References

Aleithe, S., Blietz, A., Mages, B., Hobusch, C., Härtig, W., & Michalski, D. (2019). Transcriptional Response and Morphological Features of the Neurovascular Unit and Associated Extracellular Matrix After Experimental Stroke in Mice. *Molecular Neurobiology*, 1–20.

Alzheimer Association. (2015). Alzheimer's Association Report 2015 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *11*(3), 332–384.

Angelucci, F., Spalletta, G., Iulio, F., Ciaramella, A., Salani, F., Varsi, A. E., … Bossu, P. (2010). Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) Patients are Characterized by Increased BDNF Serum Levels. *Current Alzheimer Research*, *7*(1), 15–20.

Apostolova, L. G. (2016). Alzheimer Disease. *Continuum: Lifelong Learning in Neurology*, *22*(2 Dementia), 419.

Aravin, A. A., Sachidanandam, R., Girard, A., Fejes-toth, K., & Hannon, G. J. (2007). Developmentally regulated piRNA clusters implicate MILI in transposon control. *Science*, *316*(5825), 744–747.

Baddeley, A. (1992). Working Memory : The Interface between Memory and Cognition. *Journal of Cognitive Neuroscience*, *4*(3), 281–288.

Barage, S. H., & Sonawane, K. D. (2015). Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. *Neuropeptides*, *52*, 1–18.

Beauquis, J., Pavía, P., Pomilio, C., Vinuesa, A., Podlutskaya, N., Galvan, V., & Saravia, F. (2013). Environmental enrichment prevents astroglial pathological changes in the hippocampus of APP transgenic mice, model of Alzheimer's disease. *Experimental Neurology*, *239*, 28–37.

Bell-temin, H., Culver-cochran, A. E., Chaput, D., Carlson, C. M., Kuehl, M., Burkhardt, B. R., … Stevens Jr., S. M. (2015). Novel Molecular Insights into Classical and Alternative Activation States of Microglia as Revealed by Stable Isotope Labeling by Amino Acids in Cell Culture (SILAC)-based Proteomics. *Molecular & Cellular Proteomics*, *14*(12), 3173–3184.

Berardi, N., Braschi, C., Capsoni, S., Cattaneo, A., & Maffei, L. (2007). Environmental Enrichment Delays the Onset of Memory Deficits and Reduces Neuropathological Hallmarks in a Mouse Model of Alzheimer-Like Neurodegeneration. *Journal of Alzheimer's Disease*, *11*(3), 359–370.

Bhat, R. K., Rudnick, W., Antony, J. M., Maingat, F., Ellestad, K. K., & Power, C. (2014). Human Endogenous Retrovirus-K(II) Envelope Induction Protects Neurons during HIV/AIDS. *PLoS One*, *9*(7), e97984.

Bherer, L., Erickson, K. I., & Liu-ambrose, T. (2013). A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults. *Journal of Aging Research*, *2013*.

Binder, D. K. (2004). The Role of BDNF in Epilepsy and Other Diseases of the Mature Nervous System. In *Recent Advances in Epilepsy* (pp. 34–56). Boston: Springer.

Birks, J. (2006). Cholinesterase inhibitors for Alzheimer's disease (Review). *Cochrane Database of Systematic Reviews*, (1).

Brion, J., Anderton, B. H., Authelet, M., Dayanandan, R., Leroy, K., Lovestone, S., … Tremp, G. (2001). Neurofibrillary tangles and tau phosphorylation. In *Biochemical society symposia* (Vol. 67, pp. 81–88). Portland Press Limited.

Budni, J., Bellettini-santos, T., Mina, F., Garcez, M. L., & Zugno, A. I. (2015). The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. *Aging and Disease*, *6*(5), 331.

Bunsey, M., & Eichenbaum, H. (1996). Conservation of hippocampal memory function in rats and humans. *Nature*, *379*(6562), 255–257.

Butterfield, D. A., & Swomley, A. M. (2013). Amyloid β-peptide (1–42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression. *Antioxidants & Redox Signaling*, *19*(8), 823–835.

Cai, Z., Hussain, M. D., & Yan, L. (2014). Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease. *International Journal of Neuroscience*, *124*(5), 307–321.

Cao, H., Wang, L., Chen, B., Zheng, P., He, Y., Ding, Y., … Li, Y. (2016). Dna Demethylation Upregulated nrf2 expression in alzheimer ' s Disease cellular Model. *Frontiers in Aging Neuroscience*, *7*, 244.

Carrillo-mora, P., Luna, R., & Colín-barenque, L. (2014). Amyloid Beta : Multiple Mechanisms of Toxicity and Only Some Protective Effects ? *Oxidative Medicine and Cellular Longevity*, *2014*.

Cheignon, C., Tomas, M., Bonnefont-Rousselot, D., Faller, P., Hureau, C., & Collin, F. (2018). Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biology*, *14*, 450–464.

Cherry, J. D., Olschowka, J. A., & O'Banion, M. K. (2014). Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. *Journal of Neuroinflammation*, *11*(1), 98.

Cioni, G., Inguaggiato, E., & Sgandurra, G. (2016). Early intervention in neurodevelopmental disorders: underlying neural mechanisms. *Developmental Medicine & Child Neurology*, *58*, 61–66.

Congdon, E. E., & Sigurdsson, E. M. (2019). Tau-targeting therapies for Alzheimer disease. *Nature Reviews Neurology*, *14*(7), 399.

Cordeira, J. W., Frank, L., Sena-esteves, M., Pothos, E. N., & Rios, M. (2010). Brain-derived neurotrophic factor regulates hedonic feeding by acting on the mesolimbic dopamine system. *Journal of Neuroinflammation*, *30*(7), 2533–2541.

Cordell, C. B., Borson, S., Boustani, M., Chodosh, J., Reuben, D., Verghese, J., … Medicare detection of cognitive impairment workgroup. (2013). Alzheimer ' s Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimer's & Dementia*, *9*(2), 141–150.

Costa, D. A., Cracchiolo, 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.

Cummings, J. L., & Back, C. (1998). The Cholinergic Hypothesis of Neuropsychiatric Symptoms in Alzheimer's Disease. *American Journal of Geriatric Psychiatry*, *6*(2), S64–S78.

De Jonghe, C., Esselens, C., Kumar-singh, S., Craessaerts, K., Serneels, S., Checler, F., … Strooper, B. De. (2001). Pathogenic APP mutations near the γ -secretase cleavage site differentially affect A β secretion and APP C-terminal fragment stability. *Human Molecular Genetics*, *10*(16), 1665–1671.

De Montigny, A., Elhiri, I., Allyson, J., Cyr, M., & Massicotte, G. (2013). NMDA Reduces Tau Phosphorylation in Rat Hippocampal Slices by Targeting NR2A Receptors, GSK3β, and PKC Activities. *Neural Plasticity*.

De Strooper, B. (2010). The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nature Reviews Neurology*, *6*(2), 99–107.

Dowell, J. A., & Johnson, J. A. (2013). Mechanisms of Nrf2 Protection in Astrocytes as Identified by Quantitative Proteomics and siRNA Screening. *PloS One*, *8*(7), e70163.

Drolle, E., Hane, F., Lee, B., & Leonenko, Z. (2014). Atomic force microscopy to study molecular mechanisms of amyloid fibril formation and toxicity in Alzheimer's disease. *Drug Metabolism Reviews*, *46*(2), 207–223.

Durany, N., Michel, T., Kurt, J., Cruz-Sanchez, F. F., Cervo-Navarro, J., & Riederer, P. (2000). Brain-derived neurotrophic factor and neurotrophin-3 levels in Alzheimer's disease brains. *International Journal of Developmental Neuroscience*, *18*(8), 807–813.

Eckman, C. B., Mehta, N. D., Crook, R., Perez-tur, J., Prihar, G., Pfeiffer, E., … Hardy, J. (1997). A new pathogenic mutation in the APP gene (I716V) increases the relative proportion of Aβ42(43). *Human Molecular Genetics*, *6*(12), 2087–2089.

Ehninger, D., & Kempermann, G. (2003). Regional Effects of Wheel Running and Environmental Enrichment on Cell Genesis and Microglia Proliferation in the Adult Murine Neocortex. *Cerebral Cortex*, *13*(8), 845–851.

Elder, G. A., Gama-Sosa, M. A. G., & Gasperi, R. De. (2010). Transgenic Mouse Models of Alzheimer's Disease. *A Journal of Tranaslation and Personalized Medicine*, *77*(1), 69–81.

Eng, L. F., Ghirnikar, R. S., & Lee, Y. L. (2000). Glial Fibrillary Acidic Protein: GFAP-Thirty-One Years (1969–2000). *Neurochemical Research*, *25*(9–10), 1439–1451.

Eysenck, M. W., & Keane, M. T. (2010). *Cognitive Psychology - A Student's Handbook* (6th ed.). New York: Psychology Press.

Fares, R. P., Belmeguenai, A., Sanchez, P. E., Kouchi, H. Y., Bodennec, J., Morales, A., … Bezin, L. (2013). Standardized Environmental Enrichment Supports Enhanced Brain Plasticity in Healthy Rats and Prevents Cognitive Impairment in Epileptic Rats Raafat. *PloS One*, *8*(1), e53888.

Fares, R. P., Kouchi, H. Y., & Bezin, L. (2012). Marlau™ cage enables standardized and continual cognitive stimulation during environmental enrichment for rodents. *Nature Protocol Exchange*.

Faria, M. C., Gonçalves, G. S., Rocha, N. P., Moraes, E. N., Bicalho, M. A., Cintra, M. T. G., … Gomes, K. B. (2014). Increased plasma levels of BDNF and inflammatory markers in Alzheimer's disease. *Journal of Psychiatric Research*, *53*, 166–172.

Fernandez, A. M., Fernandez, S., Carrero, P., Garcia-garcia, M., & Torres-aleman, I. (2007). Calcineurin in Reactive Astrocytes Plays a Key Role in the Interplay between Proinflammatory and Anti-Inflammatory Signals. *The Journal of Neuroscience*, *27*(33), 8745–8756.

Ferreira-vieira, T. H., Guimaraes, I. M., Silva, F. R., & Ribeiro, F. M. (2016). Alzheimer's Disease: Targeting the Cholinergic System. *Current Neuropharmacology*, *14*(1), 101–115.

Gendreau, K. L., & Hall, G. F. (2013). Tangles, toxicity, and tau secretion in AD–new approaches to a vexing problem. *Frontiers in Neurology*, *4*, 160.

González-reyes, R. E., Nava-mesa, M. O., Vargas-sánchez, K., Ariza-salamanca, D., & Mora-muñoz, L. (2017). Involvement of Astrocytes in Alzheimer's Disease from a Neuroinflammatory and Oxidative Stress Perspective. *Frontiers in Molecular Neuroscience*, *10*, 427.

Grazioli, E., Dimauro, I., Mercatelli, N., Wang, G., Pitsiladis, Y., Luigi, L. Di, & Caporossi, D. (2017). Physical activity in the prevention of human diseases: role of epigenetic modifications. *BMC Genomics*, *18*(8), 802.

Griñán-ferré, C., Izquierdo, V., Otero, E., Puigoriol-illamola, D., Corpas, R., Sanfeliu, C., … Pallàs, M.

(2018). Environmental Enrichment Improves Cognitive Deficits, AD Hallmarks and Epigenetic Alterations Presented in 5xFAD Mouse Model. *Frontiers in Cellular Neuroscience*, *12*, 224.

Griñan-ferré, C., Puigoriol-illamola, D., Palomera-ávalos, V., Pérez-cáceres, D., Companys-alemany, J., Camins, A., … Pallàs, M. (2016). Environmental Enrichment Modified Epigenetic Mechanisms in SAMP8 Mouse Hippocampus by Reducing Oxidative Stress and Inflammaging and Achieving Neuroprotection. *Frontiers in Aging Neuroscience*, *8*, 241.

Hall, A. M., & Roberson, E. D. (2012). Mouse Models of Alzheimer's Disease. *Brain Research Bulletin*, *88*(1), 3–12.

Hardy, J., & Selkoe, D. J. (2002). The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. *Science*, *297*(5580), 353–356.

He, C., Tsipis, C. P., LaManna, J. C., & Xu, K. (2017). Environmental Enrichment Induces Increased Cerebral Capillary Density and Improved Cognitive Function in Mice. In *Advances in Experimental Medicine and Biology* (pp. 175–181). AG: Springer International Publishing. https://doi.org/10.1007/978-3-319-55231-6

Heneka, M. T., Carson, M. J., Khoury, J. El, Gary, E., Brosseron, F., Feinstein, D. L., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's Disease. *The Lancet Neurology*, *14*(4), 388–405.

Heurtaux, T., Michelucci, A., Losciuto, S., Gallotti, C., Felten, P., Dorban, G., … Heuschling, P. (2010). Microglial activation depends on beta-amyloid conformation: role of the formylpeptide receptor 2. *Journal of Neurochemistry*, *114*(2), 576–586. https://doi.org/10.1111/j.1471-4159.2010.06783.x

Hooper, C., Killick, R., & Lovestone, S. (2008). The GSK3 hypothesis of Alzheimer's disease. *Journal of Neurochemistry*, *104*(6), 1433–1439.

Hu, X., Bergström, S., Brink, M., Rönnbäck, A., & Dahlqvist, P. (2010). Enriched environment increases spinophilin mRNA expression and spinophilin immunoreactive dendritic spines in hippocampus and cortex. *Neuroscience Letters*, *476*(2), 79–83.

Huang, W.-J., Zhang, X., & Chen, W.-W. (2016). Role of oxidative stress in Alzheimer's disease (Review). *Biomedical Reports*, *4*(5), 519–522.

Hüttenrauch, M., Salinas, G., & Wirths, O. (2016). Effects of long-term environmental enrichment on anxiety, memory, hippocampal plasticity and overall brain gene expression in C57BL6 mice. *Frontiers in Human Neuroscience*, *9*, 62.

Hynd, M. R., Scott, H. L., & Dodd, P. R. (2004). Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. *Neurochemistry International*, *45*(5), 583–595.

Imai, Y., & Kohsaka, S. (2002). Intracellular signaling in M-CSF-induced microglia activation: role of Iba1. *Glia*, *40*(2), 164–174.

Ito, D., Imai, Y., Ohsawa, K., Nakajima, K., Fukuuchi, Y., & Kohsaka, S. (1998). Microglia-specific localisation of a novel calcium binding protein, Iba1. *Molecular Brain Research*, *57*(1), 1–9.

Iwata, N., Mizukami, H., Shirotani, K., Takaki, Y., Muramatsu, S., Lu, B., … Saido, T. C. (2004). Presynaptic Localization of Neprilysin Contributes to Efficient Clearance of Amyloid-β Peptide in Mouse Brain. *Journal of Neuroscience*, *24*(4), 991–998.

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues Clinical Neuroscience*, *15*(4), 445.

Jankowsky, J. L., Melnikova, T., Fadale, D. J., Xu, G. M., Slunt, H. H., Gonzales, V., … Savoneko, A. V. (2005). Environmental Enrichment Mitigates Cognitive Deficits in a Mouse Model of

Alzheimer's Disease. *Journal of Neuroscience*, *25*(21), 5217–5224.

Jankowsky, J. L., & Zheng, H. (2017). Practical considerations for choosing a mouse model of Alzheimer's disease. *Molecular Degeneration*, *12*(1), 89.

Janssen, H., Ada, L., Bernhardt, J., McElduff, P., Pollack, M., Nilsson, M., & Spratt, N. J. (2014). An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomized controlled trial Article. *Disability and Rehabilitation*, *36*(3), 255–262.

Johnson, D. A., Amirahmadi, S., Ward, C., Fabry, Z., & Johnson, J. A. (2009). The Absence of the Pro-antioxidant Transcription Factor Nrf2 Exacerbates Experimental Autoimmune Encephalomyelitis. *Toxicological Sciences*, *114*(2), 237–246.

Jones, M. W., & Wilson, M. A. (2005). Theta Rhythms Coordinate Hippocampal – Prefrontal Interactions in a Spatial Memory Task. *PLoS Biology*, *3*(12), e402.

Kanekiyo, T., Xu, H., & Bu, G. (2014). ApoE and Aβ in Alzheimer's disease: accidental encounters or partners? *Neuron*, *81*(4), 740–754.

Katsimpardi, L., & Lledo, P. (2018). Regulation of neurogenesis in the adult and aging brain. *Current Opinion in Neurobiology*, *53*, 131–138.

Kayed, R., & Lasagna-reeves, C. A. (2013). Molecular mechanisms of amyloid oligomers toxicity. *Journal of Alzheimer's Disease*, *33*(s1), S67–S78.

Kelleher, R. J., & Shen, J. (2017). Presenilin-1 mutations and Alzheimer's disease. *Proceedings of the National Academy of Sciences*, *114*(4), 629–631.

Kim, J., Basak, J. M., & Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. *Neuron*, *63*(3), 287–303.

Körholz, J. C., Zocher, S., Grzyb, A. N., Morisse, B., Poetzsch, A., Ehret, F., … Kempermann, G. (2018). Selective increases in inter-individual variability in response to environmental enrichment in female mice. *Elife*, *7*, e35690.

Kraeuter, A., Guest, P. C., & Sarnyai, Z. (2019). The Y-Maze for Assessment of Spatial Working and Reference Memory in Mice. In *Pre-Clinical Models* (Vol. 1916, pp. 105–111). New York.

Kumar, K., Kumar, A., Keegan, R. M., & Deshmukh, R. (2018). Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease. *Biomedicine & Pharmacotherapy*, *98*, 297–307.

Lanctot, K. L., Amatniek, J., Ancoli-israel, S., Arnold, S. E., Ballard, C., Cohen-mansfield, J., … Boot, B. (2017). Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *3*(3), 440–449.

Lasagna-reeves, C. A., & Kayed, R. (2011). Astrocytes contain amyloid-β annular protofibrils in Alzheimer's disease brains. *FEBS Letters*, *585*(19), 3052–3057. Retrieved from http://dx.doi.org/10.1016/j.febslet.2011.08.027

Laske, C., Stransky, E., Leyhe, T., Eschweiler, G. W., Wittorf, A., Richartz, E., … Schott, K. (2006). Stage-dependent BDNF serum concentrations in Alzheimer's disease. *Journal of Neural Transmission*, *113*(9), 1217–1224.

Lazarov, O., Robinson, J., Tang, Y., Hairston, I. S., Korade-mirnics, Z., Lee, V. M., … Sisodia, S. S. (2005). Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice. *Cell*, *120*(5), 701–713.

Lee, C. Y. D., & Landreth, G. E. (2010). The role of microglia in amyloid clearance from the AD brain. *Journal of Neural Transmission*, *117*(8), 949–960.

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*(7638), 481.

Lista, S., O'Bryant, S. E., Blennow, K., Dubois, B., Hugon, J., Zetterberg, H., & Hampel, H. (2015). Biomarkers in Sporadic and Familial Alzheimer's Disease. *Journal of Alzheimer's Disease*, *47*(2), 291–317.

Lovatel, G. A., Elsner, V. R., Bertoldi, K., Vanzella, C., Moysés, F. dos S., Vizuete, A., … Siqueira, I. R. (2013). Treadmill exercise induces age-related changes in aversive memory, neuroinflammatory and epigenetic processes in the rat hippocampus. *Neurobiology of Learning and Memory*, *101*, 94–102.

Lu, B., Nagappan, G., & Lu, Y. (2014). BDNF and Synaptic Plasticity, Cognitive Function, and Dysfunction. In *Neurotrophic factors* (pp. 223–250). Berlin.

Lyketsos, C. G., Carrillo, M. C., Ryan, J. M., Khachaturian, A. S., Trzepacz, P., Amatniek, J., … Miller, D. S. (2011). Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimer's & Dementia*, *7*, 532–539.

Maccioni, R. B., Farias, G., Morales, I., & Navarrete, L. (2010). The revitalized tau hypothesis on Alzheimer's disease. *Archives of Medical Research*, *41*(3), 226–231.

Masuda, A., Kobayashi, Y., Kogo, N., Saito, T., Saido, T. C., & Itohara, S. (2016). Cognitive deficits in single App knock-in mouse models Akira. *Neurobiology of Learning and Memory*, *135*, 73–82.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 263–269.

Mesa-gresa, P., Ramos-campos, M., & Redolat, R. (2014). Behavioral effects of different enriched environments in mice treated with the cholinergic agonist PNU-282987. *Behavioural Processes*, *103*, 117–124.

Mesulam, M. M. (2013). Cholinergic Circuitry of the Human Nucleus Basalis and Its Fate in Alzheimer's Disease. *Journal of Comparative Neurology*, *521*(18), 4124–4144.

Middeldorp, J., & Hol, E. M. (2011). GFAP in health and disease. *Progress in Neurobiology*, *93*(3), 421–443.

Mitsis, E. M., Reech, K. M., Bois, F., Tamagnan, G. D., Macavoy, M. G., Seibyl, J. P., … van Dyck, C. H. (2009). 123I-5-IA-85380 SPECT Imaging of Nicotinic Receptors in Alzheimer Disease and Mild Cognitive Impairment. *Journal of Nuclear Medicine*, *50*(9), 1455–1463.

Mitsuishi, Y., Taguchi, K., Kawatani, Y., Shibata, T., Nukiwa, T., Aburatani, H., … Motohashi, H. (2012). Nrf2 Redirects Glucose and Glutamine into Anabolic Pathways in Metabolic Reprogramming. *Cancer Cell*, *22*(1), 66–79.

Morales, I., Guzmán-martínez, L., Cerda-troncoso, C., Farías, G. A., & Maccioni, R. B. (2014). Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Frontiers in Cellular Neuroscience*, *8*, 112.

Mudher, A., & Lovestone, S. (2002). Alzheimer's disease – do tauists and baptists finally shake hands? *Trends in Neurosciences*, *25*(1), 22–26.

Mutter, F. E., Park, B. K., & Copple, I. M. (2015). Value of monitoring Nrf2 activity for the detection of chemical and oxidative stress. *Biochemical Society Transactions*, *43*(4), 657–662.

Nalivaeva, N. N., Beckett, C., Belyaev, N. D., & Turner., A. J. (2012). Introduction : the dynamic nature of amyloid Amyloid-degrading enzymes : the key players and strategies for manipulation Neprilysin and related peptidases (NEP , ECE-1 ,. *Journal of Neurochemistry*, *120*, 167–185.

Neal, M., Luo, J., Harischandra, D. S., Gordon, R., Sarkar, S., Jin, H., … Kanthasamy, A. (2018). Prokineticin-2 promotes chemotaxis and alternative A2 reactivity of astrocytes. *Glia*, *66*(10), 2137–2157.

Ng, T. K. S., Ho, C. S. H., Tam, W. W. S., Kua, E. H., & Ho, R. C.-M. (2019). Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences*, *20*(2), 257.

Nguyen, T., Nioi, P., & Pickett, C. B. (2009). The Nrf2-Antioxidant Response Element Signaling Pathway and Its Activation by Oxidative Stress. *Journal of Biological Chemistry*, *284*(20), 13291–13295.

Nilsson, P., Saito, T., & Saido, T. C. (2014). New Mouse Model of Alzheimer's. *ACS Chemical Neuroscience*, *5*, 499–502.

O'Brien, R. J., & Wong, P. C. (2011). Amyloid Precursor Protein Processing and Alzheimer's Disease. *Annual Review of Neuroscience*, *34*, 185–204.

O'Donnell, K. A., An, W., Schrum, C. T., Wheelan, S. J., & Boeke, J. D. (2013). Controlled insertional mutagenesis using a LINE-1 (ORFeus) gene-trap mouse model. *Proceedings of the National Academy of Sciences*, *110*(29), e2706.

Obiang, P., Maubert, E., Bardou, I., Nicole, O., Launay, S., Bezin, L., … Agin, V. (2011). Enriched housing reverses age-associated impairment of cognitive functions and tPA-dependent maturation of BDNF. *Neurobiology of Learning and Memory*, *96*(2), 121–129.

Oddo, S., Caccamo, A., Kitazawa, M., Tseng, B. P., & Laferla, F. M. (2003). Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. *Neurobiology of Aging*, *24*(8), 1063–1070.

Olivares, D., Deshpande, V. K., Shi, Y., Lahiri, D. K., Greig, N. H., Rogers, J. T., & Huang, X. (2012). N-Methyl D-Aspartate (NMDA) Receptor Antagonists and Memantine Treatment for Alzheimer's Disease, Vascular Dementia and Parkinson's Disease. *Current Alzheimer Research*, *9*(6), 746–758.

Pareja-galeano, H., Sanchis-gomar, F., & Garcıa-Gimenez, J. L. (2014). Physical Exercise and Epigenetic Modulation: Elucidating Intricate Mechanism. *Sport Medicine*, *44*(4), 429–436.

Paresce, D. M., Ghosh, R. N., & Maxfield, F. R. (1996). Microglial Cells Internalize Aggregates of the Alzheimer's Disease Amyloid β-Protein Via a Scavenger Receptor. *Neuron*, *17*(3), 553–565.

Park, D. C., & Bischof, G. N. (2013). The aging mind: neuroplasticity in response to cognitive training. *Dialogues in Clinical Neuroscience*, *15*(1), 109.

Pekny, M., & Nilsson, M. (2005). Astrocyte Activation and Reactive Gliosis. *Glia*, *50*(4), 427–434.

Perry, G., Cash, A. D., & Smith, M. A. (2002). Alzheimer Disease and Oxidative Stress. *BioMed Research International*, *2*(3), 120–123.

Prado-Lima, M. G., Schimidt, H. L., Garcia, A., Daré, L. R., Carpes, F. P., Izquierdo, I., & Mello-Carpes, P. B. (2018). Environmental enrichment and exercise are better than social enrichment to

reduce memory deficits in amyloid beta neurotoxicity. *Proceedings of the National Academy of Sciences*, *115*(10), E2403–E2409.

Prior, H., Schwegler, H., & Ducker, G. (1997). Dissociation of spatial reference memory, spatial working memory, and hippocampal mossy fiber distribution in two rat strains differing in emotionality. *Behavioural Brain Research*, *87*(2), 183–194.

Renner, M., & Rosenzweig, M. (1986). Social interactions among rats housed in grouped and enriched conditions. *Developmental Psychoniology: The Journal of the International Society for Develpomental Psychobiology*, *19*(4), 303–313.

Rodríguez, J. J., Noristani, H. N., Olabarria, M., Fletcher, J., Somerville, T. D. D., Yeh, C. Y., & Verkhratsky, A. (2011). Voluntary running and environmental enrichment restores impaired hippocampal neurogenesis in a triple transgenic mouse model of Alzheimer's disease. *Current Alzheimer Research*, *8*(7), 707–717.

Rolls, A., Schori, H., London, A., & Schwartz, M. (2008). Decrease in hippocampal neurogenesis during pregnancy: a link to immunity. *Molecular Psychiatry*, *13*(5), 468.

Rosbergen, I. C. M., Brauer, S. G., Fitzhenry, S., Grimley, R. S., & Hayward, K. S. (2017). Qualitative investigation of the perceptions and experiences of nursing and allied health professionals involved in the implementation of an enriched environment in an Australian acute stroke unit. *BMJ Open*, *7*(12), e018226.

Sabbagh, M. N., Daniel, L. L., & Jiong, F. (2017). Increasing Precision of Clinical Diagnosis of Alzheimer's Disease Using a Combined Algorithm Incorporating Clinical and Novel Biomarker Data. *Neurology and Therapy*, *6*(1), 83–95.

Saito, T., Matsuba, Y., Mihira, N., Takano, J., Nilsson, P., Itohara, S., … Saido, T. C. (2014). Single App knock-in mouse models of Alzheimer's disease. *Nature Neuroscience*, *17*(5), 661.

Sakakibara, Y., Sekiya, M., Saito, T., Saido, T. C., & Iijima, K. M. (2018). Cognitive and emotional alterations in App knock-in mouse models of Aβ amyloidosis. *BMC Neuroscience*, *19*(1), 46.

Sakimoto, S., Kidoya, H., Naito, H., Kamei, M., Sakaguchi, H., Goda, N., … Takakura, N. (2012). A role for endothelial cells in promoting the maturation of astrocytes through the apelin / APJ system in mice. *Development*, *139*(7), 1327–1335.

Salmin, V. V, Komleva, Y. K., Kuvacheva, N. V, Morgun, A. V, Khilazheva, E. D., Lopatina, O. L., … Salmina, A. B. (2017). Differential Roles of Environmental Enrichment in Alzheimer's Type of Neurodegeneration and Physiological Aging. *Frontiers in Aging Neuroscience*, *9*, 245.

Sarlus, H., & Heneka, M. T. (2017). Microglia in Alzheimer's disease, *127*(9), 3240–3249.

Schwarzmana, A. L., Gregoria, L., Vitekb, M. P., Lyubskic, S., Strittmatterd, W. J., Enghildee, J. A. N. J., … Goldgabera, D. (1994). Transthyretin sequesters amyloid ft protein and prevents amyloid formation. *Proceedings of the National Academy of Sciences*, *91*(18), 8368–8372.

Serrano-pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *1*(1), a006189.

Shaffer, L. M., Dority, M. D., Gupta-Bansal, R., Frederickson, R. C., Younkin, S. G., & Brunden, K. R. (1995). Amyloid β protein (Aβ) removal by neuroglial cells in culture. *Neurobiology of Aging*, *16*(5), 737–745.

Sharma, S., Rakoczy, S., & Brown-borg, H. (2010). Assessment of spatial memory in mice. *Life Science*, *87*(17–18), 521–536.

Sheng, M., Sabatini, B. L., & Sudhof, T. C. (2012). Synapses and Alzheimer's Disease. *Cold Spring Harbor Perspectives in Medicine*, *4*(5), a005777.

Simard, A. R., Soulet, D., Gowing, G., Julien, J., & Rivest, S. (2006). Bone Marrow-Derived Microglia Play a Critical Role in Restricting Senile Plaque Formation in Alzheimer's Disease. *Neuron*, *49*(4), 489–502.

Sleiman, S. F., Henry, J., Al-haddad, R., Hayek, L. El, Haidar, E. A., Stringer, T., … Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. *Elife*, *5*, e15092.

Stranahan, A. M., Lee, K., Martin, B., Maudsley, S., Golden, E., Cutler, R. G., & Mattson, M. P. (2009). Voluntary Exercise and Caloric Restriction Enhance Hippocampal Dendritic Spine Density and BDNF Levels in Diabetic Mice. *Hippocampus*, *19*(10), 951–961.

Suemaru, K., Yoshikawa, M., Aso, H., & Watanabe, M. (2018). Environmental enrichment alleviates cognitive and behavioral impairments in EL mice. *Epilepsy & Behavior*, *85*, 227–233. https://doi.org/10.1016/j.yebeh.2018.06.016

Talalay, P., & Dinkova-Kostova, A. T. (2004). Role of nicotinamide quinone oxidoreductase 1 (NQO1) in protection against toxicity of electrophiles and reactive oxygen intermediates. In *Method in Enzymology* (Vol. 382, pp. 355–364). Academic Press.

Tayeb, H. O., Duk, H., Price, B. H., & Tarazi, F. I. (2012). Pharmacotherapies for Alzheimer's disease: Beyond cholinesterase inhibitors. *Pharmacology and Therapeutics*, *134*(1), 8–25.

Terry, A. V, & Buccafusco, J. J. (2003). The Cholinergic Hypothesis of Age and Alzheimer's Disease-Related Cognitive Deficits: Recent Challenges and Their Implications for Novel Drug Development. *Journal of Pharmacology and Experimental Therapeutics*, *306*(3), 821–827.

Thal, D. R. (2012). The role of astrocytes in amyloid β-protein toxicity and clearance. *Experimental Neurology*, *236*(1), 1–5.

Toth, L. A., Kregel, K., Leon, L., & Musch, T. I. (2011). Environmental Enrichment of Laboratory Rodents: The Answer Depends on the Question, *61*(4), 314–321.

United Nation. (2017). *World Population Ageing*.

Van Asselen, M., Kessels, R. P. C., Neggers, S. F. W., Kappelle, L. J., Frijns, C. J. M., & Postma, A. (2006). Brain areas involved in spatial working memory. *Neuropsychologia*, *44*(7), 1185–1194.

van Meer, P., & Raber, J. (2005). Mouse behavioural analysis in systems biology. *Biochemical Journal*, *389*(3), 593–610.

van Waas, M., & Soffie, M. (1996). Differential Environmental Modulations on Locomotor Activity, Exploration and Spatial Behaviour in Young and Old Rats. *Physiology & Behavior*, *59*(2), 265–271.

Vargas, M. R., & Johnson, J. A. (2017). The Nrf2-ARE cytoprotective pathway in astrocytes. *Expert Reviews in Molecular Medicine*, *11*, e17.

Verghese, P. B., Castellano, J. M., & Holtzman, D. M. (2011). Apolipoprotein E in Alzheimer's disease and other neurological disorders. *The Lancet Neurology*, *10*(3), 241–252.

Vorhees, C. V, & Williams, M. T. (2014). Assessing Spatial Learning and Memory in Rodents. *Ilar Journal*, *55*(2), 310–332.

Walker, D. G., & Lue, L. (2015). Immune phenotypes of microglia in human neurodegenerative

disease: challenges to detecting microglial polarization in human brains. *Alzheimer's Research & Therapy*, *7*(1), 56.

Walter, T. J., & Crews, F. T. (2017). Microglial depletion alters the brain neuroimmune response to acute binge ethanol withdrawal. *Journal of Neuroinflammation*, *14*(1), 86.

WHO. (2019). Dementia. Retrieved May 15, 2019, from https://www.who.int/news-room/fact-sheets/detail/dementia

Whyte, L. S., Hemsley, K. M., Lau, A. A., Saito, T., Saido, T. C., Hopwood, J. J., & Sargeant, T. J. (2018). Reduction in open field activity in the absence of memory deficits in the APPnl− G− F knock-in mouse model of Alzheimer's disease. *Behavioural Brain Research*, *336*, 177–181.

Williamson, L. L., Chao, A., & Bilbo, S. D. (2012). Environmental enrichment alters glial antigen expression and neuroimmune function in the adult rat hippocampus. *Brain, Behavior, and Immunity*, *26*(3), 500–510.

Wilson, R. S., De Leon, C. F. M., 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.

Wolf, A., Bauer, B., Abner, E. L., Ashkenazy-frolinger, T., & Anika, M. (2016). A Comprehensive Behavioral Test Battery to Assess Learning and Memory in 129S6 / Tg2576 Mice. *PLoS One*, *11*(1), e0147733.

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.

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

Xu, X. H., Gelyana, X. E., Rajsombath, X. M., Yang, T., Li, S., & Selkoe, D. (2016). Environmental enrichment potently prevents microglia-mediated neuroinflammation by human amyloid β-protein oligomers. *Journal of Neuroscience*, *36*(35), 9041–9056.

Yamaguchi, H., Sugihara, S., Ogawa, A., Saido, T. C., & Ihara, Y. (1998). Diffuse plaques associated with astroglial amyloid β protein, possibly showing a disappearing stage of senile plaques. *Acta Neuropathologica*, *95*(3), 217–222.

Yamazaki, T., Chang, T., Haass, C., & Ihara, Y. (2001). Accumulation and aggregation of amyloid β-protein in late endosomes of Niemann-pick type C cells. *Journal of Biological Chemistry*, *276*(6), 4454–4460.

Yang, S., Shi, Y., Wang, Q., Peng, J., & Li, B. (2014). Neuronal representation of working memory in the medial prefrontal cortex of rats. *Molecular Brain*, *7*(1), 61.

Yeung, S. T., Martinez-Coria, H., Ager, R. R., Rodriguez-Ortiz, C. J., Baglietto-Vargas, D., & LaFerla, F. M. (2015). Repeated cognitive stimulation alleviates memory impairments in an Alzheimer's disease mouse model. *Brain Research Bulletin*, *117*, 10–15.

Yiannopoulou, K. G., & Papageorgiou, S. G. (2013). Current and future treatments for Alzheimer's disease. *Therapeutic Advances in Neurological Disorders Review*, *6*(1), 19–33. https://doi.org/10.1177/1756285612461679

Ziegler-waldkirch, S., Marksteiner, K., Stoll, J., D'Errico, P., Friesen, M., Eiler, D., … Meyer-Luehmann, M. (2018). Environmental enrichment reverses Aβ pathology during pregnancy in a mouse

model of Alzheimer's disease. *Acta Neuropathologica Communications*, *6*(1), 44.

Zuroff, L., Daley, D., Black, K. L., & Koronyo-Hamaoui, M. (2017). *Clearance of cerebral Aβ in Alzheimer's disease: reassessing the role of microglia and monocytes*. *Cellular and Molecular Life Sciences* (Vol. 74). Springer International Publishing.