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Alterations in Hippocampal Activity and Alzheimer's Disease

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Abstract

The aging population and those with amnestic mild cognitive impairment (aMCI) are at increased risk for developing Alzheimer's disease (AD). Individuals with aMCI in particular may display pathological changes in brain function that may ultimately result in a diagnosis of AD. This review focuses specifically on hippocampal hyperexcitability, a pathology that is sometimes detectable years before diagnosis, which has been observed in individuals with aMCI. We describe how changes in hippocampal activity are associated with, or in some cases may be permissive for, the development of AD. Finally, we describe how lifestyle changes, including exercise and dietary changes can attenuate cognitive decline and hippocampal hyperexcitability, potentially reducing the risk of developing AD.

Introduction

With the increase in life expectancy, the prevalence of age-related impairments in cognitive ability and memory has increased and is expected to increase even more in the next 20 years. While a minority of aged individuals will maintain peak cognitive performance during senescence (Rowe & Kahn, 1987), characterized by low probability of disease, high cognitive and physical functional capacity, and active life engagement (Rowe & Kahn, 1997), many individuals in their 7th and 8th decades will display detrimental changes in memory. A deterioration in episodic memory (memory of autobiographical events), in some cases detectable as early as middle-age (Small, Stern, Tang, & Mayeux, 1999; Verhaeghen, Vandenbroucke, & Dierckx, 1998), may be indicative of the likelihood to develop mild cognitive impairment (MCI) and the debilitating and progressive neurodegenerative condition, Alzheimer's disease (AD) (Small, Dixon, & McArdle, 2011).

Generally, MCI consists of several characteristics that set this diagnosis apart from AD, leading some researchers to categorize the two disorders as completely separate entities (Albert et al., 2011). Those with amnestic MCI (aMCI) in particular, which is specifically characterized by memory loss, will often exhibit impairment of episodic memory in the absence of beta-amyloid (Aβ) plaques, tau tangles, and neuronal loss, all of which are hallmark characteristics observed in patients with AD (Albert et al., 2011). However,

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because of the considerably accelerated rate at which these individuals progress to AD compared to healthy age-matched individuals, aMCI has frequently been viewed as the prodromal stage of Alzheimer's disease (Mauri, Sinforiani, Zucchella, Cuzzoni, & Bono, 2012). Cognitive tests assessing episodic memory are useful to both determine the extent of memory impairment in these patients and to identify individuals who are most likely to develop AD (Albert et al., 2011; Petersen, 2004). Interestingly, in the years preceding AD diagnosis, individuals with aMCI often exhibit excess activation (hyperexcitability) in brain regions responsible for memory, including the hippocampus. This excess activation is often measured using high-resolution fMRI scan while the individual performs a memory task and is correlated to the degree of memory impairment in diagnostic tests for presence of aMCI and later the likelihood to develop AD (Bakker et al., 2012). However, it is important to note that excess hippocampal activation cannot yet be considered a biomarker of AD development. Nevertheless, understanding the relationship between the hippocampal hyperactivity exhibited in individuals diagnosed with aMCI and the correlation to development of AD is crucial. In this section, we highlight how age-related changes in the hippocampus can result in hyperexcitability leading to cognitive impairment and the potential development of AD.

Hippocampal Hyperexcitability

As individuals age, prominent deficits in spatial learning, working memory, and episodic memory can be observed (Gallagher & Rapp, 1997). These specific types of memory-related deficits have a common neurobiological source, the hippocampus (Wilson, Gallagher, Eichenbaum, & Tanila, 2006). In the years prior to AD diagnosis, a hyperactivity or excess activation of the memory network, comprised of the hippocampus, medial temporal lobe, and several cortical regions, is detectable (Sperling et al., 2010). Hippocampal hyperactivity has been observed in numerous studies examining individuals at genetic or familial risk of AD (Bondi, Houston, Eyler, & Brown, 2005; Quiroz et al., 2010), as well as asymptomatic and minimally impaired older individuals with Aβ deposition (Sperling et al., 2010). In longitudinal studies, the degree of hippocampal overactivation correlates with declines in memory (Bookheimer et al., 2000).

For many years, this hyperactivity was thought to be a compensatory response for deteriorating neuronal circuitry such that greater cognitive effort was needed to achieve comparable (or less than comparable) performance (Bondi et al., 2005), but more recent evidence suggests hyperactivity of the memory network may signify neuronal excitotoxicity, a pathological process in which neurons are killed due to overactivation, and could be permissive for the development of AD, making it a potential therapeutic target. With age-associated memory deficits, as seen in aMCI, the hippocampal neurons are usually intact with little to no detectable neuron loss (Geinisman et al., 2004; Rapp & Gallagher, 1996). Rather, there are age-related alterations in the functional connections of the cell groups that comprise the hippocampus, and these changes may be permissive for the development of AD.

The hippocampus is comprised of three distinct subregions, the dentate gyrus (DG), cornu ammonis 3 (CA3), and cornu ammonis 1 (CA1). Flow from layer 2 of the entorhinal cortex

enters the DG through what is termed the perforant pathway, which projects to the CA3 through the mossy fiber pathway. Neurons in the CA3 then connect to the CA1 via the schaffer-collateral pathway. Each of these subregions has specific characteristics that distinguish them from one another. With increasing age, hyperxcitability exhibited in these subregions will affect learning and memory in different ways (Ji & Maren, 2008).

Loss in synaptic strength in the DG is observed in both aMCI patients and aged animals with memory impairment. Aged rats exhibiting memory deficits have approximately a fourth to a third fewer synaptic connections from the entorhinal cortex (EC) to the DG along the perforant pathway (Geinisman, deToledo-Morrell, Morrell, Persina, & Rossi, 1992; Smith, Adams, Gallagher, Morrison, & Rapp, 2000). The greater the loss of these synaptic connections, the more severe the memory deficits observed (Smith et al., 2000). Though the loss of inputs from the EC is associated with less excitation in the DG of aged rats exhibiting memory impairments (Barnes & McNaughton, 1980), the individual synapses are actually more powerful due to an increase in quantal size, defined as the synaptic response to the release of a neurotransmitter from a single vesicle (Foster, Barnes, Rao, & McNaughton, 1991). Patients with aMCI also have fewer synapses in the DG compared to age-matched controls without memory impairments (Scheff, Price, Schmitt, & Mufson, 2006). Furthermore, older individuals with memory impairment exhibit atrophy of the perforant pathway that connects the EC to the DG (Kalus et al., 2006).

Conversely, the firing rates of CA3 cells are actually increased in aged, memory-impaired rats (Wilson, Ikonen, Gallagher, Eichenbaum, & Tanila, 2005). This hyperexcitability of the CA3 may be due to the diminished input from the EC to the CA3 (Barnes & McNaughton, 1980; Geinisman et al., 1992; Smith et al., 2000), without a commiserate loss of the excitatory recurrent synapses in the CA3 (Rapp & Gallagher, 1996; Rapp, Stack, & Gallagher, 1999; Rapp, Stack., & Gallagher, 1999; Smith et al., 2000). Findings of age-related CA3 hyperexcitability are not limited to rodents. Studies utilizing fMRI technology showcase a greater hippocampal activation, as indicated by increased blood-oxygen level dependent (BOLD) activation along the DG-CA3 pathway in aged individuals with poor memory performance, as well as aMCI patients (Dickerson et al., 2004; Sperling, 2007), and this activation is predictive of both the degree and rate of conversion to AD (Miller, Fenstermacher, Bates, Blacker, Sperling, Dickerson, 2008).

The last region discussed, the CA1, is perhaps the most studied of all the hippocampal subregions in rodents. CA1-related memory deficits observed in aged, memory-impaired rats are not associated with a loss of synapses from the CA3 or EC inputs (Geinisman et al., 2004; Smith et al., 2000), but rather are believed to result from an increase in the number of silent synapses (or synapses without excitatory glutamatergic AMPA receptors) and calcium channels, which result in long lasting excitation signals. (Nicholson, Yoshida, Berry, Gallagher, & Geinisman, 2004; Thibault & Landfield, 1996). The latter is thought to explain why CA1 neurons are highly sensitive to excitotoxicity and more susceptible to loss in AD (West, Kawas, Martin, & Troncoso, 2000). Though the alterations described are relatively subtle compared to the robust alterations in neuronal functioning observed in AD, these changes in neural network activity may serve not only as a future biomarker for AD but also

could be permissive for the development of AD, by propagating pathologies exhibited during the disease progression.

Animal studies demonstrate that increases in neural activity increase processing of the amyloid precursor protein (APP), leading to an increased production of Aβ, a hallmark of AD (Kamenetz et al., 2003). Thus, the age-related increase in CA3 activity observed in aged, memory-impaired rats and aMCI patients (Bakker et al., 2012; Yassa et al., 2010) could increase Aβ production and deposition, eventually leading to the formation of Aβ plaques. Additional support comes from mouse models of AD in which Aβ plaques are found specifically within the vicinity of hyperactive neurons (Busche et al., 2008). The role of hyperactivity in mediating Aβ levels has recently been confirmed in studies using chemogenetic modulation of neural activity to either decrease or increase neuronal activity, leading to markedly decreased or increased Aβ aggregation and deposition, respectively (Yuan & Grutzendler, 2016). Furthermore, circumstantial evidence from patients with temporal lobe epilepsy exhibiting elevated neuronal activity show that amyloid plaques develop as early as 30 years of age (Mackenzie & Miller, 1994), suggesting the increased activity resulting from epilepsy may drive Aβ production and deposition.

The effect of hyperactivity is not limited to Aβ. Tau propagation and pathology, the second hallmark of AD, is also enhanced by neural activity (Wu et al., 2016). Increased neuronal activity promotes trans-synaptic spread of tau pathology, in which tau can be released into the extracellular space independently of cell death (Chai, Dage, & Citron, 2012) and compromise the functionality of tau within a neighboring, healthy neuron, thereby inducing further tau aggregation (Clavaguera et al., 2009). In addition, in tau −/− mice, an animal model in which tau has been genetically removed, seizure susceptibility and cognitive impairment are attenuated, suggesting that the relationship between tau pathology and hyperactivity is likely cyclical. Indeed, in mouse and Drosopholia genetic models of epilepsy, characterized by excess neuronal activation, tau removal dampens the hyperexcitability observed by reducing seizure-related mortalities (Holth et al., 2013). Thus, reduction in tau levels and hyperexcitability represent viable therapeutic targets for AD currently being pursued (Himmelstein, Ward, Lancia, Patterson, & Binder, 2012; Holth et al., 2013).

The network dysfunction observed in those at risk for AD may also explain the prevalence of epilepsy in AD patients. For example, increased incidence of seizures is highest among those with early onset dementia, remaining increased compared to the general population as these individuals progress to severe dementia (Cloyd et al., 2006). Pharmaceuticals that attenuate this excess activation, such as the anti-epileptic drug levetiracetem, can dose-dependently improve memory in aged rats (Koh, Haberman, Foti, McCown, & Gallagher, 2010) and reduce both hippocampal hyperactivity and memory impairments in patients with aMCI, as indicated by decreased BOLD activation (Bakker et al., 2012). Together, these studies suggest increased hippocampal activation is not merely a compensatory response but a dysfunctional condition, and a condition that may be permissive for the development of AD. Below, we discuss lifestyle changes that may attenuate this hippocampal hyperexcitability, thereby reducing the risk of developing AD.

Lifestyle Factors that Influence the Risk for Alzheimer's Disease

With aging comes a normal decline in cognition as well as increased susceptibility to developing fatal diseases, such as AD. While the cause of age-related decline may be self-evident (decrease in brain volume, slowing of neurogenesis, loss of synapses, etc.), the mechanisms underlying AD are more complex and may result from numerous machinations that are not well understood. However, because these age-related changes in brain function are so detrimental, and in some cases deadly, much research has focused on potential preventative measures that can be taken in order to slow the progression from excess neuronal activation to cognitive decline or to prevent development altogether. These measures include, but are not limited to exercise and dietary changes. Below we summarize the ways in which changes in exercise habits and dietary choices may prevent or slow cognitive decline through a common mechanism, an increase in brain derived neurotrophic factor (BDNF), a protein responsible for maintaining neuronal growth and survival.

Exercise

Aerobic exercise has many benefits for the aging population, including improved performance on cognitively demanding tasks, as well as reduced risk of neurodegenerative conditions, such as Alzheimer's and Parkinson's disease (Kalaria et al., 2008). The mechanisms by which exercise can serve as a cognitive enhancer have been of interest in the literature. Exercise training aids in the growth of neurons in aged rodents exposed to voluntary wheel running, an effect associated with an increase in BDNF levels (Littlefield, Setti, Priester, & Kohman, 2015). Additionally, BDNF may play a major role in the reduction of hyperexcitability potentially by preventing glutamate release from the presynaptic neuron, while selectively enhancing the firing of postsynaptic glutamate receptors, which promote learning and memory (Kang & Schuman, 1995). Reduction of this neuronal activity is also important for the prevention of seizures, which are more prevalent in AD patients compared to age-matched individuals without memory deficits (Cloyd, et al., 2006). While exercise can also protect against seizure susceptibility (Epps et al., 2013), the mechanisms are unclear. However, there is evidence to suggest that galanin, a peptide involved in a variety of physiological and behavioral functions, acts as an anticonvulsant after aerobic exercise. Rats that undergo chronic wheel running exhibit increased latency to induced motor seizures, which is associated with an increase in galanin mRNA (Epps et al., 2013). Reducing seizure susceptibility through exercise is important, even if seizures are eventually found to be an epiphenomenon rather than directly linked to pathogenesis of AD, because cognitive deterioration is greater after seizure onset (Yamaguchi et al., 1997).

Diet

In addition to exercise, dietary changes, including consumption of omega-3 fatty acids and caloric restriction (CR), are also associated with reduced hippocampal hyperactivity, increased brain volume, and improvement cognitive performance on spatial memory tasks (Bauer et al., 2014). Omega-3 fatty acids, which are important for maintaining cell membranes and normal brain function, and curcumin, an anti-inflammatory molecule, elevate levels of molecules important for synaptic plasticity, including BDNF (Gomez-Pinilla, 2011). Additionally, diets of oil rich fish and certain nuts and seeds, which contain

high levels of the beneficial omega-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA), can elevate levels of BDNF and enhance cognitive function in rodents (Wu, Ying, & Gomez-Pinilla, 2004).

Caloric restriction, or reducing the amount of calories consumed, enhances synaptic plasticity by increasing BDNF levels (Lee, Seroogy, & Mattson, 2002). CR can also reduce hippocampal damage after seizure (Duan et al., 2001), attenuate AD-related pathology and behavioral deficits in AD mouse models (Lu et al., 2016), and improve memory in the elderly (Mogi et al., 1994; Witte, Fobker, Gellner, Knecht, & Floel, 2009). These results suggest that BDNF signaling pathways can be neuroprotective, potentially by reducing neuronal hyperactivity. Other dietary changes, such as the ketogenic diet, can also be protective against cognitive decline in aging. For example, a ketogenic diet, consisting of high fat and low carbohydrate content, can protect against seizures by reducing neuronal excitability (Likhodii et al., 2003; Neal et al., 2009) and is sometimes prescribed by a physician for individuals with epilepsy. This protective effect may be due to the release of ketone bodies, water-soluble molecules produced by the liver that result from a low carbohydrate intake or fasting. Ketone bodies may protect against excessive neuronal excitability, as seen in seizures, by blocking the release of glutamate into the extracellular space (Juge et al., 2010). This is important because increases in extracellular glutamate are associated with memory impairment in rodents (Hunsberger, et al., 2015) and has been linked to aging (Stephens et al., 2014) and AD (Butterfield & Pocernich, 2003).

Conclusions

Though there are many risk factors for AD, hyperexcitability is one that occurs early in the disease process and in some cases is detectable in patients with aMCI. Additionally, hyperactivity of the hippocampal network may be predictive of AD diagnosis and the rate of decline (Miller et al., 2008). While there is potential for hyperexcitability to serve as a future biomarker for AD, there is still a need for additional clinical studies to examine the progression and connections of this excess firing to AD development. In addition, future directions of basic research should aim to better understand the mechanisms underlying the lifestyle changes that reduce hyperexcitability. In this review, we discuss studies that have examined possible ways in which lifestyle changes such as diet and physical activity can protect against hippocampal hyperactivity. Specifically, aerobic exercise and diet modification reduce the risk for hyperexcitability potentially by 1) preventing the release of glutamate from presynaptic neurons, 2) increasing galanin, which is protective against seizures, 3) balancing BDNF levels, which in turn promotes cell growth, and 4) increasing levels of ketone bodies, which block the release of glutamate. As a decline in glutamate transporters and thereby increased extracellular glutamate may be permissive for cognitive decline and the spread of AD-related pathology, interventions aimed at reducing or preventing these changes could promote healthy cognitive aging. Additionally, promotion of cellular growth via increased levels of BDNF is protective against neuronal loss, one of the key hallmarks of AD. In summary, implementation of dietary changes and an aerobic exercise regimen are two attainable lifestyle changes that may prevent or delay the progression from healthy aging to aMCI and AD.

References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, … Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dementia. 2011; 7(3):270–279. DOI: 10.1016/j.jalz.2011.03.008

Bakker, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, … Gallagher M. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron. 2012; 74(3):467–474. DOI: 10.1016/j.neuron.2012.03.023 [PubMed: 22578498]

Barnes CA, McNaughton BL. Physiological compensation for loss of afferent synapses in rat hippocampal granule cells during senescence. Journal of Physiology. 1980; 309:473–485. [PubMed: 7252877]

Bauer I, Hughes M, Rowsell R, Cockerell R, Pipingas A, Crewther S, Crewther D. Omega-3 supplementation improves cognition and modifies brain activation in young adults. Human Psychopharmacology. 2014; 29(2):133–144. DOI: 10.1002/hup.2379 [PubMed: 24470182]

Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. Neurology. 2005; 64(3):501–508. DOI: 10.1212/01.wnl.0000150885.00929.7e [PubMed: 15699382]

Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk for Alzheimer's disease. New England Journal of Medicine. 2000; 343(7):450–456. DOI: 10.1056/nejm200008173430701 [PubMed: 10944562]

Burn KF, Henderson VW, Ames D, Dennerstein L, Szoeke C. Role of grandparenting in postmenopausal women's cognitive health: results from the Women's Healthy Aging Project. Menopause. 2014; 21(10):1069–1074. DOI: 10.1097/gme.0000000000000236 [PubMed: 24714623]

Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Widerhold KH, Haass C, … Garaschuk O. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science. 2008; 321(5896):1686–1689. DOI: 10.1126/science.1162844 [PubMed: 18802001]

Butterfield DA, Pocernich CB. The glutamatergic system and Alzheimer's disease: therapeutic implications. CNS Drugs. 2003; 17(9):641–652. [PubMed: 12828500]

Chai X, Dage JL, Citron M. Constitutive secretion of tau protein by an unconventional mechanism. Neurobiology of Disease. 2012; 48(3):356–366. DOI: 10.1016/j.nbd.2012.05.021 [PubMed: 22668776]

Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, … Tolnay M. Transmission and spreading of tauopathy in transgenic mouse brain. Nature Cell Biology. 2009; 11(7):909–913. DOI: 10.1038/ncb1901 [PubMed: 19503072]

Cloyd J, Hauser W, Towne A, Ramsay R, Mattson R, Gilliam F, Walczak T. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Research. 2006; 68(Suppl 1):S39–48. DOI: 10.1016/j.eplepsyres.2005.07.016 [PubMed: 16384689]

Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, … Sperling RA. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology. 2005; 65(3):404–411. 65/3/404 [pii]. [PubMed: 16087905]

Duan W, Lee J, Guo Z, mattson MP. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. Journal of Molecular Neuroscience. 2001; 16(1):1–12. DOI: 10.1385/jmn:16:1:1 [PubMed: 11345515]

Epps SA, Kahn AB, Holmes PV, Boss-Williams KA, Weiss JM, Weinshenker D. Antidepressant and anticonvulsant effects of exercise in a rat model of epilepsy and depression comorbidity. Epilepsy Behavior. 2013; 29(1):47–52. DOI: 10.1016/j.yebeh.2013.06.023 [PubMed: 23933912]

Foster TC, Barnes CA, Rao G, McNaughton BL. Increase in perforant path quantal size in aged F-344 rats. Neurobiology of Aging. 1991; 12(5):441–448. [PubMed: 1770978]

Gallagher M, Rapp PR. The use of animal models to study the effects of aging on cognition. Annual Review of Psychology. 1997; 48:339–370.

Geinisman Y, deToledo-Morrell L, Morrell F, Persina IS, Rossi M. Age-related loss of axospinous synapses formed by two afferent systems in the rat dentate gyrus as revealed by the unbiased

stereological dissector technique. Hippocampus. 1992; 2(4):437–444. DOI: 10.1002/hipo.450020411 [PubMed: 1308200]

Geinisman Y, Ganeshina O, Yoshida R, Berry RW, Disterhoft JF, Gallagher M. Aging, spatial learning, and total synapse number in the rat CA1 stratum radiatum. Neurobiology of Aging. 2004; 25(3):407–416. DOI: 10.1016/j.neurobiolaging.2003.12.001 [PubMed: 15123345]

Gomez-Pinilla F. Collaborative effects of diet and exercise on cognitive enhancement. Nutrition and Health. 2011; 20(3–4):165–169. [PubMed: 22141190]

Himmelstein DS, Ward SM, Lancia JK, Patterson KR, Binder LI. Tau as a therapeutic target in neurodegenerative disease. Pharmacology and Therapeutics. 2012; 136(1):8–22. DOI: 10.1016/j.pharmthera.2012.07.001 [PubMed: 22790092]

Holth JK, Bomben VC, Reed JG, Inoue T, Younkin L, Younkin SG, … Noebels JL. Tau loss attenuates neuronal network hyperexcitability in mouse and Drosophila genetic models of epilepsy. Journal of Neuroscience. 2013; 33(4):1651–1659. DOI: 10.1523/jneurosci.3191-12.2013 [PubMed: 23345237]

Hunsberger HC, Rudy CC, Batten SR, Gerhardt GA, Reed MN. P301L tau expression affects glutamate release and clearance in the hippocampal trisynaptic pathway. Journal of Neurochemistry. 2015; 132(2):169–182. DOI: 10.1111/jnc.12967 [PubMed: 25319522]

Hunsberger HC, Weitzner DS, Rudy CC, Hickman JE, Libell EM, Speer RR, … Reed MN. Riluzole rescues glutamate alterations, cognitive deficits, and tau pathology associated with P301L tau expression. Journal of Neurochemistry. 2015; 135(2):381–394. DOI: 10.1111/jnc.13230 [PubMed: 26146790]

Ji J, Maren S. Differential roles for hippocampal areas CA1 and CA3 in the contextual encoding and retrieval of extinguished fear. Learn and Memory. 2008; 15(4):244–251. DOI: 10.1101/lm.794808

Juge N, Gray JA, Omote H, Miyaji T, Inoue T, Hara C, … Moriyama Y. Metabolic control of vesicular glutamate transport and release. Neuron. 2010; 68(1):99–112. DOI: 10.1016/j.neuron.2010.09.002 [PubMed: 20920794]

Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, … Antuono P. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology. 2008; 7(9):812–826. DOI: 10.1016/s1474-4422(08)70169-8 [PubMed: 18667359]

Kalus P, Slotboom J, Gallinat J, Mahlberg R, Cattapan-Ludewig K, Wiest R, … Kiefer C. Examining the gateway to the limbic system with diffusion tensor imaging: The perforant pathway in dementia. Neuroimage. 2006; 30(3):713–720. DOI: 10.1016/j.neuroimage.2005.10.035 [PubMed: 16337815]

Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, … Malinow R. APP processing and synaptic function. Neuron. 2003; 37(6):925–937. [PubMed: 12670422]

Kang H, Schuman EM. Long-lasting neutrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science. 1995; 267(5204):1658–1662. DOI: 10.1126/science.7886457 [PubMed: 7886457]

Koh MT, Haberman RP, Foti S, McCown TJ, Gallagher M. Treatment strategies targeting excess hippocampal activity benefit aged rats with cognitive impairment. Neuropsychopharmacology. 2010; 35(4):1016–1025. DOI: 10.1038/npp.2009.207 [PubMed: 20032967]

Lee J, Seroogy KB, Mattson MP. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. Journal of Neurochemistry. 2002; 80(3):539–547. [PubMed: 11905999]

Likhodii SS, Serbanescu I, Cortez MA, Murphy P, Snead OC 3rd, Burnham WM. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. Annals of Neurology. 2003; 54(2):219–226. DOI: 10.1002/ana.10634 [PubMed: 12891674]

Littlefield AM, Setti SE, Priester C, Kohman RA. Voluntary exercise attenuates LPS-induced reductions in neurogenesis and increases microglia expression of a proneurogenic phenotype in aged mice. Journal of Neuroinflammation. 2015; 12:138–150. DOI: 10.1186/s12974-015-0362-0 [PubMed: 26224094]

Lu Y, Zhong C, Wang L, Wei P, He W, Huang K, … Wang L. Optogenetic dissection of ictal propagation in the hippocampal-entorhinal cortex structures. Nature Communications. 2016; 7:10962.doi: 10.1038/ncomms10962

Mackenzie IR, Miller LA. Senile plaques in temporal lobe epilepsy. Acta Neuropathologica. 1994; 87(5):504–510. [PubMed: 8059603]

Mauri M, Sinforiani E, Zucchella C, Cuzzoni MG, Bono G. Progression to dementia in a population with amnestic mild cognitive impairment: clinical variables associated with conversion. Functional Neurology. 2012; 27(1):49–54. [PubMed: 22687167]

Miller SL, Fenstermacher E, Bates J, Blacker D, Sperling RA, Dickerson BC. Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. Journal of Neurology, Neurosurgery, and Psychiatry. 2008; 79(6):630–635. DOI: 10.1136/jnnp.2007.124149

Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M, Nagatsu T. Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. Neuroscience Letters. 1994; 180(2):147–150. [PubMed: 7700568]

Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, … Cross JH. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia. 2009; 50(5):1109–1117. DOI: 10.1111/j.1528-1167.2008.01870.x [PubMed: 19054400]

Nicholson DA, Yoshida R, Berry RW, Gallagher M, Geinisman Y. Reduction in size of perforated postsynaptic densities in hippocampal axospinous synapses and age-related spatial learning impairments. Journal of Neuroscience. 2004; 24(35):7648–7653. DOI: 10.1523/JNEUROSCI.1725-04.2004 [PubMed: 15342731]

Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nature Reviews Neuroscience. 2006; 7(9):697–709. DOI: 10.1038/nrn1970 [PubMed: 16924259]

Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine. 2004; 256(3):183–194. DOI: 10.1111/j.1365-2796.2004.01388.x [PubMed: 15324362]

Quiroz, Yakeel T., Budson, Andrew E., Celone, K., Ruiz, A., Newmark, R., Castrillón, G., … Stern, CE. Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease. Annals of Neurology. 2010; 68(6):865–875. DOI: 10.1002/ana.22105 [PubMed: 21194156]

Rapp PR, Gallagher M. Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proceedings of the National Academy of Sciences U S A. 1996; 93(18):9926–9930.

Rapp PR, Stack EC, Gallagher M. Morphometric studies of the aged hippocampus: I. Volumetric analysis in behaviorally characterized rats. Journal of Comparitive Neurology. 1999; 403(4):459–470. DOI: 10.1002/(SICI)1096-9861(19990125)403:4<459::AID-CNE3>3.0.CO;2-9

Rowe JW, Kahn RL. Human aging: usual and successful. Science. 1987; 237(4811):143–149. [PubMed: 3299702]

Rowe JW, Kahn RL. Successful aging. Gerontologist. 1997; 37(4):433–440. [PubMed: 9279031]

Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiology of Aging. 2006; 27(10):1372–1384. DOI: 10.1016/j.neurobiolaging.2005.09.012 [PubMed: 16289476]

Small BJ, Dixon RA, McArdle JJ. Tracking cognition-health changes from 55 to 95 years of age. The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences. 2011; 66(Suppl 1):i153–161. DOI: 10.1093/geronb/gbq093

Small SA, Stern Y, Tang M, Mayeux R. Selective decline in memory function among healthy elderly. Neurology. 1999; 52(7):1392–1396. [PubMed: 10227623]

Smith TD, Adams MM, Gallagher M, Morrison JH, Rapp PR. Circuit-specific alterations in hippocampal synaptophysin immunoreactivity predict spatial learning impairment in aged rats. Journal of Neuroscience. 2000; 20(17):6587–6593. [PubMed: 10964964]

Sperling. Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease. Annals of the New York Academy of Sciences. 2007; 1097:146–155. DOI: 10.1196/annals.1379.009 [PubMed: 17413017]

Sperling, Dickerson BC, Pihlajamaki M, Vannini P, LaViolette PS, Vitolo OV, … Johnson KA. Functional alterations in memory networks in early Alzheimer's disease. Neuromolecular Medicine. 2010; 12(1):27–43. DOI: 10.1007/s12017-009-8109-7 [PubMed: 20069392]

Stephens ML, Williamson A, Deel ME, Bensalem-Owen M, Davis VA, Slevin J, … Gerhardt GA. Tonic glutamate in CA1 of aging rats correlates with phasic glutamate dysregulation during seizure. Epilepsia. 2014; 55(11):1817–1825. DOI: 10.1111/epi.12797 [PubMed: 25266171]

Thibault O, Landfield PW. Increase in single L-type calcium channels in hippocampal neurons during aging. Science. 1996; 272(5264):1017–1020. [PubMed: 8638124]

Verhaeghen P, Vandenbroucke A, Dierckx V. Growing slower and less accurate: adult age differences in time-accuracy functions for recall and recognition from episodic memory. Experimental Aging Research. 1998; 24(1):3–19. DOI: 10.1080/036107398244337 [PubMed: 9459060]

West MJ, Kawas CH, Martin LJ, Troncoso JC. The CA1 Region of the Human Hippocampus Is a Hot Spot in Alzheimer's Disease. Annals of the New York Academy of Sciences. 2000; 908(1):255–259. DOI: 10.1111/j.1749-6632.2000.tb06652.x [PubMed: 10911964]

Wilson IA, Gallagher M, Eichenbaum H, Tanila H. Neurocognitive aging: prior memories hinder new hippocampal encoding. Trends in Neurosciences. 2006; 29(12):662–670. S0166-2236(06)00224-4 [pii]. [PubMed: 17046075]

Wilson IA, Ikonen S, Gallagher M, Eichenbaum H, Tanila H. Age-associated alterations of hippocampal place cells are subregion specific. Journal of Neuroscience. 2005; 25(29):6877–6886. DOI: 10.1523/jneurosci.1744-05.2005 [PubMed: 16033897]

Witte AV, Fobker M, Gellner R, Knecht S, Floel A. Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences U S A. 2009; 106(4):1255–1260. DOI: 10.1073/pnas.0808587106

Wu HSA, Bastiille IM, Rodriguez GA, Mrejeru A, Rilett K, … Duff KE. Neuronal activity enhances tau propagation and tau pathology in vivo. Nature Neuroscience. 2016; 19(8):1085–1092. DOI: 10.1038/nn.4328 [PubMed: 27322420]

Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. Journal of Neurotrauma. 2004; 21(10):1457–1467. DOI: 10.1089/neu.2004.21.1457 [PubMed: 15672635]

Yamaguchi S, Meguro K, Itoh M, Hayasaka C, Shimada M, Yamazaki H, Yamadori A. Decreased cortical glucose metabolism correlates with hippocampal atrophy in Alzheimer's disease as shown by MRI and PET. Journal of Neurology, Neurosurgery, and Psychiatry. 1997; 62(6):596–600.

Yassa MA, Stark SM, Bakker A, Albert MS, Gallagher M, Stark CEL. High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment. Neuroimage. 2010; 51(3):1242–1252. DOI: 10.1016/j.neuroimage.2010.03.040 [PubMed: 20338246]

Yuan P, Grutzendler J. Attenuation of β-Amyloid deposition and neurotoxicity by chemogenetic modulation of neural activity. Journal of Neuroscience. 2016; 36(2):632–641. DOI: 10.1523/jneurosci.2531-15.2016 [PubMed: 26758850]

Public significance statement

Every 66 seconds someone in the United States is diagnosed with Alzheimer's disease and aging represents the greatest risk factor as 5.2 million people with the disease are 65 and older. Because of the lack of disease-modifying therapeutics available, it is important to educate the aging public about possible lifestyle changes that can reduce the risk for AD. Importantly, prior to late stage pathology (i.e. neuronal loss), individuals at risk for AD often exhibit excess firing, or hyperexcitability, in the hippocampal memory circuit. This excess firing could provide a therapeutic target for early intervention. This review aims to summarize the beneficial effects of exercise and diet on the aging brain and hyperexcitability, in animal models and humans.