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Glial cells and neuronal function in Alzheimer's disease

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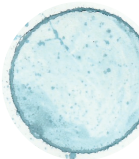
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Scope



Although the first descriptions of age-related mental deficiency date from the 7th century B.C., dementia remained largely uninvestigated and was seen as an unavoidable part of aging. Only with the introduction of the systematic classification and a scientific approach to clinical observations of mental disorders in the 19th century, different types of dementias were identified and this gained more interested in studying these (Berchtold & Cotman, 1998). In 1906, Alois Alzheimer described an unusual case of psychiatric illness and specific morphological changes in the brain of the 51-year-old Auguste Deter (Strassnig & Ganguli, 2005). The description of this clinical and neuropathological case became known as Alzheimer's disease, named after him by Emil Kraepelin. At about the same time the neuropathological hallmarks of AD were also described by Oskar Fischer (Berchtold & Cotman, 1998).

Worldwide there are currently an estimated 50 million people with dementia, of which Alzheimer's disease (AD) - affecting about 30 million people - is the most prevalent form (Patterson, 2018). In the Netherlands around 270.000 people suffer from dementia, of which 70% have AD (Stichting Alzheimer Nederland, 2018). Other forms of dementia include mixed dementia, Lewy body dementia, frontotemporal degeneration, and vascular dementia (Patterson, 2018). The impact of the disease on a person's daily life is disastrous. Over the course of several years, patients lose their independence, due to memory loss and decline in cognitive abilities. They will depend more and more on their caregivers. In the final stage, patients are bed-bound and AD is ultimately fatal (Alzheimer's Association, 2018). The prevalence of AD increases from the age of 65 onwards, and as a consequence of an increasing life expectancy (Kontis et al., 2017), the world-wide social-economic burden of AD will only further rise in the nearby future. The estimated world-wide cost of dementia is a trillion US dollars a year. This includes the estimated costs of caregivers. The number of people with dementia will only further increase, and is estimated to affect around 150 million people in 2050 (Patterson, 2018). This increasing social-economic impact indicates the importance of research into AD pathogenesis, which is essential to develop effective AD therapies.

AD is a neurodegenerative disorder that is clinically characterized by progressive memory loss and impairment in cognitive functions (Querfurth & LaFerla, 2010). Hallmarks of AD pathology are the aggregation of extracellular amyloid-beta ($A\beta$) in plaques, intraneuronal hyperphosphorylated tau tangles, reactive astrocytes and activated microglia (i.e. gliosis), and synaptic and neuronal loss (Davies, Mann, Sumpter, & Yates, 1987; Itagaki & McGeer, P.L. Akiyama, 1989; Selkoe, 1991; Kato et al., 1998). In AD, $A\beta$ peptides form long insoluble amyloid fibrils that accumulate in plaques (Haass & Selkoe, 2007). $A\beta$ peptides are produced by proteolytic cleavage of amyloid precursor protein (APP) by β - and γ -secretases (Fig.1a) (Haass & Selkoe, 2007; Qiu, Liu, Chen, Zhao, & Li, 2015). The early biochemical findings related to amyloid indicated the APP gene as a site for causative AD mutations (Haass & Selkoe, 2007). Indeed, up to now 44 different mutations in the APP gene have been discovered

in families with early-onset AD (Chartier-Harlin et al., 1991; Goate et al., 1991; Mullan et al., 1992) (<https://www.alzforum.org/mutations>). Even more, i.e. 346 mutations, have been found in the presenilin1 (PSEN1) and PSEN2 genes, which both are subunits of γ -secretase, the enzyme that cleaves APP (<https://www.alzforum.org/mutations>). Together these findings underlie the amyloid cascade hypothesis, stating that the accumulation and aggregation of A β in plaques are the first events in AD pathogenesis, eventually resulting in microglia and astrocyte activation, formation of neurofibrillary tangles, progressive neuronal loss, synaptic dysfunction, and eventually in cognitive deficits (Hardy & Allsop, 1991; Selkoe, 1991; Hardy & Higgins, 1992; Hardy & Selkoe, 2002). The refined version of the hypothesis includes A β oligomers, seen as the most toxic form of A β , as an important factor in AD pathogenesis (Selkoe & Hardy, 2016). The amyloid hypothesis and the discovery of causal mutations in the APP, PSEN1, and PSEN2 genes contributed to the generation of various transgenic AD mouse models (Elder, Gama Sosa, & De Gasperi, 2010). The APP^{swe}PS1^{dE9} mice, a widely used transgenic mouse model of AD, is a good model to study the development of both A β pathogenesis and gliosis. In these APP^{swe}PS1^{dE9} mice, reactive astrocytes and activate microglia are found surrounding A β plaques (Fig.1b-c) (Kamphuis et al., 2014; Orre et al., 2014). However, neurofibrillary tangles of hyperphosphorylated tau are not seen in AD mice, unless animals express human (mutant) tau (Duyckaerts, Potier, & Delatour, 2008; Moreno-Gonzalez, Estrada, Sanchez-Mejias, & Soto, 2013). In the hippocampus, the first synaptic loss is indicated in this model at the age of 4 months (Hong et al., 2016).

Astrocytes are the most abundant glial cells in the central nervous system (CNS) (Chung et al., 2013). They are involved in many different functions, including neurotransmitter uptake, extracellular potassium buffering, and maintaining blood-brain barrier function (Abbott, Rönnbäck, & Hansson, 2006; Seifert, Schilling, & Steinhäuser, 2006; Halassa, Fellin, & Haydon, 2007; Sofroniew & Vinters, 2010; Khakh & Sofroniew, 2015; Verkhratsky & Nedergaard, 2018). Astrocytes support neuronal function and can modulate synaptic communication and plasticity (Halassa, Fellin, & Haydon, 2007; Santello, Toni, & Volterra, 2019). Under pathological conditions, astrocytes adopt a reactive state which is characterized by an upregulation of the cytoskeletal intermediate filament proteins glial fibrillary acid protein (GFAP), vimentin, and nestin (Hol & Pekny, 2015; Pekny et al., 2016), and various functional changes. These changes include, but are not limited to, an increased intracellular calcium level, increased frequency of spontaneous calcium transients (Kuchibhotla, Lattarulo, Hyman, & Bacskaï, 2009; Delekate et al., 2014), increased gliotransmitter release (Jo et al., 2014; Yi et al., 2016), and transcriptomic changes (Wirz et al., 2013; Orre et al., 2014). The astroglial transcriptomic profile of aged APP^{swe}PS1^{dE9} mice shows a reduced expression of neuronal support genes and genes involved in neuronal communication, and an increased expression of genes involved in the immune response (Wirz et al., 2013; Orre et al., 2014). Molecular and functional changes of reactive astrocytes in AD are reviewed in detail by (Osborn, Kamphuis, Wadman, & Hol, 2016).

Microglia are the resident macrophages of the CNS (Kettenmann, Hanisch, Noda, & Verkhratsky, 2011; Ginhoux, Lim, Hoeffel, Low, & Huber, 2013), where they dynamically survey their environment (Nimmerjahn, Kirchhoff, & Helmchen, 2005; Madry et al., 2018). During development, they are involved in the modulation of neuronal circuits by pruning synapses (Paolicelli et al., 2011; Schafer et al., 2012; Weinhard et al., 2018). Animal studies show that microglia also contribute to synapse removal during AD pathogenesis (Hong et al., 2016; Luchena, Zuazo-Ibarra, Alberdi, Matute, & Capetillo-Zarate, 2018; Rajendran & Paolicelli, 2018). Other functional changes in activated microglia are changes in phagocytosis of amyloid (Wyss-Coray et al., 2001; Fu et al., 2012), seeding of A β (Venegas et al., 2017), and the release of inflammatory factors (Sarlus & Heneka, 2017).

Transcriptomic analysis identified subpopulations of microglia that are associated with AD pathology in AD mouse models, this so-called disease-associated microglia (DAM) signature revealed a reduced expression of homeostatic microglial genes, and upregulation of several genes associated with lipid metabolism and phagocytosis (Keren-Shaul et al., 2017; Krasemann et al., 2017). Human genetic studies identified several genetic loci associated with an increased AD risk. Some of the common (*ApoE*) or rare (*Trem2*, *Cd33*) genetic variants, code for proteins that are predominantly expressed in microglia (Lambert et al., 2013; Hemonnot, Hua, Ulmann, & Hirbec, 2019). Also, recent RNAseq studies showed a distinctive phenotype of microglia in AD pathology (Mathys et al., 2019; Srinivasan et al., 2019). These human genetic studies indicate a key role for microglia in AD pathogenesis.

Thesis outline

In this thesis we investigate the potential of reactive astrocytes as a treatment target in AD, the impact of aging and AD pathology on neuronal communication, the interaction of microglia with A β plaques, and A β ₁₋₄₂ oligomer-induced transcriptomic changes in a human model for microglia. While we focus in the first part (Chapter 1-3) of this thesis on the role of astrocytes and neuronal function in the AD mouse model, in the second part (Chapter 4-5) we use human brain sections, isolated primary microglia, and a microglia-like cell model to investigate microglia in AD.

In **chapter 1** we review articles that used interventions that modulate reactive astrocytes in the APPswePS1dE9 mice, an AD mouse model well suited to study amyloidosis and the development of reactive astrocytes and its consequences. We first give an overview of the model, i.e. how it is generated, the influence of the genetic background on AD pathology, and which cells express the transgenes. We then systematically review studies in which reactive astrocytes were either directly or indirectly targeted in the APPswePS1dE9 mice. We also include the effect of the interventions on A β burden, microglia activation, synaptic density, and cognitive function. Overall, studies reducing gliosis by astrocyte-specific interventions showed beneficial effects on cognition. We conclude that astrocytes

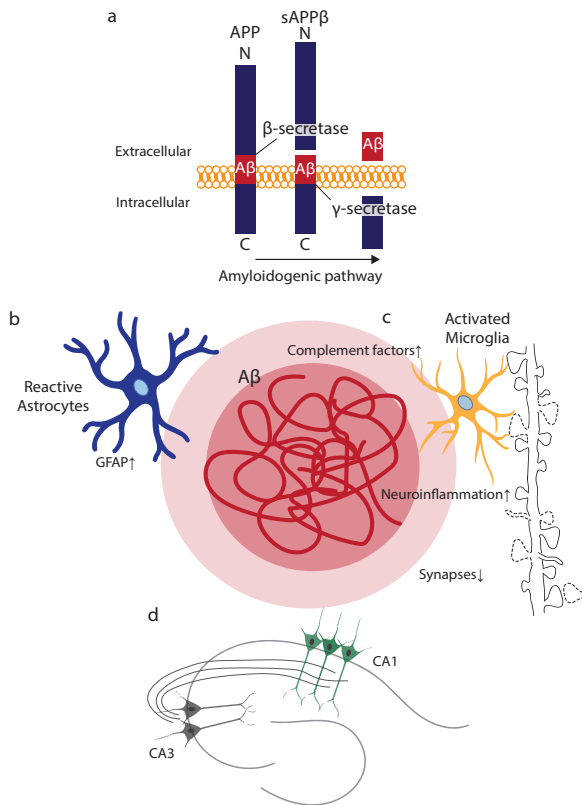


Figure 1. Overview of the thesis.

a. The amyloidogenic cleavage of APP by β - and γ -secretases results in A β peptides of different lengths. These accumulate and form extracellular plaques, surrounded by reactive astrocytes and activated microglia. b. Reactive astrocytes are classically characterized by their increased expression of GFAP. c. Activated microglia increase the expression of complement cascade factors and cytokines. d. The CA3-CA1 synapse in the hippocampus is a well-known synapse to study synaptic plasticity. A β : amyloid-beta; APP: amyloid precursor protein; CA: Cornu Ammonis; GFAP: glial fibrillary acidic protein. Scientific illustration toolkits from Motifolio were used to generate parts of this figure. Basis of synapses (Rajendral & Paolicelli, 2018).

contribute to a wide range of processes in AD pathogenesis and deserve more attention as a treatment target for cognitive decline.

In **chapter 2** we set out to investigate the use of lipopolysaccharide (LPS) application to acute hippocampal slices of wild-type mice, as an *in vitro* model for reactive gliosis. This was evaluated by qPCR, using markers for reactive astrocytes and cytokines. In a second series of experiments, we investigate the functional consequences of a glial metabolic inhibitor on neuronal excitability and spike-time dependent plasticity (STDP). This pharmacological tool could be a first tool to investigate glia-neuronal communication.

In **chapter 3**, we determine whether cellular excitability and synaptic plasticity in hippocampal pyramidal neurons are affected during early or later stages of AD pathology. We investigate physiological properties and synaptic plasticity in the CA1 region of the hippocampus of 1-, 4-, 6-, and 9-month-old APP^{swe}PS1^{dE9} mice and their wild-type littermates.

In **chapter 4**, we investigate transcriptomic changes induced by A β_{1-42} oligomers and LPS in human monocyte-derived microglia-like (MDMi) cells. First, we describe the generation of the MDMi cell model and their response to the strong inflammatory stimulus LPS.

Scope

Next, we use A β_{1-42} oligomers to investigate transcriptomic changes, and compare known microglial gene profiles from AD patients and mice to changes in gene expression found in our stimulated MDMi cell model.

In **chapter 5**, we investigate whether the microglia-plaque interaction differs between AD patients and non-demented controls with A β plaques. We categorize the A β plaques and plaque-associated microglia number, morphology, and use a lysosomal marker as an indication for microglia phagocytic activity. We also determine the levels of the pre- and postsynaptic markers, as a proxy for synapse elimination.

Chapter 6 provides a summary and general discussion of the results presented in this thesis.

References

- Abbott, N. J., Rönnebeck, L., & Hansson, E. (2006). Astrocyte-endothelial interactions at the blood-brain barrier. *Nature Reviews Neuroscience*, 7(1), 41–53. <http://doi: 10.1038/nrn1824>.
- Alzheimer's Association. (2018). 2018 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia*, 14, 367–429.
- Berchtold, N. C. & Cotman, C. W. (1998). Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiology of Aging*, 19(3), 173–189. [http://doi: 10.1016/S0197-4580\(98\)00052-9](http://doi: 10.1016/S0197-4580(98)00052-9).
- Chartier-Harlin, M. C., Crawford, F., Houlden, H., Warren, A., Hughes, D., Fidani, L., ... Mullan, M. (1991). Early-onset Alzheimer's disease caused by mutations at codon 717 of the β -amyloid precursor protein gene. *Nature*, 353(6347), 844–846. <http://doi: 10.1038/353844a0>.
- Chung, W.-S., Clarke, L. E., Wang, G. X., Stafford, B. K., Sher, A., Chakraborty, C., ... Barres, B. A. (2013). Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. *Nature*, 504, 394–400. <http://doi: 10.1038/nature12776>.
- Davies, C. A., Mann, D. M. A., Sumpter, P. Q., & Yates, P. O. (1987). A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. *Journal of the Neurological Sciences*, 78(2), 151–164. [http://doi: 10.1016/0022-510X\(87\)90057-8](http://doi: 10.1016/0022-510X(87)90057-8).
- Delekate, A., Fächtemeier, M., Schumacher, T., Ulbrich, C., Foddiss, M., & Petzold, G. C. (2014). Metabotropic P2Y1 receptor signalling mediates astrocytic hyperactivity in vivo in an Alzheimer's disease mouse model. *Nature communications*, 5, 5422. <http://doi: 10.1038/ncomms6422>.
- Duyckaerts, C., Potier, M. C., & Delatour, B. (2008). Alzheimer disease models and human neuropathology: Similarities and differences. <http://doi: 10.1007/s00401-007-0312-8>.
- Elder, G. A., Gama Sosa, M. A., & De Gasperi, R. (2010). Transgenic mouse models of Alzheimer's disease. *Mount Sinai Journal of Medicine*, 77, 69–81.
- Fu, H., Liu, B., Frost, J. L., Hong, S., Jin, M., Ostaszewski, B., ... Lemere, C. A. (2012). Complement component C3 and complement receptor type 3 contribute to the phagocytosis and clearance of fibrillar A β by microglia. *Glia*, 60(6), 993–1003. <http://doi: 10.1002/glia.22331>.
- Ginhoux, F., Lim, S., Hoeffel, G., Low, D., & Huber, T. (2013). Origin and differentiation of microglia. *Frontiers in Cellular Neuroscience*, 7(45), 1–14. <http://doi: 10.3389/fncel.2013.00045>.
- Goate, A., Chartier-Harlin, M.-C., Mullan, M., Brown, J., Crawford, F., Fidani, L., ... Hardy, J. (1991). Segregation of a missense mutation in the amyloid β -protein precursor gene with familial Alzheimer's disease. *Nature*, 349, 704–706. <http://doi: 10.1038/349704a0>.
- Haass, C. & Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid β -peptide. *Nature Reviews Molecular Cell Biology*, 8(2), 101–112. <http://doi: 10.1038/nrm2101>.
- Halassa, M. M., Fellin, T., & Haydon, P. G. (2007). The tripartite synapse: roles for gliotransmission in health and disease. *Trends in Molecular Medicine*, 13(2), 54–63. <http://doi: 10.1016/j.molmed.2006.12.005>.
- Hardy, J. A. & Higgins, G. A. (1992). Alzheimer's Disease: The Amyloid Cascade Hypothesis. *Science*, 256(5054), 184–185.
- Hardy, J. & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in Pharmacological Sciences*, 12, 383–388. [http://doi: 10.1016/0165-6147\(91\)90609-V](http://doi: 10.1016/0165-6147(91)90609-V).
- Hardy, J. & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*, 297, 353–356. <http://doi: 10.1126/science.1072994>.

- Hemonnot, A. L., Hua, J., Ulmann, L., & Hirbec, H. (2019). Microglia in Alzheimer disease: Well-known targets and new opportunities. *Frontiers in aging neuroscience*, 11(233), 1–20. <http://doi: 10.3389/fnagi.2019.00233>.
- Hol, E. M. & Pekny, M. (2015). Glial fibrillary acidic protein (GFAP) and the astrocyte intermediate filament system in diseases of the central nervous system. *Current Opinion in Cell Biology*, 32, 121–130. <http://doi: 10.1016/j.ceb.2015.02.004>.
- Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S., ... Stevens, B. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*, 352(6286), 712–716. <http://doi: 10.1126/science.aad8373>.
- Itagaki, S. & McGeer, P.L. Akiyama, S. (1989). Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *Journal of Neuroimmunology*, 24, 173–182. <http://doi: 10.1017/CBO9781107415324.004>.
- Jo, S., Yarishkin, O., Hwang, Y. J., Chun, Y. E., Park, M., Woo, D. H., ... Lee, C. J. (2014). GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. *Nature Medicine*, 20(8), 886–896. <http://doi: 10.1038/nm.3639>.
- Kamphuis, W., Middeldorp, J., Kooijman, L., Sluijs, J. a, Kooi, E.-J., Moeton, M., ... Hol, E. M. (2014). Glial fibrillary acidic protein isoform expression in plaque related astrogliosis in Alzheimer's disease. *Neurobiology of aging*, 35(3), 492–510. <http://doi: 10.1016/j.neurobiolaging.2013.09.035>.
- Kato, S., Gondo, T., Hoshii, Y., Takahashi, M., Yamada, M., & Ishihara, T. (1998). Confocal observation of senile plaques in Alzheimer's disease: Senile plaque morphology and relationship between senile plaques and astrocytes. *Pathology International*, 48(5), 332–340. <http://doi: 10.1111/j.1440-1827.1998.tb03915.x>.
- Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., ... Amit, I. (2017). A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell*, 169(7), 1276–1290.e17. <http://doi: 10.1016/j.cell.2017.05.018>.
- Kettenmann, H., Hanisch, U., Noda, M., & Verkhratsky, a. (2011). Physiology of microglia. *Physiological Reviews*, 91(2), 461–553. <http://doi: 10.1152/physrev.00011.2010>.
- Khakh, B. S. & Sofroniew, M. V. (2015). Diversity of astrocyte functions and phenotypes in neural circuits. *Nature Neuroscience*, 18(7), 942–952. <http://doi: 10.1038/nn.4043>.
- Kontis, V., Bennett, J. E., Mathers, C. D., Li, G., Foreman, K., & Ezzati, M. (2017). Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet*, 389(10076), 1323–1335. [http://doi: 10.1016/S0140-6736\(16\)32381-9](http://doi: 10.1016/S0140-6736(16)32381-9).
- Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., ... Butovsky, O. (2017). The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. *Immunity*, 47(3), 566–581.e9. <http://doi: 10.1016/j.immuni.2017.08.008>.
- Kuchibhotla, K. V, Lattarulo, C. R., Hyman, B. T., & Bacskai, B. J. (2009). Synchronous Hyperactivity and Intercellular Calcium Waves in Astrocytes in Alzheimer Mice. *Science*, 323, 1211–1216.
- Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., ... Seshadri, S. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*, 45(12), 1452–1458. <http://doi: 10.1038/ng.2802>.
- Luchena, C., Zuazo-Ibarra, J., Alberdi, E., Matute, C., & Capetillo-Zarate, E. (2018). Contribution of neurons and glial cells to complement-mediated synapse removal during development, aging and in Alzheimer's disease. *Mediators of Inflammation*, ID2530414, 1–12. <http://doi: https://doi.org/10.1155/2018/2530414>.
- Madry, C., Kyrargyri, V., Arancibia-Cárcamo, I. L., Jolivet, R., Kohsaka, S., Bryan, R. M., & Attwell, D. (2018). Microglial Ramification, Surveillance, and Interleukin-1 β Release Are Regulated by the Two-Pore Domain K⁺Channel THIK-1. *Neuron*, 97(2), 299–312.e6. <http://doi: 10.1016/j.neuron.2017.12.002>.

- Mathys, H., Davila-Velderrain, J., Peng, Z., Gao, F., Mohammadi, S., Young, J. Z., ... Tsai, L. H. (2019). Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*, 570(7761), 332–337. <http://doi: 10.1038/s41586-019-1195-2>.
- Moreno-Gonzalez, I., Estrada, L. D., Sanchez-Mejias, E., & Soto, C. (2013). Smoking exacerbates amyloid pathology in a mouse model of Alzheimer's disease. *Nature Communications*, 4. <http://doi: 10.1038/ncomms2494>.
- Mullan, M., Crawford, F., Axelman, K., Houlden, H., Lilius, L., Winblad, B., & Lannfelt, L. (1992). A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of β -amyloid. *Nature genetics*, 1(5), 345–347. <http://doi: 10.1038/ng0892-345>.
- Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Neuroforum*, 11(3), 95–96. <http://doi: 10.1515/nf-2005-0304>.
- Orre, M., Kamphuis, W., Osborn, L. M., Jansen, A. H. P. P., Kooijman, L., Bossers, K., & Hol, E. M. (2014). Isolation of glia from Alzheimer's mice reveals inflammation and dysfunction. *Neurobiology of aging*, 35(12), 2746–2760. <http://doi: 10.1016/j.neurobiolaging.2014.06.004>.
- Osborn, Iana M., Kamphuis, W., Wadman, W. J., & Hol, E. M. (2016). Progress in Neurobiology Astrogliosis : An integral player in the pathogenesis of Alzheimer ' s disease. *Progress in Neurobiology*, 144, 121–141. <http://doi: 10.1016/j.pneurobio.2016.01.001>.
- Paolicelli, R. C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., ... Gross, C. T. (2011). Development Synaptic Pruning by Microglia Is Necessary for Normal Brain Synaptic Pruning by Microglia Is Necessary for Normal Brain Development. *Science*, 333(September), 1456–1459. <http://doi: 10.1126/science.1202529>.
- Patterson, C. (2018). World Alzheimer Report 2018 - The state of the art of dementia research: New frontiers. *Alzheimer's disease international*, 1–48. <http://doi: 10.1103/PhysRevLett.78.4414>.
- Pekny, M., Pekna, M., Messing, A., Steinhäuser, C., Lee, J. M., Parpura, V., ... Verkhratsky, A. (2016). Astrocytes: a central element in neurological diseases. *Acta Neuropathologica*, 131(3), 323–345. <http://doi: 10.1007/s00401-015-1513-1>.
- Qiu, T., Liu, Q., Chen, Y. X., Zhao, Y. F., & Li, Y. M. (2015). $A\beta_{42}$ and $A\beta_{40}$: similarities and differences. *Journal of Peptide Science*, 21(7), 522–529. <http://doi: 10.1002/psc.2789>.
- Querfurth, H. W. & LaFerla, F. M. (2010). Alzheimer's disease. *The New England Journal of Medicine*, 364(6), 329–344. http://doi: 10.1007/978-1-4939-7880-9_9.
- Rajendran, L. & Paolicelli, R. C. (2018). Microglia-Mediated Synapse Loss in Alzheimer's Disease. *The Journal of Neuroscience*, 38(12), 2911–2919. <http://doi: 10.1523/JNEUROSCI.1136-17.2017>.
- Santello, M., Toni, N., & Volterra, A. (2019). Astrocyte function from information processing to cognition and cognitive impairment. *Nature Neuroscience*, 22, 154–166. <http://doi: 10.1038/s41593-018-0325-8>.
- Sarlus, H. & Heneka, M. T. (2017). Microglia in Alzheimer ' s disease. *The Journal of Clinical Investigation*, 127(9), 3240–3249. <http://doi: 10.1172/JCI90606>.
- Schafer, D., Lehrman, E., Kautzman, A., Koyama, R., Mardinly, A., Yamasaki, R., ... Stevens, B. (2012). Microglia sculpt postnatal neuronal circuits in an activity and complement-dependent manner. *Neuron*, 74(4), 691–705. <http://doi: 10.1016/j.neuron.2012.03.026>.
- Seifert, G., Schilling, K., & Steinhäuser, C. (2006). Astrocyte dysfunction in neurological disorders: a molecular perspective. *Nature reviews Neuroscience*, 7(March), 194–206. <http://doi: 10.1038/nrn1870>.
- Selkoe, D. J. (1991). The Molecular Pathology of Alzheimer's Disease. *Neuron*, 6, 487–498. [http://doi: 10.1016/0896-6273\(91\)90052-2](http://doi: 10.1016/0896-6273(91)90052-2).
- Selkoe, D. J. & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, 8(6), 595–608. <http://doi: 10.15252/emmm.201606210>.

Scope

- Sofroniew, M. V & Vinters, H. V. (2010). Astrocytes: biology and pathology. *Acta neuropathologica*, 119(1), 7–35. <http://doi: 10.1007/s00401-009-0619-8>.
- Srinivasan, K., Friedman, B. A., Etxeberria, A., Huntley, M. A., Brug, M. P. van der, Foreman, O., ... Hansen, D. (2019). Alzheimer's patient brain myeloid cells exhibit enhanced aging and unique transcriptional activation. *bioRxiv*, 610345. <http://doi: 10.1101/610345>.
- Stichting Alzheimer Nederland. (2018). Jaarverslag 2018 SHN.
- Strassnig, M. & Ganguli, M. (2005). About a Peculiar Disease of the Cerebral Cortex : Alzheimer's Original Case Translation from the original publication of Alois Alzheimer. *Psychiatry*, 2(9), 30–33.
- Venegas, C., Kumar, S., Franklin, B. S., Dierkes, T., Brinkschulte, R., Tejera, D., ... Heneka, M. T. (2017). Microglia-derived ASC specks crossseed amyloid- β in Alzheimer's disease. *Nature*, 552(7685), 355–361. <http://doi: 10.1038/nature25158>.
- Verkhatsky, A. & Nedergaard, M. (2018). Physiology of astroglia. *Physiological Reviews*, 98(1), 239–389. <http://doi: 10.1152/physrev.00042.2016>.
- Weinhard, L., Di Bartolomei, G., Bolasco, G., Machado, P., Schieber, N. L., Neniskyte, U., ... Gross, C. T. (2018). Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. *Nature Communications*, 9(1). <http://doi: 10.1038/s41467-018-03566-5>.
- Wirz, K. T. S., Bossers, K., Stargardt, A., Kamphuis, W., Swaab, D. F., Hol, E. M., & Verhaagen, J. (2013). Cortical beta amyloid protein triggers an immune response, but no synaptic changes in the APP^{swe}/PS1^{dE9} Alzheimer's disease mouse model. *Neurobiology of Aging*, 34(5), 1328–1342. <http://doi: 10.1016/j.neurobiolaging.2012.11.008>.
- Wyss-Coray, T., Lin, C., Yan, F., Yu, G. Q., Rohde, M., Mconlogue, L., ... Mucke, L. (2001). TGF- β 1 promotes microglial amyloid- β clearance and reduces plaque burden in transgenic mice. *Nature Medicine*, 7(5), 612–618. <http://doi: 10.1038/87945>.
- Yi, C., Mei, X., Ezan, P., Mato, S., Matias, I., Giaume, C., & Koulakoff, A. (2016). Astroglial connexin43 contributes to neuronal suffering in a mouse model of Alzheimer's disease. *Cell Death and Differentiation*, 23(10), 1691–1701. <http://doi: 10.1038/cdd.2016.63>.