R., Roy, A., Shalat, S. L., von Stein, R. T., Hossain, M. M., Buckley, B., … German, D. C. (2014). Elevated serum pesticide levels and risk for Alzheimer disease. *JAMA Neurology*, *71*(3), 284–290.

Richardson, J. R., Shalat, S. L., Buckley, B., Winnik, B., O'Suilleabhain, P., Diaz-Arrastia, R., … German, D. C. (2009). Elevated serum pesticide levels and risk of Parkinson disease. *Archives of Neurology*, *66*(7), 870–875.

Richter, H., Ambree, O., Lewejohann, L., Herring, A., Keyvani, K., Paulus, W., … Sachser, N. (2008). Wheel-running in a transgenic mouse model of Alzheimer's disease: Protection or symptom? *Behavioural Brain Research*, *190*(1), 74–84. http://dx.doi.org/10.1016/j.bbr.2008.02.005.

Riley, K. P., Snowdon, D. A., Desrosiers, M. F., & Markesbery, W. R. (2005). Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the Nun Study. *Neurobiology of Aging*, *26*(3), 341–347.

Roe, C. M., Fagan, A. M., Grant, E. A., Marcus, D. S., Benzinger, T. L. S., Mintun, M. A., … Morris, J. C. (2011). Cerebrospinal fluid biomarkers, education, brain volume, and future cognition. *Archives of Neurology*, *68*(9), 1145–1151.

Roe, C. M., Mintun, M. A., D'Angelo, G., Xiong, C., Grant, E. A., & Morris, J. C. (2008). Alzheimer disease and cognitive reserve: Variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. *Archives of Neurology*, *65*(11), 1467–1471.

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia: Support for the cognitive reserve hypothesis. *Neurology*, *68*(3), 223–228.

Rosen, A. C., Sugiura, L., Kramer, J. H., Whitfield-Gabrieli, S., & Gabrieli, J. D. (2011). Cognitive training changes hippocampal function in mild cognitive impairment: A pilot study. *Journal of Alzheimers Disease: JAD*, *26*(Suppl), 349–357. 3 SRC – GoogleScholar. http://dx.doi.org/10.3233/jad-2011-0009.

Rovio, S., Kåreholt, I., Helkala, E.-L., Viitanen, M., Winblad, B., Tuomilehto, J., … Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *The Lancet Neurology*, *4*(11), 705–711.

Russo-Neustadt, A., Beard, R. C., & Cotman, C. W. (1999). Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacology*, *21*(5), 679–682. doi:10.1016/S0893-133x(99)00059-7.

Saczynski, J. S., Pfeifer, L. A., Masaki, K., Korf, E. S. C., Laurin, D., White, L., & Launer, L. J. (2006). The effect of social engagement on incident dementia: The Honolulu-Asia Aging Study. *American Journal of Epidemiology*, *163*(5), 433–440.

Salazar, J. G., Ribes, D., Cabre, M., Domingo, J. L., Sanchez-Santed, F., & Colomina, M. T. (2011). Amyloid beta peptide levels increase in brain of AbetaPP Swedish mice after exposure to chlorpyrifos. *Current Alzheimer Research*, *8*(7), 732–740.

Sattler, C., Toro, P., Schönknecht, P., & Schröder, J. (2012). Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatry Research*, *196*(1), 90–95.

Scarmeas, N., Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology*, *57*(12), 2236–2242.

Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., & Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA*, *302*(6), 627–637.

Schlosser Covell, G. E., Hoffman-Snyder, C. R., Wellik, K. E., Woodruff, B. K., Geda, Y. E., Caselli, R. J., … Wingerchuk, D. M. (2015). Physical activity level and future risk of mild cognitive impairment or dementia: A critically appraised topic. *Neurologist*, *19*(3), 89–91. http://dx.doi.org/10.1097/NRL.0000000000000013.

Schweizer, T. A., Ware, J., Fischer, C. E., Craik, F. I. M., & Bialystok, E. (2012). Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, *48*(8), 991–996.

Serra, L., Cercignani, M., Petrosini, L., Basile, B., Perri, R., Fadda, L., … Bozzali, M. (2011). Neuroanatomical correlates of cognitive reserve in Alzheimer disease. *Rejuvenation Research*, *14*(2), 143–151.

Shah, R. (2013). The role of nutrition and diet in Alzheimer disease: A systematic review. *Journal of the American Medical Directors Association*, *14*(6), 398–402.

Shah, T., Verdile, G., Sohrabi, H., Campbell, A., Putland, E., Cheetham, C., … Martins, R. N. (2014). A combination of physical activity and computerized brain training improves verbal memory and increases cerebral glucose metabolism in the elderly. *Translational Psychiatry*, *4*, e487. http://dx.doi.org/10.1038/tp.2014.122.

Shea, T. B., & Remington, R. (2015). Nutritional supplementation for Alzheimer's disease? *Current Opinion in Psychiatry*, *28*(2), 141–147.

Shen, X.-L., Yu, J.-H., Zhang, D.-F., Xie, J.-X., & Jiang, H. (2014). Positive relationship between mortality from Alzheimer's disease and soil metal concentration in mainland China. *Journal of Alzheimer's Disease: JAD*, *42*(3), 893–900.

Shinto, L., Quinn, J., Montine, T., Dodge, H. H., Woodward, W., Baldauf-Wagner, S., … Kaye, J. (2014). A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *38*(1), 111–120.

Shoemark, D. K., & Allen, S. J. (2014). The microbiome and disease: Reviewing the links between the oral microbiome, aging, and Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *43*, 725–738. 3 SRC—GoogleScholar. http://dx.doi.org/10.3233/jad-141170.

Simmons-Stern, N. R., Budson, A. E., & Ally, B. A. (2010). Music as a memory enhancer in patients with Alzheimer's disease. *Neuropsychologia*, *48*(10), 3164–3167.

Simpson, J., & Kelly, J. P. (2011). The impact of environmental enrichment in laboratory rats—Behavioural and neurochemical aspects. *Behavioural Brain Research*, *222*(1), 246–264.

Singh, B., Parsaik, A. K., Mielke, M. M., Erwin, P. J., Knopman, D. S., Petersen, R. C., & Roberts, R. O. (2014). Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. *Journal of Alzheimer's Disease: JAD*, *39*(2), 271–282.

Singh, I., Sagare, A. P., Coma, M., Perlmutter, D., Gelein, R., Bell, R. D., … Deane, R. (2013). Low levels of copper disrupt brain amyloid-β homeostasis by altering its production and clearance. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(36), 14771–14776.

Singh, N., Chhillar, N., Banerjee, B., Bala, K., Basu, M., & Mustafa, M. (2013). Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. *Human & Experimental Toxicology*, *32*(1), 24–30.

Singh, N. K., Banerjee, B. D., Bala, K., Basu, M., & Chhillar, N. (2014). Polymorphism in cytochrome P450 2D6, glutathione S-transferases Pi 1 genes, and organochlorine pesticides in Alzheimer disease: A case–control study in north Indian population. *Journal of Geriatric Psychiatry and Neurology*, *27*(2), 119–127. http://dx.doi.org/10.1177/0891988714522698.

Slashinski, M. J., McCurdy, S. A., Achenbaum, L. S., Whitney, S. N., & McGuire, A. L. (2012). "Snake-oil," "quack medicine," and "industrially cultured organisms:" Biovalue and the commercialization of human microbiome research. *BMC Medical Ethics*, *13*, 28.

Smith, C. J., Emge, J. R., Berzins, K., Lung, L., Khamishon, R., Shah, P., … Gareau, M. G. (2014). Probiotics normalize the gut-brain-microbiota axis in immunodeficient mice. *American Journal of Physiology Gastrointestinal and Liver Physiology*, *307*(8), G793–G802.

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*, *277*(10), 813–817.

Snowdon, D. A., Kemper, S. J., Mortimer, J. A., Greiner, L. H., Wekstein, D. R., & Markesbery, W. R. (1996). Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA*, *275*(7), 528–532.

Snowdon, D. A., Tully, C. L., Smith, C. D., Riley, K. P., & Markesbery, W. R. (2000). Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: Findings from the Nun Study. *American Journal of Clinical Nutrition*, *71*(4), 993–998.

Soldan, A., Pettigrew, C., Li, S., Wang, M. -C., Moghekar, A., Selnes, O. A., … Team, B. R. (2013). Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. *Neurobiology of Aging*, *34*(12), 2827–2834.

Sole-Padulles, C., Llado, A., Bartres-Faz, D., Fortea, J., Sanchez-Valle, R., Bosch, B., … Rami, L. (2011). Association between cerebrospinal fluid tau and brain atrophy is not related to clinical severity in the Alzheimer's disease continuum. *Psychiatry Research*, *192*(3), 140–146. http://dx.doi.org/10.1016/j.pscychresns.2010.12.001.

Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J., & Whitmer, R. A. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dementia and Geriatric Cognitive Disorders*, *28*(1), 75–80.

Southon, A., Greenough, M. A., Ganio, G., Bush, A. I., Burke, R., & Camakaris, J. (2013). Presenilin promotes dietary copper uptake. *PLoS One*, *8*(5), e62811.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 280–292.

Spironelli, C., Bergamaschi, S., Mondini, S., Villani, D., & Angrilli, A. (2013). Functional plasticity in Alzheimer's disease: Effect of cognitive training on language-related ERP components. *Neuropsychologia*, *51*(8), 1638–1648.

Squitti, R., Siotto, M., & Polimanti, R. (2014). Low-copper diet as a preventive strategy for Alzheimer's disease. *Neurobiology of Aging*, *35*(Suppl), S40–S50. 2 SRC—GoogleScholar. http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.031.

Steffener, J., Barulli, D., Habeck, C., O'Shea, D., Razlighi, Q., & Stern, Y. (2014). The role of education and verbal abilities in altering the effect of age-related gray matter differences on cognition. *PLoS One*, *9*(3), e91196.

Steffener, J., & Stern, Y. (2012). Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta*, *1822*(3), 467–473.

Stelmashook, E. V., Isaev, N. K., Genrikhs, E. E., Amelkina, G. A., Khaspekov, L. G., Skrebitsky, V. G., & Illarioshkin, S. N. (2014). Role of zinc and copper ions in the pathogenetic mechanisms of Alzheimer's and Parkinson's diseases. *Biochemistry Biokhimiia*, *79*(5), 391–396.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028.

Stern, Y., Moeller, J. R., Anderson, K. E., Luber, B., Zubin, N. R., DiMauro, A. A., et al. (2000). Different brain networks mediate task performance in normal aging and AD: Defining compensation. *Neurology*, *15*(9), 1291–1297.

Subash, S., Braidy, N., Essa, M. M., Zayana, A. -B., Ragini, V., Al-Adawi, S., … Guillemin, G. J. (2015). Long-term (15 mo) dietary supplementation with pomegranates from Oman attenuates cognitive and behavioral deficits in a transgenic mice model of Alzheimer's disease. *Nutrition (Burbank, Los Angeles County, Calif.)*, *31*(1), 223–229.

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., … Kawashima, R. (2010). Training of working memory impacts structural connectivity. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(9), 3297–3303.

Tanner, C. M., Goldman, S. M., Ross, G. W., & Grate, S. J. (2014). The disease intersection of susceptibility and exposure: Chemical exposures and neurodegenerative disease risk. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(3 Suppl), S213–S225. http://dx.doi.org/10.1016/j.jalz.2014.04.014.

Tapia-Rojas, C., Aranguiz, F., Varela-Nallar, L., & Inestrosa, N. C. (2015). Voluntary running attenuates memory loss, decreases neuropathological changes and induces neurogenesis in a mouse model of Alzheimer's disease. *Brain Pathology (Zurich, Switzerland)*. epub ahead of print.

Tarraga, L., Boada, M., Modinos, G., Espinosa, A., Diego, S., Morera, A., … Becker, J. T. (2006). A randomised pilot study to assess the efficacy of an interactive, multimedia tool of cognitive stimulation in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(10), 1116–1121. http://dx.doi.org/10.1136/jnnp.2005.086074.

Thiel, C., Vogt, L., Tesky, V. A., Meroth, L., Jakob, M., Sahlender, S., … Banzer, W. (2012). Cognitive intervention response is related to habitual physical activity in older adults. *Aging Clinical and Experimental Research*, *24*(1), 47–55.

Treiber, K. A., Carlson, M. C., Corcoran, C., Norton, M. C., Breitner, J. C. S., Piercy, K. W., … Tschanz, J. T. (2011). Cognitive stimulation and cognitive and functional decline in Alzheimer's disease: The cache county dementia progression study. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences*, *66*(4), 416–425.

Tully, C. L., Snowdon, D. A., & Markesbery, W. R. (1995). Serum zinc, senile plaques, and neurofibrillary tangles: Findings from the Nun Study. *Neuroreport*, *6*(16), 2105–2108.

Tyas, S. L., Snowdon, D. A., Desrosiers, M. F., Riley, K. P., & Markesbery, W. R. (2007). Healthy ageing in the Nun Study: Definition and neuropathologic correlates. *Age and Ageing*, *36*(6), 650–655. http://dx.doi.org/10.1093/ageing/afm120.

Ullrich, C., & Humpel, C. (2009). Rotenone induces cell death of cholinergic neurons in an organotypic co-culture brain slice model. *Neurochemical Research*, *34*(12), 2147–2153.

Valenzuela, M. J., Sachdev, P., Wen, W., Chen, X., & Brodaty, H. (2008). Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One*, *3*(7), e2598. http://dx.doi.org/10.1371/journal.pone.0002598.

van Wijk, N., Broersen, L. M., de Wilde, M. C., Hageman, R. J., Groenendijk, M., Sijben, J. W., & Kamphuis, P. J. (2014). Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination. *Journal of Alzheimer's Disease: JAD*, *38*(3), 459–479. http://dx.doi.org/10.3233/JAD-130998.

Varamini, B., Sikalidis, A. K., & Bradford, K. L. (2014). Resveratrol increases cerebral glycogen synthase kinase phosphorylation as well as protein levels of drebrin and transthyretin in mice: An exploratory study. *International Journal of Food Sciences and Nutrition*, *65*(1), 89–96.

Varma, V. R., Chuang, Y. F., Harris, G. C., Tan, E. J., & Carlson, M. C. (2015). Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus*, *25*(5), 605–615. http://dx.doi.org/10.1002/Hipo.22397.

Vassallo, N., & Scerri, C. (2013). Mediterranean diet and dementia of the Alzheimer type. *Current Aging Science*, *6*(2), 150–162.

Vepsäläinen, S., Koivisto, H., Pekkarinen, E., Mäkinen, P., Dobson, G., McDougall, G. J., … Hiltunen, M. (2013). Anthocyanin-enriched bilberry and blackcurrant extracts modulate amyloid precursor protein processing and alleviate behavioral abnormalities in the APP/PS1 mouse model of Alzheimer's disease. *The Journal of Nutritional Biochemistry*, *24*(1), 360–370.

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., … Buschke, H. (2003). Leisure activities and the risk of dementia in the elderly. *The New England Journal of Medicine*, *348*(25), 2508–2516.

Verret, L., Krezymon, A., Halley, H., Trouche, S., Zerwas, M., Lazouret, M., … Rampon, C. (2013). Transient enriched housing before amyloidosis onset sustains cognitive improvement in Tg2576 mice. *Neurobiology of Aging*, *34*(1), 211–225.

Viola, L. F., Nunes, P. V., Yassuda, M. S., Aprahamian, I., Santos, F. S., Santos, G. D., et al. (2011). Effects of a multidisciplinary cognitive rehabilitation program for patients with mild Alzheimer's disease. *Clinics (Sao Paulo)*, *66*(8), 1395–1400.

Walker, J. M., Klakotskaia, D., Ajit, D., Weisman, G. A., Wood, W. G., Sun, G. Y., … Schachtman, T. R. (2015). Beneficial effects of dietary EGCG and voluntary exercise on behavior in an Alzheimer's disease mouse model. *Journal of Alzheimer's Disease: JAD*, *44*(2), 561–572.

Wang, C. Y., Wang, T., Zheng, W., Zhao, B. L., Danscher, G., Chen, Y. H., & Wang, Z. Y. (2010). Zinc overload enhances APP cleavage and Abeta deposition in the Alzheimer mouse brain. *PLoS One*, *5*(12), e15349. http://dx.doi.org/10.1371/journal.pone.0015349.

Wang, D. S., Iwata, N., Hama, E., Saido, T. C., & Dickson, D. W. (2003). Oxidized neprilysin in aging and Alzheimer's disease brains. *Biochemical and Biophysical Research Communications*, *310*(1), 236–241.

Wang, H., Odegaard, A., Thyagarajan, B., Hayes, J., Cruz, K. S., Derosiers, M. F., … Gross, M. D. (2012). Blood folate is associated with asymptomatic or partially symptomatic Alzheimer's disease in the Nun Study. *Journal of Alzheimer's Disease: JAD*, *28*(3), 637–645.

Wang, J., Bi, W., Cheng, A., Freire, D., Vempati, P., Zhao, W., … Pasinetti, G. M. (2014). Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease—Experimental approach and therapeutic implications. *Frontiers in Aging Neuroscience*, *6*, 42. http://dx.doi.org/10.3389/fnagi.2014.00042.

Wang, P., Su, C., Li, R., Wang, H., Ren, Y., Sun, H., … Jiang, S. (2014). Mechanisms and effects of curcumin on spatial learning and memory improvement in APPswe/PS1dE9 mice. *Journal of Neuroscience Research*, *92*(2), 218–231.

Weuve, J., Puett, R. C., Schwartz, J., Yanosky, J. D., Laden, F., & Grodstein, F. (2012). Exposure to particulate air pollution and cognitive decline in older women. *Archives of Internal Medicine*, *172*(3), 219–227.

Wiesmann, M., Jansen, D., Zerbi, V., Broersen, L. M., Garthe, A., & Kiliaan, A. J. (2013). Improved spatial learning strategy and memory in aged Alzheimer AβPPswe/PS1dE9 mice on a multi-nutrient diet. *Journal of Alzheimer's Disease: JAD*, *37*(1), 233–245.

Wilson, R. S., Boyle, P. A., Yang, J., James, B. D., & Bennett, D. A. (2015). Early life instruction in foreign language and music and incidence of mild cognitive impairment. *Neuropsychology*, *29*(2), 292–302. http://dx.doi.org/10.1037/neu0000129.

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., & Bennett, D. A. (2013). Lifespan cognitive activity, neuropathologic burden, and cognitive aging. *Neurology*, *81*(4), 314–321. http://dx.doi.org/10.1212/WNL.0b013e31829c5e8a.

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., … Bennett, D. A. (2007). Loneliness and risk of Alzheimer disease. *Archives of General Psychiatry*, *64*(2), 234–240. http://dx.doi.org/10.1001/archpsyc.64.2.234.

Wilson, R. S., Li, Y., Aggarwal, N. T., Barnes, L. L., McCann, J. J., Gilley, D. W., & Evans, D. A. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology*, *63*(7), 1198–1202.

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA*, *287*(6), 742–748.

Wilson, R. S., Nag, S., Boyle, P. A., Hizel, L. P., Yu, L., Buchman, A. S., … Bennett, D. A. (2013). Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*, *80*(13), 1202–1208. http://dx.doi.org/10.1212/WNL.0b013e3182897103.

Wilson, R. S., Scherr, P. A., Hoganson, G., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2005). Early life socioeconomic status and late life risk of Alzheimer's disease. *Neuroepidemiology*, *25*(1), 8–14. http://dx.doi.org/10.1159/000085307.

Wilson, R. S., Scherr, P. A., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*, *69*(20), 1911–1920.

Wirth, M., Villeneuve, S., La Joie, R., Marks, S. M., & Jagust, W. J. (2014). Gene-environment interactions: Lifetime cognitive activity, APOE genotype, and β-amyloid burden. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(25), 8612–8617.

Wolf, S. A., Kronenberg, G., Lehmann, K., Blankenship, A., Overall, R., Staufenbiel, M., & Kempermann, G. (2006). Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. *Biological Psychiatry*, *60*(12), 1314–1323. http://dx.doi.org/10.1016/j.biopsych.2006.04.004.

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *The Cochrane Database of Systematic Reviews*, *2*, CD005562.

Xiao, J., Li, S., Sui, Y., Wu, Q., Li, X., Xie, B., … Sun, Z. (2014). Lactobacillus casei-01 facilitates the ameliorative effects of proanthocyanidins extracted from lotus seedpod on learning and memory impairment in scopolamine-induced amnesia mice. *PLoS One*, *9*(11), e112773.

Yaffe, K., Weston, A., Graff-Radford, N. R., Satterfield, S., Simonsick, E. M., Younkin, S. G., … Harris, T. B. (2011). Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. *JAMA*, *305*(3), 261–266.

Yasuno, F., Kazui, H., Morita, N., Kajimoto, K., Ihara, M., Taguchi, A., … Kishimoto, T. (2014). Low amyloid-β deposition correlates with high education in cognitively normal older adults: A pilot study. *International Journal of Geriatric Psychiatry*, *30*(9), 919–926.

Yu, F., Bronas, U. G., Konety, S., Nelson, N. W., Dysken, M., Jack, C., Jr., … Smith, G. (2014). Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: Study protocol of a randomized controlled trial (The FIT-AD trial). *Trials*, *15*, 394. http://dx.doi.org/10.1186/1745-6215-15-394.

Yu, J., Luo, X., Xu, H., Ma, Q., Yuan, J., Li, X., … Yang, X. (2015). Identification of the key molecules involved in chronic copper exposure-aggravated memory impairment in transgenic mice of Alzheimer's disease using proteomic analysis. *Journal of Alzheimer's Disease: JAD*, *44*(2), 455–469.

Yuede, C. M., Zimmerman, S. D., Dong, H., Kling, M. J., Bero, A. W., Holtzman, D. M., … Csernansky, J. G. (2009). Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiology of Disease*, *35*(3), 426–432. http://dx.doi.org/10.1016/j.nbd.2009.06.002.

Zhao, G., Liu, H. L., Zhang, H., & Tong, X. J. (2015). Treadmill exercise enhances synaptic plasticity, but does not alter beta-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. *Neuroscience*, *298*, 357–366. http://dx.doi.org/10.1016/j.neuroscience.2015.04.038.