

---

# 8

---

REFERENCES



- 1 Charcot M. (1868) Histologie de la sclerose en plaques. *Gaz. des Hôpitaux* 41, 554–566.
- 2 Multiple Sclerosis International Federation 2013 (2013) *Atlas of MS: Mapping Multiple Sclerosis Around the World*. .
- 3 Deber C.M. & Reynolds S.J. (1991) Central nervous system myelin: structure, function, and pathology. *Clin. Biochem.* 24, 113–34.
- 4 Lopez P.H.H., Ahmad A.S., Mehta N.R., et al. (2011) Myelin-associated glycoprotein protects neurons from excitotoxicity. *J. Neurochem.* 116, 900–8.
- 5 Nguyen T., Mehta N.R., Conant K., et al. (2009) Axonal protective effects of the myelin-associated glycoprotein. *J. Neurosci.* 29, 630–7.
- 6 Compston A. & Coles A. (2002) Multiple sclerosis. *Lancet* 359, 1221–31.
- 7 McDonald W.I. & Barnes D. (1992) The ocular manifestations of multiple sclerosis. 1. Abnormalities of the afferent visual system. *J. Neurol. Neurosurg. Psychiatry* 55, 747–52.
- 8 Balcer L.J. (2006) Optic Neuritis. *N. Engl. J. Med.* 354, 1273–1280.
- 9 Betts C.D., D'Mellow M.T. & Fowler C.J. (1993) Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* 56, 245–50.
- 10 Cruccu G., Biasiotta A., Di Rezze S., et al. (2009) Trigeminal neuralgia and pain related to multiple sclerosis. *Pain* 143, 186–91.
- 11 Coelho A., Ceranic B., Prasher D., et al. (2007) Auditory efferent function is affected in multiple sclerosis. *Ear Hear.* 28, 593–604.
- 12 Prosperini L., Kouleridou A., Petsas N., et al. (2011) The relationship between infratentorial lesions, balance deficit and accidental falls in multiple sclerosis. *J. Neurol. Sci.* 304, 55–60.
- 13 Papadopoulos A., Gatzonis S., Gouliamos A., et al. (1994) Correlation between spinal cord MRI and clinical features in patients with demyelinating disease. *Neuroradiology* 36, 130–3.
- 14 Zackowski K.M., Smith S.A., Reich D.S., et al. (2009) Sensorimotor dysfunction in multiple sclerosis and column-specific magnetization transfer-imaging abnormalities in the spinal cord. *Brain* 132, 1200–9.
- 15 Kalkers N.F., Strijers R.L.M., Jasperse M.M.S., et al. (2007) Motor evoked potential: a reliable and objective measure to document the functional consequences of multiple sclerosis? Relation to disability and MRI. *Clin. Neurophysiol.* 118, 1332–40.
- 16 Bjartmar C., Kidd G., Mörk S., et al. (2000) Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. *Ann. Neurol.* 48, 893–901.
- 17 Brass S.D., Duquette P., Proulx-Therrien J., et al. (2010) Sleep disorders in patients with multiple sclerosis. *Sleep Med. Rev.* 14, 121–9.
- 18 Kaminska M., Kimoff R.J., Schwartzman K., et al. (2011) Sleep disorders and fatigue in multiple sclerosis: evidence for association and interaction. *J. Neurol. Sci.* 302, 7–13.
- 19 Janssens a C.J.W., van Doorn P. a, de Boer J.B., et al. (2004) Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression, and disease-related distress. *J. Clin. Epidemiol.* 57, 180–6.
- 20 Chiaravalloti N.D. & DeLuca J. (2008) Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 7, 1139–1151.
- 21 Lublin F.D. & Reingold S.C. (1996) Defining the clinical course of multiple sclerosis: *Neurology* 46, 907–911.
- 22 Noseworthy J., Lucchinetti C., Rodriguez M., et al. (2000) Multiple sclerosis. *N. Engl. J. Med.* 372, 1502–1517.
- 23 Antel J., Antel S., Caramanos Z., et al. (2012) Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? *Acta Neuropathol.* 123, 627–

- 38.
- 24 Thompson A.J., Polman C.H., Miller D.H., et al. (1997) Primary progressive multiple sclerosis. *Brain*, 1085–1096.
- 25 Ebers G.C. (2008) Environmental factors in multiple sclerosis. *Lancet Neurol.* 7, 268–77.
- 26 Sawcer S., Hellenthal G., Pirinen M., et al. (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 476, 214–9.
- 27 DeLuca G.C., Alterman R., Martin J.L., et al. (2013) Casting light on multiple sclerosis heterogeneity: the role of HLA-DRB1 on spinal cord pathology. *Brain* 136, 1025–34.
- 28 Ebers G. (2005) A twin consensus in MS. *Mult. Scler.* 11, 497–499.
- 29 Munger K.L., Levin L.I., Hollis B.W., et al. (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *Jama* 296, 2832–8.
- 30 Ascherio A., Munger K.L., White R., et al. (2014) Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol.* 71, 306–14.
- 31 Cepok S., Zhou D., Srivastava R., et al. (2005) Identification of Epstein-Barr virus proteins as putative targets of the immune response in multiple sclerosis. *J. Clin. Invest.* 115, 1352–1360.
- 32 Frohman T.C., Castro W., Shah A., et al. (2011) Symptomatic therapy in multiple sclerosis. *Ther. Adv. Neurol. Disord.* 4, 83–98.
- 33 Uitdehaag B., Constantinescu C., Cornelisse P., et al. (2011) Impact of exposure to interferon beta-1a on outcomes in patients with relapsing-remitting multiple sclerosis: exploratory analyses from the PRISMS long-term follow-up study. *Ther. Adv. Neurol. Disord.* 4, 3–14.
- 34 Mikol D.D., Barkhof F., Chang P., et al. (2008) Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REBif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol.* 7, 903–14.
- 35 Dhib-Jalbut S. & Marks S. (2010) Interferon-beta mechanisms of action in multiple sclerosis. *Neurology* 74 Suppl 1, S17–24.
- 36 Torkildsen O., Myhr K.M. & Bø L. (2016) Disease-modifying treatments for multiple sclerosis - a review of approved medications. *Eur. J. Neurol.* 23, 18–27.
- 37 Dörr J. & Paul F. (2015) The Transition From First-Line to Second-Line Therapy in Multiple Sclerosis. *Curr. Treat. Options Neurol.* 17.
- 38 Polman C.H., O'Connor P.W., Havrdova E., et al. (2006) A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N. Engl. J. Med.* 354, 899–910.
- 39 Kappos L., Radue E.-W., O'Connor P., et al. (2010) A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. *N. Engl. J. Med.* 362, 387–401.
- 40 Cohen J. a, Barkhof F., Comi G., et al. (2010) Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 362, 402–15.
- 41 Coles A.J., Twyman C.L., Arnold D.L., et al. (2012) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 380, 1829–1839.
- 42 Pfender N. & Martin R. (2014) Daclizumab (anti-CD25) in multiple sclerosis. *Exp. Neurol.* 262, 44–51.
- 43 Sorensen P.S. & Blinkenberg M. (2015) The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. *Ther. Adv. Neurol. Disord.*, 1–9.
- 44 Weissert R. (2013) The Immune Pathogenesis of Multiple Sclerosis. *J. Neuroimmune Pharmacol.*
- 45 Stys P.K., Zamponi G.W., van Minnen J., et al. (2012) Will the real multiple sclerosis

- please stand up? *Nat. Rev. Neurosci.* 13, 507–14.
- 46 Calabrese M., De Stefano N., Atzori M., et al. (2007) Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. *Arch. Neurol.* 64, 1416.
- 47 Bø L., Vedeler C., Nyland H., et al. (2003) Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. *Mult. Scler.* 9, 323–331.
- 48 Bø L., Vedeler C. a, Nyland H.I., et al. (2003) Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J. Neuropathol. Exp. Neurol.* 62, 723–32.
- 49 Peterson J.W., Bö L., Mörk S., et al. (2001) Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann. Neurol.* 50, 389–400.
- 50 De Santi L., Annunziata P., Sessa E., et al. (2009) Brain-derived neurotrophic factor and TrkB receptor in experimental autoimmune encephalomyelitis and multiple sclerosis. *J. Neurol. Sci.* 287, 17–26.
- 51 Bø L. (2009) The histopathology of grey matter demyelination in multiple sclerosis. *Acta Neurol. Scand.* 120, 51–57.
- 52 Petzold A., Eikelenboom M.J., Gveric D., et al. (2002) Markers for different glial cell responses in multiple sclerosis: clinical and pathological correlations. *Brain* 125, 1462–73.
- 53 Dal Bianco A., Bradl M., Frischer J., et al. (2008) Multiple sclerosis and Alzheimer's disease. *Ann. Neurol.* 63, 174–83.
- 54 Nimmerjahn A., Kirchhoff F. & Helmchen F. (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. *Science* (80-. ). 308, 1314.
- 55 Kettenmann H., Hanisch U., Noda M., et al. (2011) Physiology of Microglia. *Physiol Rev* 91, 461–553.
- 56 Kreutzberg G.W. (1996) Microglia: a sensor for pathological events in the CNS. *Trends Neurosci.* 19, 312–8.
- 57 Aguzzi A., Barres B. a & Bennett M.L. (2013) Microglia: scapegoat, saboteur, or something else? *Science* (80-. ). 339, 156–61.
- 58 Perea G., Navarrete M. & Araque A. (2009) Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci.* 32, 421–431.
- 59 Hamilton N.B. & Attwell D. (2010) Do astrocytes really exocytose neurotransmitters? *Nat. Rev. Neurosci.* 11, 227–238.
- 60 Kacem K., Lacombe P., Seylaz J., et al. (1998) Structural organization of the perivascular astrocyte endfeet and their relationship with the endothelial glucose transporter: a confocal microscopy study. *Glia* 23, 1–10.
- 61 Janzer R.C. & Raff M.C. (1987) Astrocytes induce blood-brain barrier properties in endothelial cells. *Lett. to Nat.* 325, 253–257.
- 62 Zhao B. & Schwartz J.P. (1998) Mini-Review Involvement of Cytokines in Normal CNS Development and Neurological Diseases: Recent Progress and Perspectives. *J. Neurosci. Res.* 16, 7–16.
- 63 Sims J.E. & Smith D.E. (2010) The IL-1 family: regulators of immunity. *Nat. Rev. Immunol.* 10, 89–102.
- 64 Dinarello C.A. (2009) Immunological and inflammatory functions of the interleukin-1 family. *Annu. Rev. Immunol.* 27, 519–550.
- 65 Giulian D. & Tapscott M.J. (1988) Immunoregulation of Cells within the Central Nervous System. *Brain. Behav. Immun.* 2, 352–358.
- 66 Feder L.S. & Laskin D.L. (1994) Regulation of hepatic endothelial cell and macrophage proliferation and nitric oxide production by GM-CSF, M-CSF, and IL-1 beta following acute endotoxemia. *J. Leukoc. Biol.* 55, 507–513.
- 67 Hong L., Imeri L., Opp M.R., et al. (1993) Intercellular adhesion molecule-1 expression induced by interleukin (IL)-1 [beta] or an IL-1 [beta] fragment is blocked by an IL-1 receptor antagonist and a soluble IL-1 receptor. *J. Neuroimmunol.* 44, 163–

- 170.
- 68 Perretti M., Solito E. & Parente L. (1992) Evidence that endogenous interleukin-1 is involved in leukocyte migration in acute experimental inflammation in rats and mice. *Inflamm. Res.* 35, 71–78.
- 69 Brosnan C.F., Cannella B., Battistini L., et al. (1995) Cytokine localization in multiple sclerosis lesions: Correlation with adhesion molecule expression and reactive nitrogen species. *Neurology* 45, 6–11.
- 70 Boven L.A., Van Meurs M., Van Zwam M., et al. (2006) Myelin-laden macrophages are anti-inflammatory, consistent with foam cells in multiple sclerosis. *Brain* 129, 517–26.
- 71 Murphy Á.C., Lalor S.J., Lynch M.A., et al. (2010) Infiltration of Th1 and Th17 cells and activation of microglia in the CNS during the course of experimental autoimmune encephalomyelitis. *Brain. Behav. Immun.* 24, 641–651.
- 72 Bauer J., Berkenbosch F., Van Dam A.M., et al. (1993) Demonstration of interleukin-1 [beta] in Lewis rat brain during experimental allergic encephalomyelitis by immunocytochemistry at the light and ultrastructural level. *J. Neuroimmunol.* 48, 13–21.
- 73 Mahad D.J. & Ransohoff R.M. (2003) The role of MCP-1 (CCL2) and CCR2 in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE). *Semin. Immunol.* 15, 23–32.
- 74 Conductier G., Blondeau N., Guyon A., et al. (2010) The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases. *J. Neuroimmunol.* 224, 93–100.
- 75 Bose S. & Cho J. (2013) Role of chemokine CCL2 and its receptor CCR2 in neurodegenerative diseases. *Arch. Pharm. Res.* 36, 1039–50.
- 76 Babcock A.A., Kuziel W.A., Rivest S., et al. (2003) Chemokine expression by glial cells directs leukocytes to sites of axonal injury in the CNS. *J. Neurosci.* 23, 7922–30.
- 77 Moreno M., Bannerman P., Ma J., et al. (2014) Conditional Ablation of Astroglial CCL2 Suppresses CNS Accumulation of M1 Macrophages and Preserves Axons in Mice with MOG Peptide EAE. *J. Neurosci.* 34, 8175–8185.
- 78 El-Hage N., Wu G., Wang J., et al. (2006) HIV-1 Tat and opiate-induced changes in astrocytes promote chemotaxis of microglia through the expression of MCP-1 and alternative chemokines. *Glia* 53, 132–46.
- 79 Cross A.K. & Woodroffe M.N. (1999) Chemokines induce migration and changes in actin polymerization in adult rat brain microglia and a human fetal microglial cell line in vitro. *J. Neurosci. Res.* 55, 17–23.
- 80 Hinojosa A.E., Garcia-Bueno B., Leza J.C., et al. (2011) CCL2/MCP-1 modulation of microglial activation and proliferation. *J. Neuroinflammation* 8, 77.
- 81 Yang G., Meng Y., Li W., et al. (2011) Neuronal MCP-1 mediates microglia recruitment and neurodegeneration induced by the mild impairment of oxidative metabolism. *Brain Pathol.* 21, 279–97.
- 82 Vitkovic L., Bockaert J. & Jacque C. (2000) “Inflammatory” cytokines: neuromodulators in normal brain? *J. Neurochem.* 74, 457–71.
- 83 Van Dam A.M., Brouns M., Louise S., et al. (1992) Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? *Brain Res.* 588, 291–296.
- 84 Quan N., Whiteside M. & Herkenham M. (1998) Time course and localization patterns of interleukin-1 $\beta$  messenger RNA expression in brain and pituitary after peripheral administration of lipopolysaccharide. *Neuroscience* 83, 281–293.
- 85 Palin K., Pousset F., Verrier D., et al. (2001) Characterization of interleukin-1 receptor antagonist isoform expression in the brain of lipopolysaccharide-treated rats.

- Neuroscience 103, 161–169.
- 86 Eriksson C., Nobel S., Winblad B., et al. (2000) Expression of interleukin 1 alpha and beta, and interleukin 1 receptor antagonist mRNA in the rat central nervous system after peripheral administration of lipopolysaccharides. *Cytokine* 12, 423–431.
- 87 Allan S.M., Tyrrell P.J. & Rothwell N.J. (2005) Interleukin-1 and neuronal injury. *Nat. Rev. Immunol.* 5, 629–640.
- 88 Eriksson C., Van Dam A.-M., Lucassen P., et al. (1999) Immunohistochemical localization of interleukin-1beta, interleukin-1 receptor antagonist and interleukin-1beta converting enzyme/caspase-1 in the rat brain after peripheral administration of kainic acid. *Neuroscience* 93, 915–930.
- 89 Brough D., Tyrrell P.J. & Allan S.M. (2011) Regulation of interleukin-1 in acute brain injury. *Trends Pharmacol. Sci.* 32, 617–622.
- 90 Thornberry N.A., Bull H.G., Calaycay J.R., et al. (1992) A novel heterodimeric cysteine protease is required for interleukin-1beta processing in monocytes. *Nature* 356, 768–774.
- 91 Franchi L., Eigenbrod T., Muñoz-Planillo R., et al. (2009) The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. *Nat. Immunol.* 10, 241–7.
- 92 Martinon F. & Tschopp J. (2007) Inflammatory caspases and inflammasomes: master switches of inflammation. *Cell Death Differ.* 14, 10–22.
- 93 O'Neill L.A.J. (2008) The interleukin-1 receptor / Toll-like receptor superfamily: 10 years of progress. *Immunol. Rev.* 226, 10–18.
- 94 Dinarello C.A. (1998) Biologic basis for interleukin-1 in disease. *Blood* 87, 2095–147.
- 95 Wang Y., Jin S., Sonobe Y., et al. (2014) Interleukin-1 $\beta$  induces blood-brain barrier disruption by downregulating Sonic hedgehog in astrocytes. *PLoS One* 9, e110024.
- 96 Herx L.M. & Yong V.W. (2001) Interleukin-1 beta is required for the early evolution of reactive astrogliosis following CNS lesion. *J. Neuropathol. Exp. Neurol.* 60, 961–71.
- 97 Takahashi J.L., Giuliani F., Power C., et al. (2003) Interleukin-1 $\beta$  promotes oligodendrocyte death through glutamate excitotoxicity. *Ann. Neurol.* 53, 588–595.
- 98 Sozzani S., Zhou D., Locati M., et al. (1994) Receptors and Transduction Pathways for Monocyte Chemotactic Protein-2 and Monocyte Chemotactic Protein-3. *J. Immunol.* 152, 3615–3622.
- 99 Banisadr G., Gosselin R.-D., Mechighel P., et al. (2005) Highly regionalized neuronal expression of monocyte chemoattractant protein-1 (MCP-1/CCL2) in rat brain: evidence for its colocalization with neurotransmitters and neuropeptides. *J. Comp. Neurol.* 489, 275–92.
- 100 de Haas a H., van Weering H.R.J., de Jong E.K., et al. (2007) Neuronal chemokines: versatile messengers in central nervous system cell interaction. *Mol. Neurobiol.* 36, 137–51.
- 101 Hayashi M., Laning J., Strieter R.M., et al. (1995) Production and function of monocyte chemoattractant protein-1 and other beta-chemokines in murine glial cells. *J. Neuroimmunol.* 60, 143–150.
- 102 Thompson W.L. & Van Eldik L.J. (2009) Inflammatory cytokines stimulate the chemokines CCL2/MCP-1 and CCL7/MCP-3 through NF $\kappa$ B and MAPK dependent pathways in rat astrocytes. *Brain Res.* 1287, 47–57.
- 103 Hurwitz A.A., Lyman W.D. & Berman J.W. (1995) Tumor necrosis factor beta upregulate and transforming growth factor  $\beta$  upregulate astrocyte expression of monocyte chemoattractant protein-1. *J. Neuroimmunol.* 57, 193–198.
- 104 Simpson J., Rezaie P., Newcombe J., et al. (2000) Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue. *J. Neuroimmunol.* 108, 192–200.

- 105 Boddeke E.W., Meigel I., Frentzel S., et al. (1999) Cultured rat microglia express functional beta-chemokine receptors. *J. Neuroimmunol.* 98, 176–84.
- 106 Eltayeb S., Berg A.-L., Lassmann H., et al. (2007) Temporal expression and cellular origin of CC chemokine receptors CCR1, CCR2 and CCR5 in the central nervous system: insight into mechanisms of MOG-induced EAE. *J. Neuroinflammation* 4, 14.
- 107 Salcedo R., Ponce M.L., Young H.A., et al. (2000) Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. *Blood* 96, 34–40.
- 108 Rostène W., Kitabgi P. & Melik Parsadaniantz S. (2007) Chemokines : a new class of neuromodulator? *Nat. Neurosci.* 8, 895–904.
- 109 Mellado M., Rodríguez-Frade J.M., Mañes S., et al. (2001) Chemokine signaling and functional responses: The Role of Receptor Dimerization and TK Pathway Activation. *Annu. Rev. Immunol.* 19, 397–421.
- 110 Deshmane S.L., Kremlev S., Amini S., et al. (2009) Monocyte chemoattractant protein-1 (MCP-1): an overview. *J. Interf. Cytokine Res.* 29, 313–26.
- 111 Stamatovic S.M., Keep R.F., Kunkel S.L., et al. (2003) Potential role of MCP-1 in endothelial cell tight junction “opening”: signaling via Rho and Rho kinase. *J. Cell Sci.* 116, 4615–28.
- 112 Roberts T.K., Eugenin E. a, Lopez L., et al. (2012) CCL2 disrupts the adherens junction: implications for neuroinflammation. *Lab. Investig.* 92, 1213–33.
- 113 Huang B.D., Wang J., Kivisakk P., et al. (2001) Absence of Monocyte Chemoattractant Protein 1 in Mice Leads to Decreased Local Macrophage Recruitment and Antigen-specific T Helper Cell Type 1 Immune Response in Experimental Autoimmune Encephalomyelitis. *J. Exp. Med.* 193, 713–725.
- 114 Ajami B., Bennett J.L., Krieger C., et al. (2011) Infiltrating monocytes trigger EAE progression, but do not contribute to the resident microglia pool. *Nat. Neurosci.* 14, 1142–9.
- 115 van der Star B.J., Vogel D.Y.S., Kipp M., et al. (2012) *In vitro* and *in vivo* models of multiple sclerosis. *CNS Neurol. Disord. - Drug Targets* 11, 570–88.
- 116 Denic A., Johnson A.J., Bieber A.J., et al. (2011) The relevance of animal models in multiple sclerosis research. *Pathophysiology* 18, 21–9.
- 117 Mix E., Meyer-Rienecker H., Hartung H.-P., et al. (2010) Animal models of multiple sclerosis--potentials and limitations. *Prog. Neurobiol.* 92, 386–404.
- 118 Lipton M.M. & Freund J. (1952) Encephalomyelitis in the Rat Following Intracutaneous Injection of Central Nervous System Tissue with Adjuvant. *Exp. Biol. Med.* 81, 260–261.
- 119 Lorentzen J.C., Issazadeh S., Starch M., et al. (1995) Protracted , relapsing and demyelinating experimental autoimmune encephalomyelitis in DA rats immunized with syngeneic spinal cord and incomplete Freund ’ s adjuvant. *J. Neuroimmunol.* 63, 193–205.
- 120 Fletcher J.M., Lalor S.J., Sweeney C.M., et al. (2010) T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin. Exp. Immunol.* 162, 1–11.
- 121 Constantinescu C.S., Farooqi N., O’Brien K., et al. (2011) Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *Br. J. Pharmacol.* 164, 1079–1106.
- 122 Matthaei I., Polman C.H., de Groot C.J., et al. (1989) Observer agreement in the assessment of clinical signs in experimental allergic encephalomyelitis. *J. Neuroimmunol.* 23, 25–8.
- 123 Olechowski C.J., Truong J.J. & Kerr B.J. (2009) Neuropathic pain behaviours in a chronic-relapsing model of experimental autoimmune encephalomyelitis (EAE). *Pain* 141, 156–64.



- 124 D'Intino G., Paradisi M., Fernandez M., et al. (2005) Cognitive deficit associated with cholinergic and nerve growth factor down-regulation in experimental allergic encephalomyelitis in rats. *Proc. Natl. Acad. Sci. U. S. A.* 102, 3070–5.
- 125 Ziehn M.O., Avedisian A. a, Tiwari-Woodruff S., et al. (2010) Hippocampal CA1 atrophy and synaptic loss during experimental autoimmune encephalomyelitis, EAE. *Lab. Investig.* 90, 774–786.
- 126 Rivers T.M., Sprunt D.H. & Berry G.P. (1933) Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. *J. Exp. Med.* 58, 39–53.
- 127 Meeson A.P., Piddlesden S., Morgan B.P., et al. (1994) The distribution of inflammatory demyelinated lesions in the central nervous system of rats with antibody-augmented demyelinating experimental allergic encephalomyelitis. *Exp. Neurol.* 129, 299–310.
- 128 Black J. a, Liu S., Hains B.C., et al. (2006) Long-term protection of central axons with phenytoin in monophasic and chronic-relapsing EAE. *Brain* 129, 3196–208.
- 129 Storch M.K., Stefferl A., Brehm U., et al. (1998) Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. *Brain Pathol.* 8, 681–94.
- 130 Kipp M., Clarner T., Dang J., et al. (2009) The cuprizone animal model: new insights into an old story. *Acta Neuropathol.* 118, 723–36.
- 131 Torkildsen Ø., Brunborg L.A., Myhr K.M., et al. (2008) The cuprizone model for demyelination. *Acta Neurol. Scand.* 117, 72–76.
- 132 Hiremath M.M., Saito Y., Knapp G.W., et al. (1998) Microglial/macrophage accumulation during cuprizone-induced demyelination in C57BL/6 mice. *J. Neuroimmunol.* 92, 38–49.
- 133 Xiao L., Xu H., Zhang Y., et al. (2008) Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. *Mol. Psychiatry* 13, 697–708.
- 134 Groebe A., Clarner T., Baumgartner W., et al. (2009) Cuprizone treatment induces distinct demyelination, astrogliosis, and microglia cell invasion or proliferation in the mouse cerebellum. *Cerebellum* 8, 163–74.
- 135 Norkute A., Hieble A., Braun A., et al. (2009) Cuprizone treatment induces demyelination and astrogliosis in the mouse hippocampus. *J. Neurosci. Res.* 87, 1343–55.
- 136 Taylor L.C., Gilmore W. & Matsushima G.K. (2009) SJL mice exposed to cuprizone intoxication reveal strain and gender pattern differences in demyelination. *Brain Pathol.* 19, 467–79.
- 137 Matsushima G.K. & Morell P. (2001) The neurotoxicant, cuprizone, as a model to study demyelination and remyelination in the central nervous system. *Brain Pathol.* 11, 107–116.
- 138 Blakemore W.F. (1972) Observations on oligodendrocyte degeneration, the resolution of status spongiosus and remyelination in cuprizone intoxication in mice. *J. Neurocytol.* 1, 413–426.
- 139 Venturini G. (1973) Enzymic activities and sodium, potassium and copper concentrations in mouse brain and liver after cuprizone treatment *in vivo*. *J. Neurochem.* 21, 1147–1151.
- 140 Pasquini L. a, Calatayud C. a, Bertone Uña a L., et al. (2007) The neurotoxic effect of cuprizone on oligodendrocytes depends on the presence of pro-inflammatory cytokines secreted by microglia. *Neurochem. Res.* 32, 279–92.
- 141 Dutta R., Chang A., Doud M.K., et al. (2011) Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. *Ann. Neurol.* 69, 445–54.
- 142 Geurts J.J., Bo L., Roosendaal S.D., et al. (2007) Extensive hippocampal demyelination in multiple sclerosis. *J.*

- Neuropathol. Exp. Neurol. 66, 819–827.
- 143 Vercellino M., Masera S., Lorenzatti M., et al. (2009) Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. *J. Neuropathol. Exp. Neurol.* 68, 489–502.
- 144 Papadopoulos D., Dukes S., Patel R., et al. (2009) Substantial archaeocortical atrophy and neuronal loss in multiple sclerosis. *Brain Pathol.* 19, 238–53.
- 145 Roosendaal S.D., Moraal B., Pouwels P.J.W., et al. (2009) Accumulation of cortical lesions in MS: relation with cognitive impairment. *Mult. Scler.* 15, 708–14.
- 146 Roosendaal S.D., Moraal B., Vrenken H., et al. (2008) *In vivo* MR imaging of hippocampal lesions in multiple sclerosis. *J. Magn. Reson. Imaging* 27, 726–31.
- 147 Anderson V.M., Fisniku L.K., Khaleeli Z., et al. (2010) Hippocampal atrophy in relapsing-remitting and primary progressive MS: a comparative study. *Mult. Scler.* 16, 1083–90.
- 148 Sicotte N.L., Kern K.C., Giesser B.S., et al. (2008) Regional hippocampal atrophy in multiple sclerosis. *Brain.*
- 149 Hulst H.E., Schoonheim M.M., Roosendaal S.D., et al. (2012) Functional adaptive changes within the hippocampal memory system of patients with multiple sclerosis. *Hum. Brain Mapp.* 33, 2268–80.
- 150 Duvernoy H.M. (1988) *The Human Hippocampus*. J.F. Bergmann Verlag, München.
- 151 Bliss T.V.P. & Lømo T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* 232, 331–356.
- 152 Lynch M.A. (2004) Long-Term Potentiation and Memory. *Physiol Rev* 84, 87–136.
- 153 Battaglia F.P., Benchenane K., Sirota A., et al. (2011) The hippocampus: hub of brain network communication for memory. *Trends Cogn. Sci.* 15, 310–8.
- 154 Nakazawa K., McHugh T.J., Wilson M. a, et al. (2004) NMDA receptors, place cells and hippocampal spatial memory. *Nat. Rev. Neurosci.* 5, 361–72.
- 155 Preston A.R. & Eichenbaum H. (2013) Interplay of hippocampus and prefrontal cortex in memory. *Curr. Biol.* 23, R764–73.
- 156 Deshmukh S.S. & Knierim J.J. (2011) Representation of non-spatial and spatial information in the lateral entorhinal cortex. *Front. Behav. Neurosci.* 5, 69.
- 157 Bird C.M. & Burgess N. (2008) The hippocampus and memory: insights from spatial processing. *Nat. Rev. Neurosci.* 9, 182–94.
- 158 Myhrer T. (2003) Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. *Brain Res. Rev.* 41, 268–287.
- 159 Drever B.D., Riedel G. & Platt B. (2011) The cholinergic system and hippocampal plasticity. *Behav. Brain Res.* 221, 505–14.
- 160 Muhlert N., Atzori M., De Vita E., et al. (2014) Memory in multiple sclerosis is linked to glutamate concentration in grey matter regions. *J. Neurol. Neurosurg. Psychiatry*, 1–7.
- 161 Bradford H.F., Ward H.K. & Thomas A.J. (1978) Glutamine-a major substrate for nerve endings. *J. Neurochem.* 30, 1453–1459.
- 162 Derouiche A. & Frotscher M. (1991) Astroglial processes around identified glutamatergic synapses contain glutamine syn : evidence for transmitter degradation. *Brain Res.* 552, 346–350.
- 163 Hansson E. & Rönnbäck L. (1995) Astrocytes in glutamate neurotransmission. *FASEB J.* 9, 343–350.
- 164 Traynelis S.F., Wollmuth L.P., McBain C.J., et al. (2010) Glutamate Receptor Ion Channels: Structure, Regulation, and Function. *Pharmacol. Rev.* 62, 405–496.
- 165 Bashir Z.I., Bortolotto Z.A., Davies C.H., et al. (1993) Induction of LTP in the hippocampus needs synaptic activation of

- glutamate metabotropic receptors. *Lett. to Nat.* 363, 347–350.
- 166 Mesulam M.-M. (2004) The cholinergic innervation of the human cerebral cortex. *Prog. Brain Res.* 145, 67–80.
- 167 Matthews D.A., Salvaterra P.M., Crawford G.D., et al. (1987) An immunocytochemical study of choline acetyltransferase-containing neurons and axon terminals in normal and partially deafferented hippocampal formation. *Brain Res.* 402, 30–43.
- 168 Frotscher M. & Léránth C. (1985) Cholinergic Innervation of the Rat Hippocampus as Revealed by Choline Acetyltransferase Immunocytochemistry: A Combined Light and Electron Microscopic Study. *J. Comp. Neurol.* 239, 237–246.
- 169 Oda Y. (1999) Choline acetyltransferase: The structure, distribution and pathologic changes in the central nervous system. *Pathol. Int.* 49, 921–937.
- 170 Dobransky T. & Rylett R.J. (2003) Functional Regulation of Choline Acetyltransferase by Phosphorylation\*. *Neurochem. Res.* 28, 537–542.
- 171 Schröder H., Zilles K., Maelicke A., et al. (1989) Immunohisto- and cytochemical localization of cortical nicotinic cholinergic receptors in rat and man. *Brain Res.* 502, 287–295.
- 172 Schröder H., Zilles K., Luiten P.G.M., et al. (1990) Immunocytochemical visualization of muscarinic cholinergic receptors in the human cerebral cortex. *Brain Res.* 514, 249–258.
- 173 McQuiston A.R. (2014) Acetylcholine release and inhibitory interneuron activity in hippocampal CA1. *Front. Synaptic Neurosci.* 6, 20.
- 174 Wells G.B. (2008) Structural answers and persistent questions about how nicotinic receptors work. *Front. Biosci.* 13, 5479–5510.
- 175 Soreq H. & Seidman S. (2001) Acetylcholinesterase — new roles for an old actor. *Nat. Rev. Neurosci.* 2, 294–302.
- 176 Hasselmo M.E. (2006) The role of acetylcholine in learning and memory. *Curr. Opin. Neurobiol.* 16, 710–5.
- 177 Deiana S., Platt B. & Riedel G. (2011) The cholinergic system and spatial learning. *Behav. Brain Res.* 221, 389–411.
- 178 Lombardo S. & Maskos U. (2014) Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. *Neuropharmacology*, 1–8.
- 179 Bartus R.T., Dean R.L.D., Beer B., et al. (1982) The Cholinergic Hypothesis of Geriatric Memory Dysfunction. *Science* 121, 408–417.
- 180 McBain C.J. & Fisahn A. (2001) Interneurons unbound. *Nat. Rev. Neurosci.* 2, 11–23.
- 181 Koós T. & Tepper J.M. (1999) Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nat. Neurosci.* 2, 467–472.
- 182 Pinal C. & Tobin A. (1998) Uniqueness and redundancy in GABA production. *Perspect. Dev. Neurobiol.* 5, 109–18.
- 183 Houser C.R. & Esclapez M. (1995) Localization of mRNAs encoding two forms of glutamic acid decarboxylase in the rat hippocampal formation. *Hippocampus* 4, 530–45.
- 184 Farrant M. & Kaila K. (2007) The cellular, molecular and ionic basis of GABA(A) receptor signalling. *Prog. Brain Res.* 160, 59–87.
- 185 Bettler B., Kaupmann K., Mosbacher J., et al. (2004) Molecular Structure and Physiological Functions of GABA-B Receptors. *Physiol Rev* 84, 835–867.
- 186 Davies C.H., Starkey S.J., Pozza M.F., et al. (1991) GABA<sub>B</sub> autoreceptors regulate the induction of LTP. *Lett. to Nat.* 349, 609–611.
- 187 Stelzer A., Simon G., Kovacs G., et al. (1994) Synaptic disinhibition during maintenance of long-term potentiation in the CA1 hippocampal subfield. *Proc. Natl. Acad. Sci. U. S. A.* 91, 3058–62.
- 188 Rao S., Leo G., Bernardin L., et al. (1991)

- Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 41, 685–691.
- 189 Benedict R.H.B. & Zivadinov R. (2011) Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nat. Rev. Neurol.* 7, 332–342.
- 190 Bobholz J.A. & Rao S.M. (2003) Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Curr. Opin. Neurol.* 16, 283.
- 191 Strober L.B., Rao S.M., Lee J.-C., et al. (2014) Cognitive impairment in multiple sclerosis: An 18 year follow-up study. *Mult. Scler. Relat. Disord.* 3, 473–481.
- 192 Rao S., Leo G., Ellington L., et al. (1991) Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* 41, 692–696.
- 193 Feuillet L., Reuter F., Audoin B., et al. (2007) Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult. Scler.* 13, 124–127.
- 194 Schulz D., Kopp B., Kunkel A., et al. (2006) Cognition in the early stage of multiple sclerosis. *J. Neurol.* 253, 1002–10.
- 195 Seinelä A., Hämäläinen P., Koivisto M., et al. (2002) Conscious and unconscious uses of memory in multiple sclerosis. *J. Neurol. Sci.* 198, 79–85.
- 196 Kenealy P.M., Beaumont J.G., Lintern T.C., et al. (2002) Autobiographical memory in advanced multiple sclerosis: assessment of episodic and personal semantic memory across three time spans. *J. Int. Neuropsychol. Soc.* 8, 855–60.
- 197 Benedict R.H.B., Cookfair D., Gavett R., et al. (2006) Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J. Int. Neuropsychol. Soc.* 12, 549–58.
- 198 Thornton A.E., Raz N. & Tucke K.A. (2002) Memory in multiple sclerosis: contextual encoding deficits. *J. Int. Neuropsychol. Soc.*
- 199 DeLuca J., Gaudino E. a, Diamond B.J., et al. (1998) Acquisition and storage deficits in multiple sclerosis. *J. Clin. Exp. Neuropsychol.* 20, 376–90.
- 200 Gaudino E., Chiaravalloti N., DeLuca J., et al. (2001) A comparison of memory performance in relapsing–remitting, primary progressive and secondary progressive multiple sclerosis. *Neuropsychiatry, Neuropsychol. Behav. Neurol.* 14, 32–44.
- 201 Patti F., Leone C. & D’Amico E. (2010) Treatment options of cognitive impairment in multiple sclerosis. *Neurol. Sci.* 31, S265–9.
- 202 Charil A., Zijdenbos A.P., Taylor J., et al. (2003) Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. *Neuroimage* 19, 532–544.
- 203 Tallantyre E.C., Bø L., Al-Rawashdeh O., et al. (2010) Clinico-pathological evidence that axonal loss underlies disability in progressive multiple sclerosis. *Mult. Scler.* 16, 406–11.
- 204 Lukens J.R., Gross J.M. & Kanneganti T.-D. (2012) IL-1 family cytokines trigger sterile inflammatory disease. *Front. Immunol.* 3, 1–12.
- 205 Llorens-Martín M., Blazquez-Llorca L., Benavides-Piccione R., et al. (2014) Selective alterations of neurons and circuits related to early memory loss in Alzheimer’s disease. *Front. Neuroanat.* 8, 1–12.
- 206 Lassmann H., Brück W. & Lucchinetti C.F. (2007) The immunopathology of multiple sclerosis: an overview. *Brain Pathol.* 17, 210–8.
- 207 Lassmann H. (2011) Review: the architecture of inflammatory demyelinating lesions: implications for studies on pathogenesis. *Neuropathol. Appl. Neurobiol.* 37, 698–710.
- 208 Barkhof F. (2002) The clinico-radiological paradox in multiple sclerosis revisited. *Curr. Opin. Neurol.* 15, 239–245.
- 209 Kutzelnigg A., Lucchinetti C.F., Stadelmann C., et al. (2005) Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain* 128, 2705–2712.

- 210 Gilmore C.P., Donaldson I., Bö L., et al. (2009) Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. *J. Neurol. Neurosurg. Psychiatry* 80, 182–7.
- 211 Bagnato F., Butman J.A., Gupta S., et al. (2006) *In vivo* Detection of Cortical Plaques by MR. *Am. J. Neuroradiol.* 27, 2161–2167.
- 212 Calabrese M., Rocca M.A., Atzori M., et al. (2009) Cortical lesions in primary progressive multiple sclerosis A 2-year longitudinal MR study. *Neurology* 72, 1330–1336.
- 213 Filippi M., Preziosa P., Pagani E., et al. (2012) Microstructural magnetic resonance imaging of cortical lesions in multiple sclerosis. *Mult. Scler. J.* 0, 1–9.
- 214 Sethi V., Yousry T.A., Muhlert N., et al. (2012) Improved detection of cortical MS lesions with phase-sensitive inversion recovery MRI. *J. Neurol. Neurosurg. Psychiatry* 83, 877–882.
- 215 Haase C.G., Tinnefeld M., Lienemann M., et al. (2003) Depression and cognitive impairment in disability-free early multiple sclerosis. *Behav. Neurol.* 14, 39–45.
- 216 Kooi E.-J., Strijbis E.M.M., van der Valk P., et al. (2012) Heterogeneity of cortical lesions in multiple sclerosis: clinical and pathologic implications. *Neurology* 79, 1369–76.
- 217 Lucchinetti C.F., Popescu B.F.G., Bunyan R.F., et al. (2011) Inflammatory cortical demyelination in early multiple sclerosis. *N. Engl. J. Med.* 365, 2188–2197.
- 218 Issazadeh S., Lorentzen J.C., Mustafa M.I., et al. (1996) Cytokines in relapsing experimental autoimmune encephalomyelitis in DA rats: persistent mRNA expression of proinflammatory cytokines and absent expression of interleukin-10 and transforming growth factor-beta. *J. Neuroimmunol.* 69, 103–15.
- 219 Martin D. (1995) Protective effect of the interleukin-1 receptor antagonist (IL-1ra) on experimental allergic encephalomyelitis in rats. *J. Neuroimmunol.* 61, 241–245.
- 220 Badovinac V., Mostarica-Stojković M., Dinarello C.A., et al. (1998) Interleukin-1 receptor antagonist suppresses experimental autoimmune encephalomyelitis (EAE) in rats by influencing the activation and proliferation of encephalitogenic cells. *J. Neuroimmunol.* 85, 87–95.
- 221 Furlan R., Bergami A., Brambilla E., et al. (2007) HSV-1-mediated IL-1 receptor antagonist gene therapy ameliorates MOG35-55-induced experimental autoimmune encephalomyelitis in C57BL/6 mice. *Gene Ther.* 14, 93–98.
- 222 Adelman M., Wood J., Benzel I., et al. (1995) The N-terminal domain of the myelin oligodendrocyte glycoprotein (MOG) induces acute demyelinating experimental autoimmune encephalomyelitis in the Lewis rat. *J. Neuroimmunol.* 63, 17–27.
- 223 Paxinos G., Watson C., Pennisi M., et al. (1985) Bregma, lambda and the interaural midpoint in stereotaxic surgery with rats of different sex, strain and weight. *J. Neurosci. Methods* 13, 139–43.
- 224 Young W. (1990) *In situ* hybridization histochemistry. In *Handbook of Chemical Neuroanatomy* (Björklund A., Hökfelt T., Wouterlood F.T., et al., eds.), pp. 481–512.
- 225 Schotanus K., Holtkamp G. & Meloen R. (1995) Domains of rat interleukin 1 beta involved in type I receptor binding. *Endocrinology* 136, 332–339.
- 226 Van Dam A.M., Poole S., Schultzberg M., et al. (1995) Effects of Peripheral Administration of LPS on the Expression of Immunoreactive Interleukin-1 $\alpha$ ,  $\beta$ , and Receptor Antagonist in Rat Brain. *Ann. N. Y. Acad. Sci.* 840, 128–138.
- 227 Dijkstra C.D., Döpp E. a, Joling P., et al. (1985) The heterogeneity of mononuclear phagocytes in lymphoid organs: distinct macrophage subpopulations in the rat recognized by monoclonal antibodies ED1, ED2 and ED3. *Immunology* 54, 589–99.
- 228 Wierinckx A., Brevé J., Mercier D., et al.

- (2005) Detoxication enzyme inducers modify cytokine production in rat mixed glial cells. *J. Neuroimmunol.* 166, 132–43.
- 229 Storch M.K., Bauer J., Linington C., et al. (2006) Cortical demyelination can be modeled in specific rat models of autoimmune encephalomyelitis and is major histocompatibility complex (MHC) haplotype-related. *J. Neuropathol. Exp. Neurol.* 65, 1137–42.
- 230 McGuinness M.C., Powers J.M., Bias W.B., et al. (1997) Human leukocyte antigens and cytokine expression in cerebral inflammatory demyelinating lesions of X-linked adrenoleukodystrophy and multiple sclerosis. *J. Neuroimmunol.* 75, 174–82.
- 231 Laman J.D., van Meurs M., Schellekens M.M., et al. (1998) Expression of accessory molecules and cytokines in acute EAE in marmoset monkeys (*Callithrix jacchus*). *J. Neuroimmunol.* 86, 30–45.
- 232 Murugesan N., Paul D., Lemire Y., et al. (2012) Active induction of experimental autoimmune encephalomyelitis by MOG35-55 peptide immunization is associated with differential responses in separate compartments of the choroid plexus. *Fluids Barriers CNS* 9, 15.
- 233 Dujmovic I., Mangano K., Pekmezovic T., et al. (2009) The analysis of IL-1 beta and its naturally occurring inhibitors in multiple sclerosis: The elevation of IL-1 receptor antagonist and IL-1 receptor type II after steroid therapy. *J. Neuroimmunol.* 207, 101–6.
- 234 Kleine T.O., Zwerenz P., Graser C., et al. (2003) Approach to discriminate subgroups in multiple sclerosis with cerebrospinal fluid (CSF) basic inflammation indices and TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8. *Brain Res. Bull.* 61, 327–346.
- 235 Dragunow M. (2013) Meningeal and choroid plexus cells--novel drug targets for CNS disorders. *Brain Res.* 1501, 32–55.
- 236 Nisticò R., Mango D., Mandolesi G., et al. (2013) Inflammation subverts hippocampal synaptic plasticity in experimental multiple sclerosis. *PLoS One* 8, e54666.
- 237 Batoulis H., Uhl M., Addicks K., et al. (2012) The magnitude of the Antigen-Specific T cell response is separated from the severity of spinal cord histopathology in remitting-relapsing experimental autoimmune encephalomyelitis. *Glia* 60, 794–805.
- 238 Li Q., Powell N., Zhang H., et al. (2011) Endothelial IL-1R1 is a critical mediator of EAE pathogenesis. *Brain. Behav. Immun.* 25, 160–167.
- 239 Van Dam A.-M., De Vries H.E., Kuiper J., et al. (1996) Interleukin-1 receptors on rat brain endothelial cells: a role in neuroimmune interaction? *FASEB J.* 10, 351–6.
- 240 Graeber M.B. & Streit W.J. (2010) Microglia: biology and pathology. *Acta Neuropathol.* 119, 89–105.
- 241 Li H., Cuzner M.L. & Newcombe J. (1996) Microglia-derived macrophages in early multiple sclerosis plaques. *Neuropathol. Appl. Neurobiol.* 22, 207–215.
- 242 Gay F.W., Drye T.J., Dick G.W., et al. (1997) The application of multifactorial cluster analysis in the staging of plaques in early multiple sclerosis. Identification and characterization of the primary demyelinating lesion. *Brain* 120, 1461–1483.
- 243 Ferrari C.C., Depino A.M., Prada F., et al. (2004) Reversible demyelination, blood-brain barrier breakdown, and pronounced neutrophil recruitment induced by chronic IL-1 expression in the brain. *Am. J. Pathol.* 165, 1827–1837.
- 244 Jana M. & Pahan K. (2005) Redox regulation of cytokine-mediated inhibition of myelin gene expression in human primary oligodendrocytes. *Free Radic. Biol. Med.* 39, 823–831.
- 245 Thornton P., Pinteaux E., Gibson R.M., et al. (2006) Interleukin-1-induced neurotoxicity is mediated by glia and requires caspase activation and free radical release. *J. Neurochem.* 98, 258–266.
- 246 Li Y., Liu L., Barger S.W., et al. (2003)

- Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. *J. Neurosci.* 23, 1605–1611.
- 247 Rossi S., Furlan R., De Chiara V., et al. (2012) Interleukin-1 $\beta$  causes synaptic hyperexcitability in multiple sclerosis. *Ann. Neurol.* 71, 76–83.
- 248 Moreno B., Jukes J.-P.P., Vergara-Irigaray N., et al. (2011) Systemic inflammation induces axon injury during brain inflammation. *Ann. Neurol.* 70, 932–942.
- 249 Cai Z., Lin S., Pang Y., et al. (2004) Brain injury induced by intracerebral injection of interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  in the neonatal rat. *Pediatr. Res.* 56, 377–384.
- 250 Fan L.-W., Mitchell H.J., Tien L.-T., et al. (2009) Interleukin-1 $\beta$ -induced brain injury in the neonatal rat can be ameliorated by  $\alpha$ -phenyl-n-tert-butyl-nitrone. *Exp. Neurol.* 220, 143–53.
- 251 Fan L.W., Tien L.T., Zheng B., et al. (2010) Interleukin-1 $\beta$ -induced brain injury and neurobehavioral dysfunctions in juvenile rats can be attenuated by  $\alpha$ -phenyl-n-tert-butyl-nitrone. *Neuroscience* 168, 240–252.
- 252 White S. & Barnes C. (1975) Spinal and spino-bulbo-spinal reflexes in rats with experimental allergic encephalomyelitis. *Brain Res.* 84, 123–128.
- 253 Sloane E., Ledebor A., Seibert W., et al. (2009) Anti-inflammatory cytokine gene therapy decreases sensory and motor dysfunction in experimental Multiple Sclerosis: MOG-EAE behavioral and anatomical symptom treatment with cytokine gene therapy. *Brain. Behav. Immun.* 23, 92–100.
- 254 Thibault K., Calvino B. & Pezet S. (2011) Characterisation of sensory abnormalities observed in an animal model of multiple sclerosis: a behavioural and pharmacological study. *Eur. J. Pain* 15, 231. e1–16.
- 255 Hobom M., Storch M.K., Weissert R., et al. (2004) Mechanisms and time course of neuronal degeneration in experimental autoimmune encephalomyelitis. *Brain Pathol.* 14, 148–57.
- 256 Quinn T., Dutt M. & Shindler K. (2011) Optic neuritis and retinal ganglion cell loss in a chronic murine model of multiple sclerosis. *Front. Neurol.* 2, 50.
- 257 Dutt M., Tabuena P., Ventura E., et al. (2010) Timing of corticosteroid therapy is critical to prevent retinal ganglion cell loss in experimental optic neuritis. *Invest. Ophthalmol. Vis. Sci.* 51, 1439–45.
- 258 Shindler K., Ventura E. & Rex T. (2007) SIRT1 activation confers neuroprotection in experimental optic neuritis. *Invest. Ophthalmol. Vis. Sci.* 48, 3602–3609.
- 259 de Groot V., Beckerman H., Uitdehaag B.M., et al. (2009) Physical and cognitive functioning after 3 years can be predicted using information from the diagnostic process in recently diagnosed multiple sclerosis. *Arch. Phys. Med. Rehabil.* 90, 1478–88.
- 260 Pollak Y., Orion E., Goshen I., et al. (2002) Experimental autoimmune encephalomyelitis-associated behavioral syndrome as a model of “depression due to multiple sclerosis”. *Brain. Behav. Immun.* 16, 533–43.
- 261 Musgrave T., Benson C., Wong G., et al. (2011) The MAO inhibitor phenelzine improves functional outcomes in mice with experimental autoimmune encephalomyelitis (EAE). *Brain. Behav. Immun.* 25, 1677–88.
- 262 Ziehn M.O., Avedisian A.A., Tiwari-Woodruff S., et al. (2010) Hippocampal CA1 atrophy and synaptic loss during experimental autoimmune encephalomyelitis, EAE. *Lab. Investig.* 0, 1–13.
- 263 Winocur G. (1985) The hippocampus and thalamus: their roles in short- and long-term memory and the effects of interference. *Behav. Brain Res.* 16, 135–52.
- 264 Lecourtier L. & Kelly P.H. (2007) A

- conductor hidden in the orchestra? Role of the habenular complex in monoamine transmission and cognition. *Neurosci. Biobehav. Rev.* 31, 658–72.
- 265 Rimvall K., Keller F. & Waser P.G. (1985) Development of cholinergic projections in organotypic cultures of rat septum, hippocampus and cerebellum. *Brain Res.* 351, 267–78.
- 266 Benedict R.H.B., Ramasamy D., Munschauer F., et al. (2009) Memory impairment in multiple sclerosis: correlation with deep grey matter and mesial temporal atrophy. *J. Neurol. Neurosurg. Psychiatry* 80, 201–6.
- 267 Kooi E.-J., Prins M., Bajic N., et al. (2011) Cholinergic imbalance in the multiple sclerosis hippocampus. *Acta Neuropathol.* 122, 313–22.
- 268 Lauterborn J.C., Isackson P.J., Montalvo R., et al. (1993) In situ hybridization localization of choline acetyltransferase mRNA in adult rat brain and spinal cord. *Mol. Brain Res.* 17, 59–69.
- 269 Tago H., McGeer P.L., McGeer E.G., et al. (1989) Distribution of choline acetyltransferase immunopositive structures in the rat brainstem. *Brain Res.* 495, 271–97.
- 270 Rada P., Mark G.P., Vitek M.P., et al. (1991) Interleukin-1 beta decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain Res.* 550, 287–90.
- 271 Taepavarapruk P. & Song C. (2010) Reductions of acetylcholine release and nerve growth factor expression are correlated with memory impairment induced by interleukin-1beta administrations: effects of omega-3 fatty acid EPA treatment. *J. Neurochem.* 112, 1054–64.
- 272 Giovannini M.G., Scali C., Prosperi C., et al. (2002)  $\beta$ -Amyloid-Induced Inflammation and Cholinergic Hypofunction in the Rat Brain *in vivo*: Involvement of the p38MAPK Pathway. *Neurobiol. Dis.* 11, 257–274.
- 273 Garcia J.H., Liu K.F. & Relton J.K. (1995) Interleukin-1 receptor antagonist decreases the number of necrotic neurons in rats with middle cerebral artery occlusion. *Am. J. Pathol.* 147, 1477.
- 274 Vogt C., Hailer N.P., Ghadban C., et al. (2008) Successful inhibition of excitotoxic neuronal damage and microglial activation after delayed application of interleukin-1 receptor antagonist. *J. Neurosci. Res.* 86, 3314–3321.
- 275 Mulcahy N.J., Ross J., Rothwell N.J., et al. (2009) Delayed administration of interleukin-1 receptor antagonist protects against transient cerebral ischaemia in the rat. *Br. J. Pharmacol.* 140, 471–476.
- 276 Palin K., Verrier D., Tridon V., et al. (2004) Influence of the course of brain inflammation on the endogenous IL-1beta/IL-1Ra balance in the model of brain delayed-type hypersensitivity response to bacillus Calmette-Guerin in Lewis rats. *J. Neuroimmunol.* 149, 22–30.
- 277 Dinarello C. a & Thompson R.C. (1991) Blocking IL-1: interleukin 1 receptor antagonist *in vivo* and *in vitro*. *Immunol. Today* 12, 404–10.
- 278 Granowitz E., Clark B., Vannier E., et al. (1992) Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: I. IL-1 receptor antagonist inhibits IL-1-induced cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes. *Blood* 79, 2356–2363.
- 279 Arend W.P., Welgus H.G., Thompson R.C., et al. (1990) Biological Properties of Recombinant Human Monocyte-derived Interleukin 1 Receptor Antagonist. *J. Clin. Invest.* 85, 1694–1697.
- 280 Loddick S. a & Rothwell N.J. (1996) Neuroprotective effects of human recombinant interleukin-1 receptor antagonist in focal cerebral ischaemia in the rat. *J. Cereb. Blood Flow Metab.* 16, 932–40.
- 281 Nicoletti F., Patti F., DiMarco R., et al. (1996) Circulating serum levels of IL-1ra in patients with relapsing remitting multiple sclerosis are normal during remission phases but significantly increased either during exacerbations or in response to IFN-



- beta treatment. *Cytokine* 8, 395–400.
- 282 Burger D., Molnarfi N., Weber M.S., et al. (2009) Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1beta in human monocytes and multiple sclerosis. *Proc. Natl. Acad. Sci. U. S. A.* 106, 4355–9.
- 283 Comabella M., Julià E., Tintoré M., et al. (2008) Induction of serum soluble tumor necrosis factor receptor II (sTNF-RII) and interleukin-1 receptor antagonist (IL-1ra) by interferon beta-1b in patients with progressive multiple sclerosis. *J. Neurol.* 255, 1136–41.
- 284 Liu J.S., Amaral T.D., Brosnan C.F., et al. (1998) IFNs are critical regulators of IL-1 receptor antagonist and IL-1 expression in human microglia. *J. Immunol.* 161, 1989–96.
- 285 Vercellino M., Plano E., Votta B., et al. (2005) Grey matter pathology in multiple sclerosis. *J. Neuropathol. Exp. Neurol.* 64, 1101–7.
- 286 Huitinga I., De Groot C.J.A., Van der Valk P., et al. (2001) Hypothalamic lesions in multiple sclerosis. *J. Neuropathol. Exp. Neurol.* 60, 1208–1218.
- 287 Kutzelnigg A., Faber-Rod J.C., Bauer J., et al. (2007) Widespread demyelination in the cerebellar cortex in multiple sclerosis. *Brain Pathol.* 17, 38–44.
- 288 Kutzelnigg A., Lucchinetti C.F., Stadelmann C., et al. (2005) Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain* 128, 2705–2712.
- 289 Lucchinetti C., Brück W., Parisi J., et al. (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann. Neurol.* 47, 707–17.
- 290 Martin R., McFarland H.F. & McFarlin D.E. (1992) Immunological aspects of demyelinating diseases. *Annu. Rev. Immunol.* 10, 153–87.
- 291 Sospedra M. & Martin R. (2005) Immunology of multiple sclerosis. *Annu. Rev. Immunol.* 23, 683–747.
- 292 Tran E.H., Hoekstra K., Rooijen N. Van, et al. (1998) Immune Invasion of the Central Nervous System Parenchyma and Experimental Allergic Encephalomyelitis, But Not Leukocyte Extravasation from Blood, Are Prevented in Macrophage-Depleted Mice. *J. Immunol.* 161, 3767–3775.
- 293 O'Connor R.A., Prendergast C.T., Catherine A., et al. (2008) Cutting Edge: Th1 Cells Facilitate the Entry of Th17 Cells to the Central Nervous System during Experimental Autoimmune Encephalomyelitis. *J. Immunol.* 181, 3750–3754.
- 294 Popescu B.F.G., Bunyan R.F., Parisi J.E., et al. (2011) A case of multiple sclerosis presenting with inflammatory cortical demyelination. *Neurology* 76, 1705–10.
- 295 Brink B.P., Veerhuis R., Breij E.C.W., et al. (2005) The pathology of multiple sclerosis is location-dependent: no significant complement activation is detected in purely cortical lesions. *J. Neuropathol. Exp. Neurol.* 64, 147–55.
- 296 Zhang J., Shi X.Q., Echeverry S., et al. (2007) Expression of CCR2 in both resident and bone marrow-derived microglia plays a critical role in neuropathic pain. *J. Neurosci.* 27, 12396–406.
- 297 Brini E., Ruffini F., Bergami A., et al. (2009) Administration of a monomeric CCL2 variant to EAE mice inhibits inflammatory cell recruitment and protects from demyelination and axonal loss. *J. Neuroimmunol.* 209, 33–9.
- 298 Tanuma N., Sakuma H., Sasaki A., et al. (2006) Chemokine expression by astrocytes plays a role in microglia/macrophage activation and subsequent neurodegeneration in secondary progressive multiple sclerosis. *Acta Neuropathol.* 112, 195–204.
- 299 Simpson J.E., Newcombe J., Cuzner M.L., et al. (1998) Expression of monocyte chemoattractant protein-1 and other beta-chemokines by resident glia and inflammatory cells in multiple sclerosis

- lesions. *J. Neuroimmunol.* 84, 238–49.
- 300 Van Der Voorn P, Tekstra J, Beelen R.H., et al. (1999) Expression of MCP-1 by reactive astrocytes in demyelinating multiple sclerosis lesions. *Am. J. Pathol.* 154, 45–51.
- 301 Dutta R., Chomyk A.M., Chang A., et al. (2013) Hippocampal demyelination and memory dysfunction are associated with increased levels of the neuronal microRNA miR-124 and reduced AMPA receptors. *Ann. Neurol.* 73, 637–45.
- 302 Todorov I.T., Werness B. a, Wang H.Q., et al. (1998) HsMCM2/BM28: a novel proliferation marker for human tumors and normal tissues. *Lab. Investig.* 78, 73–8.
- 303 Bö L., Mörk S., Kong P. a, et al. (1994) Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions. *J. Neuroimmunol.* 51, 135–46.
- 304 Trapp B.D., Peterson J., Ransohoff R.M., et al. (1998) Axonal transection in the lesions of multiple sclerosis. *N. Engl. J. Med.* 338, 278–85.
- 305 van der Valk P. & De Groot C.J. (2000) Staging of multiple sclerosis (MS) lesions: pathology of the time frame of MS. *Neuropathol. Appl. Neurobiol.* 26, 2–10.
- 306 Ledebuer A., Breve J.J.P., Wierinckx A., et al. (2002) Expression and regulation of interleukin-10 and interleukin-10 receptor in rat astroglial and microglial cells. *Eur. J. Neurosci.* 16, 1175–1185.
- 307 Matute C. (2011) Glutamate and ATP signalling in white matter pathology. *J. Anat.* 219, 53–64.
- 308 Franke H., Verkhatsky A., Burnstock G., et al. (2012) Pathophysiology of astroglial purinergic signalling. *Purinergic Signal.* 8, 629–57.
- 309 Panenka W., Jijon H., Herx L.M., et al. (2001) P2X7-like receptor activation in astrocytes increases chemokine monocyte chemoattractant protein-1 expression via mitogen-activated protein kinase. *J. Neurosci.* 21, 7135–42.
- 310 Shin N., Baribaud F, Wang K., et al. (2009) Pharmacological characterization of INCB3344, a small molecule antagonist of human CCR2. *Biochem. Biophys. Res. Commun.* 387, 251–5.
- 311 Brodmerkel C.M., Huber R., Covington M., et al. (2005) Discovery and Pharmacological Characterization of a Novel Rodent-Active CCR2 Antagonist, INCB3344. *J. Immunol.* 175, 5370–5378.
- 312 Rudick R. a, Lee J.-C., Nakamura K., et al. (2009) Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. *J. Neurol. Sci.* 282, 106–11.
- 313 Fisher E., Lee J.-C., Nakamura K., et al. (2008) Gray matter atrophy in multiple sclerosis: a longitudinal study. *Ann. Neurol.* 64, 255–65.
- 314 Fisniku L.K., Chard D.T., Jackson J.S., et al. (2008) Gray matter atrophy is related to long-term disability in multiple sclerosis. *Ann. Neurol.* 64, 247–54.
- 315 McManus C., Berman J.W., Brett F.M., et al. (1998) MCP-1, MCP-2 and MCP-3 expression in multiple sclerosis lesions: an immunohistochemical and in situ hybridization study. *J. Neuroimmunol.* 86, 20–9.
- 316 Butt A.M., Fern R.F. & Matute C. (2014) Neurotransmitter signaling in white matter. *Glia*, 1–18.
- 317 Buschmann J.P., Berger K., Awad H., et al. (2012) Inflammatory response and chemokine expression in the white matter corpus callosum and gray matter cortex region during cuprizone-induced demyelination. *J. Mol. Neurosci.* 48, 66–76.
- 318 Matyash V. & Kettenmann H. (2010) Heterogeneity in astrocyte morphology and physiology. *Brain Res. Rev.* 63, 2–10.
- 319 Hewett J. a (2009) Determinants of regional and local diversity within the astroglial lineage of the normal central nervous system. *J. Neurochem.* 110, 1717–36.
- 320 Goursaud S., Kozlova E.N., Maloteaux J.-M., et al. (2009) Cultured astrocytes derived

- from corpus callosum or cortical grey matter show distinct glutamate handling properties. *J. Neurochem.* 108, 1442–52.
- 321 Prins M., Eriksson C., Wierinckx A., et al. (2013) Interleukin-1 $\beta$  and Interleukin-1 Receptor Antagonist Appear in Grey Matter Additionally to White Matter Lesions during Experimental Multiple Sclerosis. *PLoS One* 8, e83835.
- 322 Biber K., Neumann H., Inoue K., et al. (2007) Neuronal “On” and “Off” signals control microglia. *Trends Neurosci.* 30, 596–602.
- 323 Chavarría A. & Cárdenas G. (2013) Neuronal influence behind the central nervous system regulation of the immune cells. *Front. Integr. Neurosci.* 7, 64.
- 324 Tian L., Rauvala H. & Gahmberg C.G. (2009) Neuronal regulation of immune responses in the central nervous system. *Trends Immunol.* 30, 91–9.
- 325 van Horssen J., Brink B.P., de Vries H.E., et al. (2007) The blood-brain barrier in cortical multiple sclerosis lesions. *J. Neuropathol. Exp. Neurol.* 66, 321–8.
- 326 Mittelbronn M., Dietz K., Schluesener H.J., et al. (2001) Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magnitude. *Acta Neuropathol.* 101, 249–255.
- 327 Gehrmann J., Banati R.B. & Kreutzberg G.W. (1993) Microglia in the immune surveillance of the brain: human microglia constitutively express HLA-DR molecules. *J. Neuroimmunol.* 48, 189–98.
- 328 Hart A.D., Wyttenbach A., Perry V.H., et al. (2012) Age related changes in microglial phenotype vary between CNS regions: grey versus white matter differences. *Brain. Behav. Immun.* 26, 754–65.
- 329 Li T., Pang S., Yu Y., et al. (2013) Proliferation of parenchymal microglia is the main source of microgliosis after ischaemic stroke. *Brain* 136, 3578–88.
- 330 Sørensen T.L., Tani M., Jensen J., et al. (1999) Expression of specific chemokines and chemokine receptors in the central nervous system of multiple sclerosis patients. *J. Clin. Invest.* 103, 807–15.
- 331 Furtado G.C., Marcondes M.C.G., Tsai J., et al. (2008) Swift Entry of Myelin-Specific T Lymphocytes into the Central Nervous System in Spontaneous Autoimmune Encephalomyelitis. *J. Immunol.* 181, 4648–4655.
- 332 McFarland H.F. & Martin R. (2007) Multiple sclerosis: a complicated picture of autoimmunity. *Nat. Immunol.* 8, 913–9.
- 333 Traugott U., Reinherz E.L. & Raine C.S. (1983) Multiple sclerosis. Distribution of T cells, T cell subsets and Ia-positive macrophages in lesions of different ages. *J. Neuroimmunol.* 4, 201–21.
- 334 Weiss H. a., Millward J.M. & Owens T. (2007) CD8+ T cells in inflammatory demyelinating disease. *J. Neuroimmunol.* 191, 79–85.
- 335 Howell O.W., Reeves C. a, Nicholas R., et al. (2011) Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. *Brain* 134, 2755–71.
- 336 Choi S.R., Howell O.W., Carassiti D., et al. (2012) Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. *Brain* 135, 2925–37.
- 337 Bakshi R. (2003) Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult. Scler.* 9, 219–227.
- 338 Comi G., Leocani L., Rossi P., et al. (2001) Physiopathology and treatment of fatigue in multiple sclerosis. *J. Neurol.* 248, 174–179.
- 339 Induruwa I., Constantinescu C.S. & Gran B. (2012) Fatigue in multiple sclerosis - a brief review. *J. Neurol. Sci.* 323, 9–15.
- 340 Amor S., Puentes F., Baker D., et al. (2010) Inflammation in neurodegenerative diseases. *Immunology* 129, 154–69.
- 341 Stadelmann C., Wegner C. & Brück W. (2011) Inflammation, demyelination, and degeneration - recent insights from MS pathology. *Biochim. Biophys. Acta* 1812,

- 275–82.
- 342 Barnett M.H. & Prineas J.W. (2004) Relapsing and Remitting Multiple Sclerosis: Pathology of the Newly Forming Lesion. *Ann. Neurol.* 55, 458–68.
- 343 Henderson A.P., Barnett M.H., Parratt J.D., et al. (2009) Multiple sclerosis: distribution of inflammatory cells in newly forming lesions. *Ann Neurol* 66, 739–753.
- 344 Marik C., Felts P. a, Bauer J., et al. (2007) Lesion genesis in a subset of patients with multiple sclerosis: a role for innate immunity? *Brain* 130, 2800–15.
- 345 Trapp B.D. & Nave K.-A. (2008) Multiple sclerosis: an immune or neurodegenerative disorder? *Annu. Rev. Neurosci.* 31, 247–69.
- 346 Way S.W., Podojil J.R., Clayton B.L., et al. (2015) Pharmaceutical integrated stress response enhancement protects oligodendrocytes and provides a potential multiple sclerosis therapeutic. *Nat. Commun.* 6, 6532.
- 347 Kolbe S.C., Marriott M., Walt A. Van Der, et al. (2012) Diffusion tensor imaging correlates of visual impairment in multiple sclerosis and chronic optic neuritis. *Invest. Ophthalmol. Vis. Sci.* 53, 825–32.
- 348 Popescu B.F.G. & Lucchinetti C.F. (2012) Pathology of Demyelinating Diseases. *Annu. Rev. Pathol.* 7, 185–217.
- 349 van Waesberghe J.H., Kamphorst W., De Groot C.J., et al. (1999) Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann. Neurol.* 46, 747–54.
- 350 van der Valk P. & Amor S. (2009) Preactive lesions in multiple sclerosis. *Curr. Opin. Neurol.* 22, 207–13.
- 351 Singh S., Metz I., Amor S., et al. (2013) Microglial nodules in early multiple sclerosis white matter are associated with degenerating axons. *Acta Neuropathol.* 125, 595–608.
- 352 Bö L., Geurts J.J.G., van der Valk P, et al. (2007) Lack of Correlation Between Cortical Demyelination and White Matter Pathologic Changes in Multiple Sclerosis. *Arch. Neurol.* 64, 76–80.
- 353 Feinstein A., Roy P., Lobaugh N., et al. (2004) Structural brain abnormalities in multiple sclerosis patients with major depression. *Neurology* 62, 586–90.
- 354 Booss J., Esiri M.M., Tourtellotte W.W., et al. (1983) Immunohistological analysis of T lymphocyte subsets in the central nervous system in chronic progressive multiple sclerosis. *J. Neurol. Sci.* 62, 219–32.
- 355 Wucherpfennig B.K.W., Newcombe J., Li H., et al. (1992) T Cell Receptor Valpha-Vbeta Repertoire and Cytokine Gene Expression in Active Multiple Sclerosis Lesions. *J. Exp. Med.* 175, 993–1002.
- 356 Disanto G., Morahan J.M., Barnett M.H., et al. (2012) The evidence for a role of B cells in multiple sclerosis. *Neurology* 78, 823–32.
- 357 Kaur G., Trowsdale J. & Fugger L. (2013) Natural killer cells and their receptors in multiple sclerosis. *Brain* 136, 2657–76.
- 358 Bar-Or A. & Darlington P.J. (2011) The immunology of multiple sclerosis. In *Multiple Sclerosis Therapeutics* (Cohen J.A. & Rudick R.A., eds.), Fourth edi, pp. 20–34. Cambridge University Press, Cambridge.
- 359 Huitinga I., van Rooijen N., de Groot C.J., et al. (1990) Suppression of experimental allergic encephalomyelitis in Lewis rats after elimination of macrophages. *J. Exp. Med.* 172, 1025–33.
- 360 Mosser D.M. & Edwards J.P. (2008) Exploring the full spectrum of macrophage activation. *Nat. Rev. Immunol.* 8, 958–69.
- 361 Vogel D.Y.S., Vereyken E.J.F., Glim J.E., et al. (2013) Macrophages in inflammatory multiple sclerosis lesions have an intermediate activation status. *J. Neuroinflammation* 10, 35.
- 362 Owens T., Bechmann I. & Engelhardt B. (2008) Perivascular Spaces and the Two Steps to Neuroinflammation. *J. Neuropathol. Exp. Neurol.* 67, 1113–1121.
- 363 Ballabh P., Braun A. & Nedergaard M. (2004) The blood-brain barrier: an

- overview: structure, regulation, and clinical implications. *Neurobiol. Dis.* 16, 1–13.
- 364 Zlokovic B. V. (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 57, 178–201.
- 365 Ley K., Laudanna C., Cybulsky M.I., et al. (2007) Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat. Rev. Immunol.* 7, 678–89.
- 366 Kebir H., Kreymborg K., Ifergan I., et al. (2007) Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat. Med.* 13, 1173–5.
- 367 Agrawal S., Anderson P., Durbeej M., et al. (2006) Dystroglycan is selectively cleaved at the parenchymal basement membrane at sites of leukocyte extravasation in experimental autoimmune encephalomyelitis. *J. Exp. Med.* 203, 1007–19.
- 368 Metz I., Lucchinetti C.F., Openshaw H., et al. (2007) Autologous haematopoietic stem cell transplantation fails to stop demyelination and neurodegeneration in multiple sclerosis. *Brain* 130, 1254–62.
- 369 Benarroch E.E. (2013) Microglia: Multiple roles in surveillance, circuit shaping, and response to injury. *Neurology*, 1–10.
- 370 Jack C., Antel J. & Uck W.B.R. (2007) Contrasting Potential of Nitric Oxide and Peroxynitrite to Mediate Oligodendrocyte Injury in Multiple Sclerosis. 934, 926–934.
- 371 Stadelmann C., Kerschensteiner M., Misgeld T., et al. (2002) BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune and neuronal cells? *Brain* 125, 75–85.
- 372 Farina C., Aloisi F. & Meinl E. (2007) Astrocytes are active players in cerebral innate immunity. *Trends Immunol.* 28, 138–45.
- 373 Dong Y. & Benveniste E.N. (2001) Immune Function of Astrocytes. *Glia* 190, 180–190.
- 374 Ponomarev E.D., Shriver L.P., Maresz K., et al. (2005) Microglial cell activation and proliferation precedes the onset of CNS autoimmunity. *J. Neurosci. Res.* 81, 374–89.
- 375 D'Amelio F.E., Smith M.E. & Eng L.F. (1990) Sequence of tissue responses in the early stages of experimental allergic encephalomyelitis (EAE): Immunohistochemical, light microscopic, and ultrastructural observations in the spinal cord. *Glia* 3, 229–240.
- 376 Morcos Y., Lee S.M. & Levin M.C. (2003) A role for hypertrophic astrocytes and astrocyte precursors in a case of rapidly progressive multiple sclerosis. *Mult. Scler.* 9, 332–341.
- 377 Heppner F.L., Greter M., Marino D., et al. (2005) Experimental autoimmune encephalomyelitis repressed by microglial paralysis. *Nat. Med.* 11, 146–52.
- 378 Xiao Y., Jin J., Chang M., et al. (2013) Peli1 promotes microglia-mediated CNS inflammation by regulating Traf3 degradation. *Nat. Med.* 19, 595–602.
- 379 Skripuletz T., Hackstette D., Bauer K., et al. (2013) Astrocytes regulate myelin clearance through recruitment of microglia during cuprizone-induced demyelination. *Brain* 136, 147–67.
- 380 Kotter M.R., Zhao C., van Rooijen N., et al. (2005) Macrophage-depletion induced impairment of experimental CNS remyelination is associated with a reduced oligodendrocyte progenitor cell response and altered growth factor expression. *Neurobiol. Dis.* 18, 166–75.
- 381 Voss E.V., Škuljec J., Gudi V., et al. (2012) Characterisation of microglia during de- and remyelination: can they create a repair promoting environment? *Neurobiol. Dis.* 45, 519–28.
- 382 Rawji K.S. & Yong V.W. (2013) The benefits and detriments of macrophages/microglia in models of multiple sclerosis. *Clin. Dev. Immunol.* 2013, 1–13.
- 383 Miljković D., Timotijević G. & Mostarica Stojković M. (2011) Astrocytes in the tempest of multiple sclerosis. *FEBS Lett.*

- 585, 3781–8.
- 384 Peferoen L.A.N., Vogel D.Y.S., Ummenthum K., et al. (2015) Activation Status of Human Microglia Is Dependent on Lesion Formation Stage and Remyelination in Multiple Sclerosis. *J. Neuropathol. Exp. Neurol.* 74, 48–63.
- 385 Politis M., Giannetti P., Su P., et al. (2012) Increased PK11195 PET binding in the cortex of patients with MS correlates with disability. *Neurology* 79, 523–30.
- 386 Peterson J.W., Bö L., Mörk S., et al. (2002) VCAM-1-positive microglia target oligodendrocytes at the border of multiple sclerosis lesions. *J. Neuropathol. Exp. Neurol.* 61, 539–46.
- 387 Davalos D., Ryu J.K., Merlini M., et al. (2012) Fibrinogen-induced perivascular microglial clustering is required for the development of axonal damage in neuroinflammation. *Nat. Commun.* 3, 1227.
- 388 di Penta A., Moreno B., Reix S., et al. (2013) Oxidative stress and proinflammatory cytokines contribute to demyelination and axonal damage in a cerebellar culture model of neuroinflammation. *PLoS One* 8, e54722.
- 389 Yates R.L., Esiri M.M., Palace J., et al. (2015) The influence of HLA-DRB1\*15 on motor cortical pathology in multiple sclerosis. *Neuropathol. Appl. Neurobiol.* 41, 371–384.
- 390 Napoli I. & Neumann H. (2010) Protective effects of microglia in multiple sclerosis. *Exp. Neurol.* 225, 24–8.
- 391 Melief J., Schuurman K.G., van de Garde M.D.B., et al. (2013) Microglia in normal appearing white matter of multiple sclerosis are alerted but immunosuppressed. *Glia* 61, 1848–61.
- 392 Takahashi K., Rochford C.D.P. & Neumann H. (2005) Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. *J. Exp. Med.* 201, 647–57.
- 393 Piccio L., Buonsanti C., Mariani M., et al. (2007) Blockade of TREM-2 exacerbates experimental autoimmune encephalomyelitis. *Eur. J. Immunol.* 37, 1290–301.
- 394 Kotter M.R., Li W.-W., Zhao C., et al. (2006) Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. *J. Neurosci.* 26, 328–32.
- 395 Bannerman P., Hahn A., Soulika A., et al. (2007) Astroglia in EAE Spinal Cord: Derivation from Radial Glia, and Relationships to Oligodendroglia. *Glia* 64, 57–64.
- 396 Clarner T., Diederichs F., Berger K., et al. (2012) Myelin debris regulates inflammatory responses in an experimental demyelination animal model and multiple sclerosis lesions. *Glia* 60, 1468–80.
- 397 Prins M., Dutta R., Baselmans B., et al. (2014) Discrepancy in CCL2 and CCR2 expression in white versus grey matter hippocampal lesions of Multiple Sclerosis patients. *Acta Neuropathol. Commun.* 2, 98.
- 398 Haider L., Simeonidou C., Steinberger G., et al. (2014) Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. *J. Neurol. Neurosurg. Psychiatry*, 1–10.
- 399 Giannetti P., Politis M., Su P., et al. (2015) Increased PK11195-PET binding in normal-appearing white matter in clinically isolated syndrome. *Brain* 138, 110–119.
- 400 Calabrese M., Battaglini M., Giorgio A., et al. (2010) Imaging distribution and frequency of cortical lesions in patients with multiple sclerosis. *Neurology* 75, 1234–1240.
- 401 Ingram G., Loveless S., Howell O.W., et al. (2014) Complement activation in multiple sclerosis plaques: an immunohistochemical analysis. *Acta Neuropathol. Commun.* 2, 53.
- 402 Pham H., Ramp A. a, Klonis N., et al. (2009) The astrocytic response in early experimental autoimmune encephalomyelitis occurs across both the grey and white matter compartments. *J.*

- Neuroimmunol. 208, 30–9.
- 403 Schwartz M., Kipnis J., Rivest S., et al. (2013) How Do Immune Cells Support and Shape the Brain in Health, Disease, and Aging? *J. Neurosci.* 33, 17587–17596.
- 404 Baruch K., Ron-Harel N., Gal H., et al. (2013) CNS-specific immunity at the choroid plexus shifts toward destructive Th2 inflammation in brain aging. *Proc. Natl. Acad. Sci. U. S. A.* 110, 2264–2269.
- 405 Reboldi A., Coisne C., Baumjohann D., et al. (2009) C-C chemokine receptor 6-regulated entry of TH-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. *Nat. Immunol.* 10, 514–23.
- 406 Wright G.J., Jones M., Puklavec M.J., et al. (2001) The unusual distribution of the neuronal/lymphoid cell surface CD200 (OX2) glycoprotein is conserved in humans. *Immunology* 102, 173–9.
- 407 Hernangómez M., Mestre L., Correa F.G., et al. (2012) CD200-CD200R1 interaction contributes to neuroprotective effects of anandamide on experimentally induced inflammation. *Glia* 60, 1437–50.
- 408 Smith R.E., Patel V., Seatter S.D., et al. (2003) A novel MyD-1 (SIRP-1alpha) signaling pathway that inhibits LPS-induced TNFalpha production by monocytes. *Blood* 102, 2532–40.
- 409 Oldenburg P. a, Gresham H.D. & Lindberg F.P. (2001) CD47-signal regulatory protein alpha (SIRPalpha) regulates Fcgamma and complement receptor-mediated phagocytosis. *J. Exp. Med.* 193, 855–62.
- 410 Koning N., Swaab D.F., Hoek R.M., et al. (2009) Distribution of the immune inhibitory molecules CD200 and CD200R in the normal central nervous system and multiple sclerosis lesions suggests neuron-glia and glia-glia interactions. *J. Neuropathol. Exp. Neurol.* 68, 159–67.
- 411 Gitik M., Liraz-Zaltsman S., Oldenburg P.-A., et al. (2011) Myelin down-regulates myelin phagocytosis by microglia and macrophages through interactions between CD47 on myelin and SIRPα (signal regulatory protein-α) on phagocytes. *J. Neuroinflammation* 8, 24.
- 412 Koning N., Bö L., Hoek R.M., et al. (2007) Downregulation of macrophage inhibitory molecules in multiple sclerosis lesions. *Ann. Neurol.* 62, 504–14.
- 413 Tian L., Lappalainen J., Autero M., et al. (2008) Shedded neuronal ICAM-5 suppresses T-cell activation. *Blood* 111, 3615–25.
- 414 Harrison J.K., Jiang Y., Chen S., et al. (1998) Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. *Proc. Natl. Acad. Sci. U. S. A.* 95, 10896–901.
- 415 Smolders J., Remmerswaal E.B.M., Schuurman K.G., et al. (2013) Characteristics of differentiated CD8(+) and CD4 (+) T cells present in the human brain. *Acta Neuropathol.* 126, 525–35.
- 416 Cardona A.E., Pioro E.P., Sasse M.E., et al. (2006) Control of microglial neurotoxicity by the fractalkine receptor. *Nat. Neurosci.* 9, 917–24.
- 417 Mizuno T., Kawanokuchi J., Numata K., et al. (2003) Production and neuroprotective functions of fractalkine in the central nervous system. *Brain Res.* 979, 65–70.
- 418 Niswender C.M. & Conn P.J. (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu. Rev. Pharmacol. Toxicol.* 50, 295–322.
- 419 Taylor D.L., Diemel L.T. & Pocock J.M. (2003) Activation of Microglial Group III Metabotropic Glutamate Receptors Protects Neurons against Microglial Neurotoxicity. *J. Neurosci.* 23, 2150–2160.
- 420 Pocock J.M. & Kettenmann H. (2007) Neurotransmitter receptors on microglia. *TRENDS Neurosci.* 30, 527–35.
- 421 Kukley M., Capetillo-Zarate E. & Dietrich D. (2007) Vesicular glutamate release from axons in white matter. *Nat. Neurosci.* 10, 311–20.

- 422 Jensen J.E., Frederick B.D.B. & Renshaw P.F. (2005) Grey and white matter GABA level differences in the human brain using two-dimensional, J-resolved spectroscopic imaging. *NMR Biomed.* 18, 570–6.
- 423 Gudi V., Moharreggh-Khiabani D., Skripuletz T., et al. (2009) Regional differences between grey and white matter in cuprizone induced demyelination. *Brain Res.* 1283, 127–38.
- 424 Lawson L.J., Perry V.H., Dri P., et al. (1990) Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience* 39, 151–70.
- 425 Nacken W., Roth J., Sorg C., et al. (2003) S100A9/S100A8: Myeloid representatives of the S100 protein family as prominent players in innate immunity. *Microsc. Res. Tech.* 60, 569–80.
- 426 Merkler D., Böske R., Schmelting B., et al. (2006) Differential Macrophage / Microglia Activation in Neocortical EAE Lesions in the Marmoset Monkey. *Brain Pathol.* 16, 117–123.
- 427 Benedict R.H.B., Cookfair D., Gavett R., et al. (2006) Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J. Int. Neuropsychol. Soc.* 12, 549–58.
- 428 Squire L.R., Stark C.E. & Clark R.E. (2004) The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- 429 Gold S.M., Kern K.C., O'Connor M.-F., et al. (2010) Smaller cornu ammonis 2-3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. *Biol. Psychiatry* 68, 553–559.
- 430 Roosendaal S.D., Hulst H.E., Vrenken H., et al. (2010) Structural and Functional Hippocampal Changes in Multiple Sclerosis Patients with Intact Memory Function. *Radiology* 255, 595–604.
- 431 Drachman D.A. & Leavitt J. (1974) Human memory and the cholinergic system. A relationship to aging? *Arch. Neurol.* 30, 113–121.
- 432 Everitt B.J. & Robbins T.W. (1997) Central cholinergic systems and cognition. *Annu. Rev. Psychol.* 48, 649 – 684.
- 433 Contestabile A. & Ciani E. (2008) The place of choline acetyltransferase activity measurement in the “cholinergic hypothesis” of neurodegenerative diseases. *Neurochem. Res.* 33, 318–327.
- 434 Davies P. & Maloney A.J.F. (1976) Selective loss of central cholinergic neurons in Alzheimer’s Disease. *Lancet*, 1403.
- 435 Francis P.T., Palmer A.M., Snape M., et al. (1999) The cholinergic hypothesis of Alzheimer’s disease: a review of progress. *J. Neurol. Neurosurg. Psychiatry* 66, 137–147.
- 436 Henke H. & Lang W. (1983) Cholinergic Enzymes in Neocortex, Hippocampus and Basal Forebrain of Non-Neurological and Senile Dementia of Alzheimer-Type Patients\*. *Brain Res.* 267, 281–291.
- 437 Perry E.K., Tomlinson B.E., Blessed G., et al. (1978) Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Br. Med. J.* 2, 1457–1459.
- 438 Sims N.R., Bowen D.M., Allen S.J., et al. (1983) Presynaptic Cholinergic Dysfunction in Patients with Dementia. *J. Neurochem.* 40, 503–509.
- 439 Wilcock G.K., Esiri M., Bowen D., et al. (1982) Alzheimer’s disease: correlation of cortical choline acetyltransferase activity with the severity of dementia and histological abnormalities. *J. Neurol. Sci.* 57, 407–417.
- 440 Whitehouse P.J., Price D.L., Struble R.G., et al. (1982) Alzheimer’s Disease and Senile Dementia: Loss of Neurons in the Basal Forebrain. *Science* (80-. ). 215, 1237–1239.
- 441 Perry E.K., Perry R.H., Blessed G., et al. (1978) Changes in brain cholinesterases in senile dementia of Alzheimer type. *Neuropathol. Appl. Neurobiol.* 4, 273–277.
- 442 Birks J. (2006) Cholinesterase inhibitors for Alzheimer’s disease. *Cochrane Database Syst Rev* CD005593.



- 443 Braak H. & Braak E. (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–259.
- 444 Fonnum F. (1975) A rapid radiochemical method for determination of choline acetyltransferase. *J. Neurochem.* 24, 407–409.
- 445 Minger S.L., Esiri M.M., McDonald B., et al. (2000) Cholinergic deficits contribute to behavioral disturbance in patients with dementia. *Neurology* 55, 1460–1467.
- 446 Karnovsky M.J. & Roots L. (1964) A “direct-coloring” thiocholine method for cholinesterases. *J. Histochem. Cytochem.* 12, 219–221.
- 447 Hadi A.M., Mouchaers K.T.B., Schalij I., et al. (2011) Rapid quantification of myocardial fibrosis: a new macro-based automated analysis. *Cell. Oncol.* 34, 343–354.
- 448 Virta J.R., Laatu S., Parkkola R., et al. (2011) Cerebral acetylcholinesterase activity is not decreased in MS patients with cognitive impairment. *Mult. Scler.* 17, 931–938.
- 449 Wegner C., Esiri M.M., Chance S.A., et al. (2006) Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. *Neurology* 67, 960 – 967.
- 450 Chamelian L., Bockt C., Gao F.-Q., et al. (2005) Detecting cognitive dysfunction in multiple sclerosis with a magnetic resonance imaging rating scale: a pilot study. *CNS Spectr.* 10, 394 – 401.
- 451 Nizri E., Irony-Tur-Sinai M., Faranesh N., et al. (2008) Suppression of neuroinflammation and immunomodulation by the acetylcholinesterase inhibitor rivastigmine. *J. Neuroimmunol.* 203, 12–22.
- 452 Krupp L.B., Christodoulou C., Melville P., et al. (2004) Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology* 63, 1579–1585.
- 453 Parry A.M.M., Scott R.B., Palace J., et al. (2003) Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine. *Brain* 126, 2750–2760.
- 454 Strange B.A., Witter M.P., Lein E.S., et al. (2014) Functional organization of the hippocampal longitudinal axis. *Nat. Rev. Neurosci.* 15, 655–669.
- 455 Tsien J.Z., Huerta P.T. & Tonegawa S. (1996) The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell* 87, 1327–38.
- 456 Rampon C., Tang Y.P., Goodhouse J., et al. (2000) Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nat. Neurosci.* 3, 238–44.
- 457 Andrews-Zwilling Y., Gillespie A.K., Kravitz A. V, et al. (2012) Hilar GABAergic interneuron activity controls spatial learning and memory retrieval. *PLoS One* 7, e40555.
- 458 Murray A.J., Sauer J.-F., Riedel G., et al. (2011) Parvalbumin-positive CA1 interneurons are required for spatial working but not for reference memory. *Nat. Neurosci.* 14, 297–9.
- 459 Aika Y., Ren J.Q., Kosaka K., et al. (1994) Quantitative analysis of GABA-like-immunoreactive and parvalbumin-containing neurons in the CA1 region of the rat hippocampus using a stereological method, the disector. *Exp. Brain Res.* 99, 267–76.
- 460 Fuchs E.C., Zivkovic A.R., Cunningham M.O., et al. (2007) Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. *Neuron* 53, 591–604.
- 461 Dutta R., McDonough J., Yin X., et al. (2006) Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients. *Ann. Neurol.* 59, 478–89.
- 462 Clements R.J., McDonough J. & Freeman E.J. (2008) Distribution of parvalbumin and calretinin immunoreactive interneurons in motor cortex from multiple sclerosis post-mortem tissue. *Exp. Brain Res.* 187, 459–65.

- 463 Lee M., McGeer E.G. & McGeer P.L. (2011) Mechanisms of GABA release from human astrocytes. *Glia* 59, 1600–11.
- 464 Lee M., Schwab C. & McGeer P.L. (2011) Astrocytes are GABAergic cells that modulate microglial activity. *Glia* 59, 152–65.
- 465 Parpura V., Basarsky T.A., Liu F., et al. (1994) Glutamate-mediated astrocyte-neuron signalling. *Lett. to Nat.* 369, 744–747.
- 466 Jo S., Yarishkin O., Hwang Y.J., et al. (2014) GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. *Nat. Med.* 20.
- 467 Fenalti G., Law R.H.P., Buckle A.M., et al. (2007) GABA production by glutamic acid decarboxylase is regulated by a dynamic catalytic loop. *Nat. Struct. Mol. Biol.* 14, 280–6.
- 468 Pitt D., Werner P. & Raine C.S. (2000) Glutamate excitotoxicity in a model of multiple sclerosis. *Nat. Med.* 6, 67–70.
- 469 Werner P., Pitt D. & Raine C.S. (2001) Multiple sclerosis: altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage. *Ann. Neurol.* 50, 169–80.
- 470 Srinivasan R., Sailasuta N., Hurd R., et al. (2005) Evidence of elevated glutamate in multiple sclerosis using magnetic resonance spectroscopy at 3 T. *Brain* 128, 1016–25.
- 471 Vercellino M., Merola A., Piacentino C., et al. (2007) Altered glutamate reuptake in relapsing-remitting and secondary progressive multiple sclerosis cortex: correlation with microglia infiltration, demyelination, and neuronal and synaptic damage. *J. Neuropathol. Exp. Neurol.* 66, 732–9.
- 472 Wu Z., Guo Z., Gearing M., et al. (2014) Tonic inhibition in dentate gyrus impairs long-term potentiation and memory in an Alzheimer's disease model. *Nat. Commun.* 5, 1–25.
- 473 Newcombe J., Uddin A., Dove R., et al. (2008) Glutamate receptor expression in multiple sclerosis lesions. *Brain Pathol.* 18, 52–61.
- 474 Mandolesi G., Musella A., Gentile A., et al. (2013) Interleukin-1 $\beta$  alters glutamate transmission at purkinje cell synapses in a mouse model of multiple sclerosis. *J. Neurosci.* 33, 12105–21.
- 475 Yamada M.K., Nakanishi K., Ohba S., et al. (2002) Brain-derived neurotrophic factor promotes the maturation of GABAergic mechanisms in cultured hippocampal neurons. *J. Neurosci.* 22, 7580–5.
- 476 Bhat R., Axtell R., Mitra A., et al. (2010) Inhibitory role for GABA in autoimmune inflammation. *Proc. Natl. Acad. Sci. U. S. A.* 107, 2580–5.
- 477 Reyes-García M.G., Hernández-Hernández F., Hernández-Téllez B., et al. (2007) GABA (A) receptor subunits RNA expression in mice peritoneal macrophages modulate their IL-6/IL-12 production. *J. Neuroimmunol.* 188, 64–8.
- 478 Sander M. (1898) Hirnrindenebefunde bei multipler Sklerose. *Monatsschrift Psychiatr. Neurol* IV, 427–436.
- 479 Schob F. (1907) Ein Beitrag zur pathologischen Anatomie der multiplen Sklerose. *Monatsschrift Psychiatr. Neurol* 22, 62–87.
- 480 Dinkler M. (1904) Zur Kasuistik der multiplen Herdsklerose des Gehirns und Rückenmarks. *Dtsch. Z. Nervenheilkd.* 233–247.
- 481 Dawson J. (1916) The Histology of Multiple Sclerosis. *Trans. R. Soc. Edinburgh* 50, 517–740.
- 482 Hulst H.E. & Geurts J.J.G. (2011) Gray matter imaging in multiple sclerosis: what have we learned? *BMC Neurol.* 11, 153.
- 483 Olah M., Biber K., Vinet J., et al. (2011) Microglia phenotype diversity. *CNS Neurol. Disord. Drug Targets* 10, 108–18.
- 484 El Haj M., Antoine P., Nandrino J.L., et al. (2015) Autobiographical memory decline in Alzheimer's disease, a theoretical and clinical overview. *Ageing Res. Rev.*

- 485 Vainchtein I.D., Vinet J., Brouwer N., et al. (2014) In acute experimental autoimmune encephalomyelitis, infiltrating macrophages are immune activated, whereas microglia remain immune suppressed. *Glia* 62, 1724–35.
- 486 Yamasaki R., Lu H., Butovsky O., et al. (2014) Differential roles of microglia and monocytes in the inflamed central nervous system. *J. Exp. Med.* 211, 1533–49.
- 487 Kidd D., Barkhof F., McConnell R., et al. (1999) Cortical lesions in multiple sclerosis. *Brain* 122, 17–26.
- 488 Janssen K., Rickert M., Clarner T., et al. (2015) Absence of CCL2 and CCL3 Ameliorates Central Nervous System Grey Matter But Not White Matter Demyelination in the Presence of an Intact Blood-Brain Barrier. *Mol. Neurobiol.*
- 489 Karpus W.J. & Kennedy K.J. (1997) MIP-1alpha and MCP-1 differentially regulate acute and relapsing autoimmune encephalomyelitis as well as Th1/Th2 lymphocyte differentiation. *J. Leukoc. Biol.* 62, 681–687.
- 490 Freund T.F. & Buzsáki G. (1996) Interneurons of the Hippocampus. *Hippocampus* 6, 347–47.
- 491 Hájos N., Papp E.C., Acsády L., et al. (1998) Distinct interneuron types express m2 muscarinic receptor immunoreactivity on their dendrites or axon terminals in the hippocampus. *Neuroscience* 82, 355–376.
- 492 Lawrence J.J. (2008) Cholinergic control of GABA release: emerging parallels between neocortex and hippocampus. *Trends Neurosci.* 31, 317–327.
- 493 Cea-del Rio C. a, McBain C.J. & Pelkey K. a (2012) An update on cholinergic regulation of cholecystokinin-expressing basket cells. *J. Physiol.* 590, 695–702.
- 494 Yirmiya R. & Goshen I. (2011) Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain. Behav. Immun.* 25, 181–213.
- 495 Ross F.M., Allan S.M., Rothwell N.J., et al. (2003) A dual role for interleukin-1 in LTP in mouse hippocampal slices. *J. Neuroimmunol.* 144, 61–67.
- 496 Goshen I., Kreisel T., Ounallah-Saad H., et al. (2007) A dual role for interleukin-1 in hippocampal-dependent memory processes. *Psychoneuroendocrinology* 32, 1106–15.
- 497 Avital A., Goshen I., Kamsler A., et al. (2003) Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. *Hippocampus* 13, 826–34.
- 498 Lee J.L.C., Everitt B.J. & Thomas K.L. (2004) Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* (80-. ). 304, 839–43.
- 499 Liu M.Y., Wang S., Yao W.F., et al. (2014) Memantine improves spatial learning and memory impairments by regulating NGF signaling in APP/PS1 transgenic mice. *Neuroscience* 273, 141–51.
- 500 Tanaka S., Ide M., Shibutani T., et al. (2006) Lipopolysaccharide-Induced Microglial Activation Induces Learning and Memory Deficits Without Neuronal Cell Death in Rats. *J. Neurosci. Res.* 83, 557–566.
- 501 Rossi S., Studer V., Motta C., et al. (2012) Inflammation inhibits GABA transmission in multiple sclerosis. *Mult. Scler. J.* 18, 1633–5.
- 502 Barrientos R.M., Sprunger D.B., Campeau S., et al. (2004) BDNF mRNA expression in rat hippocampus following contextual learning is blocked by intrahippocampal IL-1beta administration. *J. Neuroimmunol.* 155, 119–26.
- 503 Patanella A.K., Zinno M., Quaranta D., et al. (2010) Correlations between peripheral blood mononuclear cell production of BDNF, TNF-alpha, IL-6, IL-10 and cognitive performances in multiple sclerosis patients. *J. Neurosci. Res.* 88, 1106–12.
- 504 Koutsoudaki P.N., Skripuletz T., Gudi V., et al. (2009) Demyelination of the hippocampus is prominent in the cuprizone model. *Neurosci. Lett.* 451, 83–88.

- 505 Youn J., Ellenbroek B.A., van Eck I., et al. (2012) Finding the right motivation: genotype-dependent differences in effective reinforcements for spatial learning. *Behav. Brain Res.* 226, 397–403.
- 506 Pisa M., Sandberg P.R. & Fibiger H.C. (1981) Striatal Injections of Kainic Acid Selectively Impair Serial Memory Performance in the Rat. *Exp. Neurol.* 74, 633–653.
- 507 Calabrese M., Magliozzi R., Ciccarelli O., et al. (2015) Exploring the origins of grey matter damage in multiple sclerosis. *Nat. Rev. Neurosci.* 16, 147–158.
- 508 Narcisse L., Scemes E., Zhao Y., et al. (2005) The Cytokine IL-1 $\beta$  Transiently Enhances P2X7 Receptor Expression and Function in Human Astrocytes. *Glia* 49, 245–258.
- 509 Lundgaard I., Osório M.J., Kress B., et al. (2013) White matter astrocytes in health and disease. *Neuroscience*.
- 510 Oberheim N.A., Goldman S.A. & Nedergaard M. (2012) Heterogeneity of Astrocytic Form and Function. *Methods Mol. Biol.* 814, 23–45.
- 511 Moor E., DeBoer P. & Westerink B.H. (1998) GABA receptors and benzodiazepine binding sites modulate hippocampal acetylcholine release *in vivo*. *Eur. J. Pharmacol.* 359, 119–26.
- 512 Marchi M., Risso F., Viola C., et al. (2002) Direct evidence that release-stimulating  $\alpha 7$  nicotinic cholinergic receptors are localized on human and rat brain glutamatergic axon terminals. *J. Neurochem.* 80, 1071–1078.
- 513 Moor E., Schirm E. & Westerink B.H.C. (1998) Involvement of medial septal glutamate and GABA A receptors in behaviour-induced acetylcholine release in the hippocampus: A dual probe microdialysis study. *Brain Res.*, 1–8.
- 514 DeLuca G.C., Yates R.L., Beale H., et al. (2015) Cognitive Impairment in Multiple Sclerosis: Clinical, Radiologic and Pathologic Insights. *Brain Pathol.* 25, 79–98.
- 515 Langdon D.W., Amato M.P., Boringa J., et al. (2012) Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult. Scler.* 18, 891–8.
- 516 Moccia M., Lanzillo R., Palladino R., et al. (2015) Cognitive impairment at diagnosis predicts 10-year multiple sclerosis progression. *Mult. Scler.*, 1–9.

---

