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

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INTRODUCTION

Environmental factors profoundly in uence brain structure and function. Lifestyle elements such as nutrition, physical activity, exposure to chemicals, social interaction, and participation in cognitively demanding activities signi cantly 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 signi cant 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 rst experimental evidence that environmental factors are disease modulators. These experiments modi ed 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

axonal transport (for example, see Hu et al., 2010). Speci cally, 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 nepri-

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 bene t to the aging brain. For example, many studies show that lifetime bilinguals have a delayed average onset for AD (

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 uid (CSF), which is thought to be re ective of Aβ

before cognitive symptoms are observed. Cognitive reserve usually refers to increased ef ciency 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

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 ef ciency 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 signi cantly 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).

(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 neuro brillary tangles (Bennett et al., 2005a).

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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 bene cial 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, Whit eld-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 speci c 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 bene ts 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 bene cial 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 bene t may exist for musical training (Simmons-Stern, Budson, & Ally, 2010). One challenge for CST for treatment of dementia is that it can be dif cult to teach the task. Video game training shows some promise as a means of cognitive stimulation therapy. Research groups are working on making

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,3. 0.01 K/GK/GK/GK/GK/G

impairments due to DDE (

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.

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 de cits 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 /Span ≮Lang (en-US)/MCID 1113 ∋BDC BT/T1; Wang

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causative factors behind the observed modulation of AD risk (Barberger-Gateau et al., 2007). That may also help resolve some con icting 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, Zhz5iesolve some con icting evidence

Kowgier, Yu, Buchman, & Bennett, 2013

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 ef ciency 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 in ammation 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 de cits 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 de cits 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 (

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.

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