Aging, depression and dementia: The inflammatory process

Maria del Pilar Carrera-González[1,2,A,C,D,F], Vanesa Cantón-Habas[1,A,B,D,F], Manuel Rich-Ruiz[1,3,A,D,F]

[1] Department of Nursing, Pharmacology and Physiotherapy, Faculty of Medicine and Nursing, University of Córdoba, Maimonides Institute of Biomedical Research of Córdoba (IMIBIC), Reina Sofia University Hospital, Spain
[2] Experimental and Clinical Physiopathology Research Group CTS-1039, Department of Health Sciences, Faculty of Health Sciences, University of Jaén, Spain
[3] Centro de Investigación Biomédica en Red Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2022;31(5):469–473

Address for correspondence
Vanesa Cantón-Habas
E-mail: n92cahav@uco.es

Funding sources
None declared

Conflict of interest
None declared

Received on January 11, 2022
Reviewed on May 5, 2022
Accepted on May 9, 2022

Published online on May 12, 2022

Abstract

Population aging that we are currently witnessing has led to an increase in chronic age-related diseases, with dementia and depression being highlighted. Several studies establish a relationship between dementia and depression, although without defining the mechanism that links them. Some studies establish depression as a prodrome of dementia, while others consider it a risk factor for dementia. One of the events that is common between dementia and depression is the inflammatory process. In depression, an increase in inflammatory cytokines has been described, which would justify the serotonergic, noradrenergic and dopaminergic dysfunction of depression. This increase entails altering the activity of the hypothalamic–pituitary–adrenal (HPA) axis, thus linking chronic stress to depression, and the consequent weakening of the blood–brain barrier (BBB), facilitating the passage of pro-inflammatory factors. In this line, recent studies suggest that inflammation could direct the development of the pathogenesis of dementia, particularly Alzheimer's disease (AD), once the pathology has begun. In addition, sustained exposure to pro-inflammatory cytokines characteristic of aging could alter the microglial function and the expression of enzymes responsible for amyloid peptide metabolism, aggravating the pathological process. In view of the involvement of the inflammatory process in both conditions, it is necessary to investigate the events which both conditions share, such as the inflammatory process, to know the involvement of the inflammatory process in both dementia and depression, possible relationship of these 2 conditions, and consequently, to establish the clinical approach to both conditions.

Key words: dementia, Alzheimer's disease, inflammation, depression

Cite as
Carrera-González MP, Cantón-Habas V, Rich-Ruiz M. Aging, depression and dementia: The inflammatory process. *Adv Clin Exp Med*. 2022;31(5):469–473. doi:10.17219/acem/149897

DOI
10.17219/acem/149897

Introduction

Aging is an important contributing factor in the onset and development of various neurological disorders, such as cognitive impairment or dementia. However, dementia is not a natural or inevitable consequence of aging. In fact, other clinical conditions, in this case pathological processes, have been described as being associated with an increased risk of cognitive impairment/dementia, including depression, hypertension, diabetes, hypercholesterolemia, and obesity.[1]

During aging, the brain undergoes a progressive decline in energy use,[2] and according to the free radical theory of aging, free radicals and related oxidants, both environmental and derived from cellular metabolism, would be the main cause of cellular damage, also due to their accumulation over time. Thus, the changes in energy metabolism associated with aging would be responsible for the associated functional and structural cellular problems. In other words, during the last third of our lives, our brain accumulates structural and functional damage that reduces our adaptive homeostatic capacity,[3] which possibly makes it more susceptible to harmful stimuli.

In this context, one of the most affected cell types that are susceptible to such lesions are neurons, as well as different types of glial cells. Thus, in the aging brain, there is an increase in microglia, associated with a decrease in their function. Indeed, with aging, they lose their flexibility to move, which decreases their efficiency in defending the central nervous system (CNS),[4] as well as their ability to block exogenous invasion or endogenous metabolites such as β-amyloid peptides.[5,6] In this regard, one of the most relevant facts about aged microglia is the elevated expression of pro-inflammatory molecules, such as MHC-II, CD16/32 and CD86. Even the secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6), and interleukin-1β (IL-1β), increases significantly in response to harmful stimuli.[7]

A possible interpretation of this shift from a microglial profile to an inflammatory or sensitization profile is based on 3 factors: 1) the increase in inflammatory markers and mediators; 2) the decrease in threshold and activation time; and 3) the increase in response and inflammation after this activation.[8,9]

In this regard, Chung et al.[10] established how age increases this sensitized state[10,11] – microglia develop an "alert, primed" phenotype, which contributes to the increased inflammatory state of the aging brain, as indicated by the increased inflammatory mediators and altered microglia phenotype (that occurs with age/aging). In this situation, results obtained in aged rodents following immune challenge, i.e., infection, show depressive-like behavioral complications and cognitive deficits.[12]

In the case of astrocytes, during aging, they also change their secretory phenotype to a pro-inflammatory phenotype under chronic stress. Even the aforementioned oxidative stress could induce astrocytes to secrete pro-inflammatory factors, such as IL-6, monocyte chemoattractant protein (MCP)-1 and metalloproteinase (MMP)-9, contributing to the inflammation in the senile brain, and altering the integrity of the blood–brain barrier (BBB).[13]

At this point, with the disruption of BBB integrity, it is important to note the enormous importance of the BBB in maintaining metabolic homeostasis in the CNS[14] and, consequently, the increased exposure of brain tissue to toxic molecules or inflammatory signals that circulate in the blood when BBB is disrupted.

Conditions associated with impaired BBB integrity include oxidative stress,[15] the presence of advanced glycation end products (AGEs) and their receptor (RAGE),[16] increased production of pro-inflammatory cytokines,[17] and vascular dysfunction, as well as chronic stress, depression or dementia.[18,19]

Having described the role of aging as a contributing factor in various neurological disorders, such as cognitive impairment or dementia, it is necessary to understand its relationship to various clinical situations or pathological processes, including depression and dementia.

In the case of depression and dementia, we must bear in mind that there is no single mechanism that explains both pathologies, although similar neurobiological changes or even a similar pattern of neuronal damage have been described for both conditions, thus deepening our understanding of a complex relationship between both pathologies. Cognitive changes are common in the context of depression, and mood-altering symptoms of this condition often accompany cognitive disorders of dementia.[20–23] Our research group has found that the presence of depression increases the risk of dementia by 16%. However, we have also noted factors that condition this relationship, such as age or the presence of other diseases, for example, type II diabetes.[24]

Both dementia and depression present biological mechanisms that link them, such as vascular disease, atrophy of the hippocampus, a larger deposit of β-amyloid plaques, and inflammatory alterations.[25,26] In this sense, according to the latest studies, and as we have explained throughout this section, the inflammatory process is an important key effector in both processes.[27,28]

This common point between depression and dementia is a promising research focus with clear clinical applicability for addressing both conditions.

Depression and inflammation

Although the main approach to depression is based on the historically accepted "monoamine depletion hypothesis,"[29,30] this hypothesis is not sufficient to explain the depressive disorder; especially in the last 20 years,

several studies are pointing to the involvement of the inflammatory process in the disorder. This fact would justify the serotonergic, noradrenergic and dopaminergic dysfunction[31,32] inherent to depression; thus, we can speak of an "inflammatory hypothesis". Authors such as Liu et al.[28] link depression to the inflammatory process through increased levels of pro-inflammatory cytokines such as TNF-α and IL-6, decreased circulating levels of IL-1β and IL-8 in blood and cerebrospinal fluid,[33] and increased corticotropin-releasing hormone levels; the latter results in an increase in the activity of the hypothalamic–pituitary–adrenal (HPA) axis, which in turn introduces stress into the process.

Chronic stress induces the weakening of BBB (described in animal experiments) and the consequent passage of circulating pro-inflammatory mediators.[34] Therefore, authors such as Dudek et al.[34] describe how stress-induced alteration of BBB permeability is linked to the inflammation of endothelium and involvement of tight junctions.

Furthermore, as noted above, increased IL-6 and C-reactive protein (CRP) levels could predict the development of depressive symptoms.[35,36] Both molecules are predictive, indicating that inflammation precedes depression, but are also associated with cognitive symptoms of depression.[37]

Therefore, the passage of peripheral myeloid cells into the brain in depressive processes would constitute an important clue supporting the existence of a central inflammatory response in depression that would be mainly driven by peripheral inflammatory events.[38]

The verification of this inflammatory response in depression suggests the possible existence of other causal biological pathways/processes in depressive processes[39] and opens the door to the improvement of the response of current antidepressant therapies since, as reported by authors such as Miller and Raison,[31] 30–50% of depressed people do not respond to commonly prescribed antidepressant treatments and only 30% of patients remit.

Dementia and inflammation

In recent years, the inflammatory process has become important in the neurodegenerative pathology of Alzheimer's disease (AD). Inflammation can "conduct" the pathogenesis of AD once the pathological process has begun.[40,41] Even the studies conducted by Lee et al.[42] highlight the ability of pro-inflammatory microglia activation to aggravate and initiate the pathological process. At present, AD is considered to be a tauopathy initiated by β-amyloid peptide accompanied by neuroinflammation, thus connecting the 3 pathophysiological and anatomopathological events typical of AD.[42–45]

In elderly population, age affects the microglial function and is associated with an alteration in amyloid metabolism, aggravated by sustained exposure to pro-inflammatory cytokines, such as TNF-α, and the whole process can inhibit microglial function.[46]

In this regard, the disruption of BBB by inflammatory mediators during the progression of AD has been described. In the BBB, the neurovascular unit (NVU) is responsible for neurovascular coupling, i.e., the interaction of neuronal (neurons and glia) and vascular tissues (endothelial cells, pericytes and adventitial cells).[14] Several authors show how this coupling is impaired in AD,[47] suggesting the important role of NVU in the progression of cognitive impairment. Other situations in which this coupling is also altered, and which are also related to AD, are hypertension[48] and ischemic stroke[49] (postmortem studies emphasize the important role of vascular pathology in a significant percentage of AD patients).[50]

In this way, aging appears to be an aggravating factor in the development of neurodegenerative diseases such as AD. In addition, and based on the studies reviewed, aging also contributes to an increase in vulnerability to certain conditions such as depression,[51,52] through sustained activation of pro-inflammatory signals (Fig. 1).

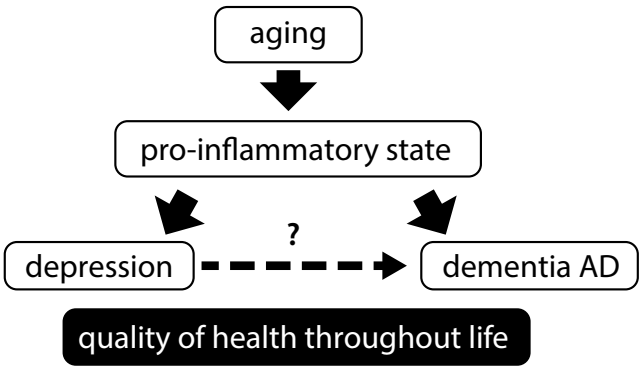

Fig. 1. Scheme linking aging, depression and dementia

AD – Alzheimer's disease.

Given this knowledge, it is necessary to develop new research lines in order to establish the link between depression and dementia; and, based on what is known, to establish strategies of modulation of pro-inflammatory states that could modify the prevalence of neurodegenerative diseases such as dementia.

ORCID iDs

Maria del Pilar Carrera-González https://orcid.org/0000-0001-6575-8240
Vanesa Cantón-Habas https://orcid.org/0000-0002-3928-0092
Manuel Rich-Ruiz https://orcid.org/0000-0003-3317-267X

References

1. Chowdhary N, Barbui C, Anstey KJ, et al. Reducing the risk of cognitive decline and dementia: WHO recommendations. *Front Neurol*. 2021;12:765584. doi:10.3389/fneur.2021.765584
2. Hoyer S. The young-adult and normally aged brain – its blood flow and oxidative metabolism: A review. Part I. *Arch Gerontol Geriatr*. 1982;1(2):101–116. doi:10.1016/0167-4943(82)90010-3
3. Pomatto LCD, Davies KJA. Adaptive homeostasis and the free radical theory of ageing. *Free Radic Biol Med*. 2018;124:420–430. doi:10.1016/j.freeradbiomed.2018.06.016

4. Lee S, Wu Y, Shi XQ, Zhang J. Characteristics of spinal microglia in aged and obese mice: Potential contributions to impaired sensory behavior. *Immun Ageing*. 2015;12:22. doi:10.1186/s12979-015-0049-5
5. Schutze S, Ribes S, Kaufmann A, et al. Higher mortality and impaired elimination of bacteria in aged mice after intracerebral infection with *E. coli* are associated with an age-related decline of microglia and macrophage functions. *Oncotarget*. 2014;5(24):12573–12592. doi:10.18632/oncotarget.2709
6. Babcock AA, Ilkjaer L, Clausen BH, et al. Cytokine-producing microglia have an altered beta-amyloid load in aged APP/PS1 Tg mice. *Brain Behav Immun*. 2015;48:86–101. doi:10.1016/j.bbi.2015.03.006
7. Lourbopoulos A, Erturk A, Hellal F. Microglia in action: How aging and injury can change the brain's guardians. *Front Cell Neurosci*. 2015;9:54. doi:10.3389/fncel.2015.00054
8. Henry CJ, Huang Y, Wynne AM, Godbout JP. Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. *Brain Behav Immun*. 2009;23(3):309–317. doi:10.1016/j.bbi.2008.09.002
9. Norden DM, Godbout JP. Review. Microglia of the aged brain: Primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol*. 2013;39(1):19–34. doi:10.1111/j.1365-2990.2012.01306.x
10. Chung HY, Cesari M, Anton S, et al. Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Res Rev*. 2009;8(1):18–30. doi:10.1016/j.arr.2008.07.002
11. Schuitemaker A, van der Doef TF, Boellaard R, et al. Microglial activation in healthy aging. *Neurobiol Aging*. 2012;33(6):1067–1072. doi:10.1016/j.neurobiolaging.2010.09.016
12. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: The devil is in the details. *J Neurochem*. 2016;139(Suppl 2):136–153. doi:10.1111/jnc.13607
13. Salminen A, Ojala J, Kaarniranta K, Haapasalo A, Hiltunen M, Soininen H. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. *Eur J Neurosci*. 2011;34(1):3–11. doi:10.1111/j.1460-9568.2011.07738.x
14. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and dysfunction of the blood–brain barrier. *Cell*. 2015;163(5):1064–1078. doi:10.1016/j.cell.2015.10.067
15. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. *Biomed Rep*. 2016;4(5):519–522. doi:10.3892/br.2016.630
16. Sasaki N, Fukatsu R, Tsuzuki K, et al. Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *Am J Pathol*. 1998;153(4):1149–1155. doi:10.1016/S0002-9440(10)65659-3
17. Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010;68(10):930–941. doi:10.1016/j.biopsych.2010.06.012
18. Nehra G, Bauer B, Hartz AMS. Blood–brain barrier leakage in Alzheimer's disease: From discovery to clinical relevance. *Pharmacol Ther*. 2022;234:108119. doi:10.1016/j.pharmthera.2022.108119
19. Tanaka M, Vecsei L. Editorial of Special Issue "Crosstalk between depression, anxiety, and dementia: Comorbidity in behavioral neurology and neuropsychiatry". *Biomedicines*. 2021;9(5):517. doi:10.3390/biomedicines9050517
20. Gatchel JR, Rabin JS, Buckley RF, et al. Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Netw Open*. 2019;2(8):e198964. doi:10.1001/jamanetworkopen.2019.8964
21. Battaglia S. Neurobiological advances of learned fear in humans. *Adv Clin Exp Med*. 2022;31(3):217–221. doi:10.17219/acem/146756
22. Torok N, Tanaka M, Vecsei L. Searching for peripheral biomarkers in neurodegenerative diseases: The tryptophan–kynurenine metabolic pathway. *Int J Mol Sci*. 2020;21(24):9338. doi:10.3390/ijms21249338
23. Battaglia S, Harrison BJ, Fullana MA. Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions. *Mol Psychiatry*. 2022;27(2):784–786. doi:10.1038/s41380-021-01326-4
24. Canton-Habas V, Rich-Ruiz M, Romero-Saldana M, Carrera-Gonzalez MDP. Depression as a risk factor for dementia and Alzheimer's disease. *Biomedicines*. 2020;8(11):457. doi:10.3390/biomedicines8110457
25. Sacuiu S, Insel PS, Mueller S, et al. Chronic depressive symptomatology in mild cognitive impairment is associated with frontal atrophy rate which hastens conversion to Alzheimer dementia. *Am J Geriatr Psychiatry*. 2016;24(2):126–135. doi:10.1016/j.jagp.2015.03.006
26. Steffens DC. Late-life depression and the prodromes of dementia. *JAMA Psychiatry*. 2017;74(7):673–674. doi:10.1001/jamapsychiatry.2017.0658
27. Finneran DJ, Nash KR. Neuroinflammation and fractalkine signaling in Alzheimer's disease. *J Neuroinflamm*. 2019;16(1):30. doi:10.1186/s12974-019-1412-9
28. Liu CH, Zhang GZ, Li B, et al. Role of inflammation in depression relapse. *J Neuroinflamm*. 2019;16(1):90. doi:10.1186/s12974-019-1475-7
29. Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: Neuroplasticity and epigenetic changes in a transgenic mouse model of depression. *Philos Trans R Soc Lond B Biol Sci*. 2012;367(1601):2485–2494. doi:10.1098/rstb.2012.0212
30. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: A review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;53:23–34. doi:10.1016/j.pnpbp.2014.01.013
31. Miller AH, Raison CL. The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22–34. doi:10.1038/nri.2015.5
32. Song C, Wang H. Cytokines mediated inflammation and decreased neurogenesis in animal models of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(3):760–768. doi:10.1016/j.pnpbp.2010.06.020
33. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: Depression fans the flames and feasts on the heat. *Am J Psychiatry*. 2015;172(11):1075–1091. doi:10.1176/appi.ajp.2015.15020152
34. Dudek KA, Dion-Albert L, Lebel M, et al. Molecular adaptations of the blood–brain barrier promote stress resilience vs. depression. *Proc Natl Acad Sci U S A*. 2020;117(6):3326–3336. doi:10.1073/pnas.1914655117
35. Jokela M, Virtanen M, Batty GD, Kivimaki M. Inflammation and specific symptoms of depression. *JAMA Psychiatry*. 2016;73(1):87–88. doi:10.1001/jamapsychiatry.2015.1977
36. Smith KJ, Au B, Ollis L, Schmitz N. The association between C-reactive protein, interleukin-6 and depression among older adults in the community: A systematic review and meta-analysis. *Exp Gerontol*. 2018;102:109–132. doi:10.1016/j.exger.2017.12.005
37. Gimeno D, Kivimaki M, Brunner EJ, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med*. 2009;39(3):413–423. doi:10.1017/S0033291708003723
38. Krugel U, Fischer J, Radicke S, Sack U, Himmerich H. Antidepressant effects of TNF-alpha blockade in an animal model of depression. *J Psychiatr Res*. 2013;47(5):611–616. doi:10.1016/j.jpsychires.2013.01.007
39. Carvalho LA, Torre JP, Papadopoulos AS, et al. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. *J Affect Disord*. 2013;148(1):136–140. doi:10.1016/j.jad.2012.10.036
40. Metcalfe MJ, Figueiredo-Pereira ME. Relationship between tau pathology and neuroinflammation in Alzheimer's disease. *Mt Sinai J Med*. 2010;77(1):50–58. doi:10.1002/msj.20163
41. Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G. Neuroinflammation pathways: A general review. *Int J Neurosci*. 2017;127(7):624–633. doi:10.1080/00207454.2016.1212854
42. Lee DC, Rizer J, Selenica ML, et al. LPS-induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. *J Neuroinflamm*. 2010;7:56. doi:10.1186/1742-2094-7-56
43. Herber DL, Mercer M, Roth LM, et al. Microglial activation is required for Abeta clearance after intracranial injection of lipopolysaccharide in APP transgenic mice. *J Neuroimmune Pharmacol*. 2007;2(2):222–231. doi:10.1007/s11481-007-9069-z
44. Shaftel SS, Kyrkanides S, Olschowka JA, Miller JN, Johnson RE, O'Banion MK. Sustained hippocampal IL-1 beta overexpression mediates chronic neuroinflammation and ameliorates Alzheimer plaque pathology. *J Clin Invest*. 2007;117(6):1595–1604. doi:10.1172/JCI31450
45. Lee S, Varvel NH, Konerth ME, et al. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. *Am J Pathol*. 2010;177(5):2549–2562. doi:10.2353/ajpath.2010.100265
46. Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci*. 2008;28(33):8354–8360. doi:10.1523/JNEUROSCI.0616-08.2008

47. Viticchi G, Falsetti L, Vernieri F, et al. Apolipoprotein E genotype and cerebrovascular alterations can influence conversion to dementia in patients with mild cognitive impairment. *J Alzheimers Dis*. 2014;41(2):401–410. doi:10.3233/JAD-132480
48. Presa JL, Saravia F, Bagi Z, Filosa JA. Vasculo-neuronal coupling and neurovascular coupling at the neurovascular unit: Impact of hypertension. *Front Physiol*. 2020;11:584135. doi:10.3389/fphys.2020.584135
49. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283(16):2122–2127. doi:10.1001/jama.283.16.2122
50. Falsetti L, Viticchi G, Zaccone V, et al. Shared molecular mechanisms among Alzheimer's disease, neurovascular unit dysfunction and vascular risk factors: A narrative review. *Biomedicines*. 2022;10(2):439. doi:10.3390/biomedicines10020439
51. Sibille E. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. *Dialogues Clin Neurosci*. 2013;15(1):53–65. doi:10.31887/DCNS.2013.15.1/esibille
52. Bartsch T, Wulff P. The hippocampus in aging and disease: From plasticity to vulnerability. *Neuroscience*. 2015;309:1–16. doi:10.1016/j.neuroscience.2015.07.084