Monitoring and Modulating Inflammation-Associated Alterations in Synaptic Plasticity: Role of Brain Stimulation and the Blood–Brain Interface

Maximilian Lenz 1,*, Amelie Eichler 1© and Andreas Vlachos 1,2,3,*

1 Department of Neuroanatomy, Institute of Anatomy and Cell Biology, Faculty of Medicine, University of Freiburg, 79104 Freiburg, Germany
2 Center Brain Links Brain Tools, University of Freiburg, 79110 Freiburg, Germany
3 Center for Basics in NeuroModulation (NeuroModulBasics), Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany
* Correspondence: maximilian.lenz@anat.uni-freiburg.de (M.L.); andreas.vlachos@anat.uni-freiburg.de (A.V.)

Abstract: Inflammation of the central nervous system can be triggered by endogenous and exogenous stimuli such as local or systemic infection, trauma, and stroke. In addition to neurodegeneration and cell death, alterations in physiological brain functions are often associated with neuroinflammation. Robust experimental evidence has demonstrated that inflammatory cytokines affect the ability of neurons to express plasticity. It has been well-established that inflammation-associated alterations in synaptic plasticity contribute to the development of neuropsychiatric symptoms. Nevertheless, diagnostic approaches and interventional strategies to restore inflammatory deficits in synaptic plasticity are limited. Here, we review recent findings on inflammation-associated alterations in synaptic plasticity and the potential role of the blood–brain interface, i.e., the blood–brain barrier, in modulating synaptic plasticity. Based on recent findings indicating that brain stimulation promotes plasticity and modulates vascular function, we argue that clinically employed non-invasive brain stimulation techniques, such as transcranial magnetic stimulation, could be used for monitoring and modulating inflammation-induced alterations in synaptic plasticity.

Keywords: synaptic plasticity; lipopolysaccharide; interleukin 10; transcranial magnetic stimulation

1. Introduction

Inflammatory processes aim at resolving tissue damage by facilitating repair and recovery mechanisms [1]. However, unrestrained inflammation can cause damage, which may induce inflammatory-associated pathologies [2]. Adaptive and acquired immune responses consist of complex pro- and anti-inflammatory signaling pathways that regulate inflammatory processes through distinct positive and negative feedback mechanisms [3]. Dysregulation of these processes may disturb physiological repair and recovery mechanisms, thus contributing to disease progression and infarct outcomes, which has been demonstrated in meningitis, encephalitis, and multiple sclerosis [4–6].

Two millennia ago, seminal work by Aulus Cornelius Celsus described signs of inflammation including heat, redness, swelling and pain, suggesting a prominent role of the vascular system in inflammation. Indeed, altered vascular function has been determined to be a common feature of inflammatory processes [7]. Meanwhile, cellular and molecular mechanisms that modulate vascular function during inflammation have been identified. In addition to circulating and local endothelial factors that control vascular tone and permeability, the regulation of cell migration across endothelial barriers has been recognized to be a key step in inflammatory processes [8–10].

In the 18th century Rudolph Virchow emphasized the disturbance of function (“funcio laesa”) as an important feature of inflammation [11,12]. However, the factors that promote inflammation-related tissue dysfunction remained unknown. Notably, Virchow was among
the first scientists to characterize a glial (non-neuronal) cell type in the brain similar to macrophages of the immune system [13–15]. An early study determined that these cells contribute to inflammation in the central nervous system, e.g., through phagocytosis [16]. This initial work paved the way for a deeper understanding of the function of microglia and the immune system in the brain [17].

The brain is an immune-privileged organ [18]. It is protected by the blood–brain interface (also referred to as the blood–brain barrier), which consists of tight junctions between endothelial cells, the basal lamina of the endothelial cells, and astrocyte endfeet processes [19]. A substantial body of research is currently focused on investigating the neuroimmune communication in healthy and diseased states including the role of blood–brain interfaces and more accessible meninges [20–23]. Here, we describe recent work that has identified a critical role for inflammatory cytokines in synaptic plasticity. We discuss the interplay between endogenous sources of cytokines, such as microglial tumor necrosis factor alpha (TNFα), and peripheral immune mediators (Figure 1). Finally, we highlight the potential diagnostic and therapeutic use of brain stimulation, i.e., repetitive transcranial magnetic stimulation (rTMS), which may be used as a tool for monitoring and modulating inflammation-associated disturbances of synaptic function.

![Figure 1. Blood–brain communication is a crucial regulatory element in neural circuit function. Neurons and glial cells bilaterally influence their function through various mediators, such as neurotransmitters, metabolites and brain derived cytokines. Moreover, soluble and cellular blood components can enter the central nervous system, when the permeability of the blood–brain interface changes. This intriguing blood–brain interaction can influence distinct features of neural circuits, e.g., network activity and the expression of synaptic plasticity.](image)

2. Effects of Pro-Inflammatory Cytokines on Synaptic Plasticity in Health and Disease

It has been well-established that inflammation affects cognitive function and behavior, including the ability of neurons to express synaptic plasticity [24–26]. While the mechanisms through which pro-inflammatory cytokines affect complex brain functions have recently begun to be elucidated [27,28], little is known about their physiological relevance. Similarly, mechanisms that prevent or control inflammation, maintaining or restoring plasticity in healthy and disease states, have not yet been well characterized.
The role of the pro-inflammatory cytokine TNFα in the modulation of synaptic plasticity has been studied extensively [29–32]. TNFα is a prominent mediator of inflammation, which can be expressed by peripheral immune cells and central microglia [33–35]. Recent experimental work has demonstrated concentration-dependent effects of TNFα on synaptic plasticity [36]. High concentrations—as seen under conditions of inflammation—impair long-term potentiation (LTP) of excitatory neurotransmission. Conversely, low concentrations of TNFα facilitate synaptic plasticity [36]. These findings support the biological significance of TNFα-mediated synaptic plasticity in health and disease.

Robust experimental evidence has demonstrated a role for microglia in physiological brain function when inflammation is absent. Microglia assist in shaping neural connectivity by pruning synapses [37] and have been recently linked to brain homeostasis under conditions of hyperexcitability [38]. Moreover, microglia have been identified as a major source of TNFα [39]. TNFα has been shown to modulate synaptic neurotransmission by acting on astrocytes, providing evidence for a relevant crosstalk between glial cells [40]. While the precise mechanisms through which distinct TNFα levels affect microglia–astrocyte interactions and modulate synaptic plasticity have not yet been well characterized, it is conceivable that a pathological increase in brain TNFα levels—as seen under conditions of local or systemic inflammation—may induce dysregulation of synaptic transmission and plasticity.

This hypothesis has been supported by research describing the effects of the bacterial endotoxin lipopolysaccharide (LPS) on synaptic plasticity: Several studies have shown that systemic (intraperitoneal) administration of LPS promotes a substantial increase in brain TNFα levels, which impairs synaptic plasticity [34,41–44]. Consistent with these findings, we have recently shown that application of LPS directly to cultured brain tissue triggers microglial TNFα expression and leads to alterations in synaptic plasticity [34]. Further evidence comes from animal models of experimental autoimmune encephalomyelitis [45], demonstrating that IL1β, which is produced by microglia and infiltrating lymphocytes, promotes long-term potentiation but effectively prevents long-term depression of excitatory neurotransmission [46]. Accordingly, systemic and local inflammation are expected to have a major impact on brain function by triggering immune responses that induce the expression of TNFα, IL1β, and other cytokines above physiological levels.

Apparently, more work is required to determine how complex cytokine patterns affect the balance and interplay between distinct forms of synaptic plasticity in health and disease. It will be also important to gain further insights on the neuronal targets and precise cellular and molecular downstream mechanisms through which inflammation affects synaptic plasticity and brain function (c.f., [31,40,47]).

3. Restraining Inflammation Restores Alterations in Synaptic Plasticity

The balance between pro- and anti-inflammatory factors determines the course and the outcome of inflammatory processes in various organ systems [48–50]. However, in the brain our knowledge about anti-inflammatory signaling pathways and their impact on synaptic function is limited.

Among anti-inflammatory cytokines, interleukin 10 (IL10) plays a crucial role in restraining and eventually terminating inflammatory processes [51–53]. A deficiency or impairment in IL10 signaling has been linked with aggravated and prolonged inflammation with detrimental clinical outcomes; an example of this includes inflammatory bowel diseases [54]. Accordingly, it is well established that IL10 inhibits the production of pro-inflammatory cytokines by assembling heterodimeric receptors consisting of IL10R1 and IL10R2 at the cellular surface [55].

Recent work has linked IL10 to the modulation of excitatory neurotransmission [56,57]. Consistent with recent in vivo studies [39], our own work in organotypic brain tissue cultures showed that IL10 restores LPS-induced alterations in synaptic plasticity while limiting the expression of pro-inflammatory cytokines, including TNFα, IL6, IL1β and IFNγ [34]. It is not clear, however, whether IL10 acts directly on neurons and their synapses...
(c.f., Figure 1). Alternatively, IL10 may enhance synaptic plasticity indirectly by modulating microglial cytokine expression and/or microglia-astrocyte interactions.

Another major question is focused on identifying the source of IL10. Transcriptome analyses of microglia isolated from various animal disease models have failed to demonstrate IL10 expression in microglia [39]. In many studies, macrophages, natural killer-cells and neutrophils which can enter the central nervous system via the blood–brain interface have been identified as the major sources of IL10 [39,58]. Microglial IL10 expression has also been demonstrated in cultured microglia [59,60]. While these in vitro findings have been critically discussed since cultured microglia can adapt a gene expression signature that resembles macrophages [61,62], a recent study demonstrated that microglia in organotypic tissue cultures maintain their characteristic tissue imprints, such as Sall1 expression [63].

Indeed, we were recently able to demonstrate that LPS triggers the endogenous expression of IL10 in brain tissue cultures [34]. Interestingly, application of exogenous (recombinant) IL10 hampered the LPS-induced increase in IL10-mRNA in our tissue cultures [34]. These findings are consistent with a negative feedback mechanism in which circulating IL10 in the blood or peripheral IL10-expressing immune cells that enter the brain under pathological conditions suppress the endogenous expression of microglial IL10.

Together, these findings emphasize an important role for the blood–brain interface in mediating and modulating inflammation-associated alterations in synaptic plasticity. On the one hand, alterations in the blood–brain interface function, as seen for example in the context of systemic inflammation, may allow serum cytokines and other blood-derived factors to enter the brain and act either directly on neurons or indirectly by affecting neurotransmission and plasticity through activation of microglia. On the other hand, anti-inflammatory mechanisms, including migration of peripheral immune cells across the blood–brain interface, may counter and restore inflammation-associated alterations in synaptic plasticity. Whether endogenous (brain) and exogenous (blood) pro- and anti-inflammatory cytokines assert distinct effects on synaptic plasticity is currently unknown. Certainly, the stimuli driving their expression in health (e.g., modulation of synaptic plasticity) and disease (e.g., inflammation and tissue repair) appears to be distinct.

4. Non-Invasive Brain Stimulation as a Tool to Monitor and Potentially Modulate Cytokine Expression

Non-invasive brain stimulation techniques are widely used in research and clinical practice [64]. Among them, rTMS has been shown to induce long-lasting changes in cortical excitability by depolarizing cortical neurons through the intact skin and skull [65–67]. Notably, rTMS has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression [68]. However, the cellular and molecular mechanisms through which FDA-approved rTMS protocols assert their positive effects remain unknown. Meanwhile, robust experimental evidence from animal studies (both in vivo and in vitro) has been provided that rTMS induces structural and functional synaptic changes consistent with a long-term potentiation (LTP) of excitatory neurotransmission [69–71]. In line with the observation that LPS-induced inflammation affects the ability of neurons to express synaptic plasticity, we recently showed that LPS also hampers the ability of neurons to express rTMS-induced synaptic plasticity [34]. Moreover, IL10 restored the ability of neurons to express rTMS-induced synaptic plasticity while limiting the LPS-induced production of pro-inflammatory cytokines [34]. These findings provide a biological basis for the use of rTMS as a diagnostic tool for monitoring inflammation-associated alterations in synaptic plasticity.

In contrast, the therapeutic effects of rTMS have been critically discussed. The rTMS-related (exogenous) induction of synaptic plasticity, i.e., LTP, which is only transiently detected in humans, might not represent a suitable explanation for therapeutic effects with a delayed onset and a duration of several weeks and months [72,73]. In this context, it is interesting to speculate that rTMS may assert its therapeutic effects by modulating microglia function. While some evidence has indicated that low intensity rTMS affects local responses of glia [74], the impact of microglia on rTMS-induced synaptic plasticity has not
yet been characterized. However, microglia are known to respond to changes in network activity [75], while those changes can modulate TNFα expression at the same time [32]. Network activity and glial TNFα expression have been demonstrated to be negatively related, and TNFα promotes compensatory, i.e., homeostatic synaptic plasticity [32,76,77]. Based on this, it is possible that rTMS, which activates neurons and may also act directly on microglia, could affect complex brain function by modulating microglial cytokine expression and subsequent glial-neuron interactions.

The effects of rTMS on blood–brain interfaces is another area of open investigation. A recent study reported an rTMS-induced increase in vascular permeability, indicating increased opening of the blood–brain barrier ([78], but see also [79,80]). Although earlier studies failed to provide evidence that rTMS affects the blood–brain barrier, previous work that has shown changes in vascular permeability in the context of hyperexcitability and epileptic seizures supports the potential role of rTMS-mediated network excitation acting at the blood–brain interface [81,82]. However, it remains to be determined whether rTMS acts directly on endothelial cells, the vasculature and/or astrocytes that are part of the blood–brain interface.

Regardless of these considerations, we are confident that a better understanding of rTMS-driven effects at neuroimmune synapses [83] and blood–brain communication will be instrumental in designing translational experiments for deciphering the cellular and molecular mechanisms of synaptic plasticity in health and disease. Organotypic tissue cultures prepared from transgenic mice [84,85] and human cortical access material [86] are ideal tools to study the interplay of central and peripheral immune mediators in this context, since they are blood-free preparations that are not connected to the body’s immune system.

**Funding:** Supported by EQUIP Medical Scientist Program and Deutsche Forschungsgemeinschaft (CRC/TRR 167—Project-ID B14).

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. DiSabato, D.J.; Quan, N.; Godbout, J.P. Neuroinflammation: The devil is in the details. *J. Neurochem.* 2016, 139 (Suppl. 2), 136–153. [CrossRef]
2. Cicchese, J.M.; Evans, S.; Hult, C.; Joslyn, L.R.; Wessler, T.; Millar, J.A.; Marino, S.; Cilfone, N.A.; Mattila, J.T.; Linderman, J.J.; et al. Dynamic balance of pro- and anti-inflammatory signals controls disease and limits pathology. *Immunol. Rev.* 2018, 285, 147–167. [CrossRef]
3. Cho, H.; Proll, S.C.; Szretter, K.J.; Katze, M.G.; Gale, M., Jr.; Diamond, M.S. Differential innate immune response programs in neuronal subtypes determine susceptibility to infection in the brain by positive-stranded RNA viruses. *Nat. Med.* 2013, 19, 458–464. [CrossRef] [PubMed]
4. Biswas, S.M.; Kar, S.; Singh, R.; Chakraborty, D.; Vipat, V.; Raut, C.G.; Mishra, A.C.; Gore, M.M.; Ghosh, D. Immunomodulatory cytokines determine the outcome of Japanese encephalitis virus infection in mice. *J. Med. Virol.* 2010, 82, 304–310. [CrossRef] [PubMed]
5. Girdharan, V.V.; Collodel, A.; Generoso, J.S.; Scaini, G.; Wassather, R.; Selvaraj, S.; Hasbun, R.; Dal-Pizzol, F.; Petronilho, F.; Barichello, T. Neuroinflammation trajectories precede cognitive impairment after experimental meningitis-evidence from an in vivo PET study. *J. Neuroinflammation* 2020, 17, 5. [CrossRef]
6. Soldan, S.S.; Alvarez Retuerto, A.I.; Sicotte, N.L.; Voskuhl, R.R. Dysregulation of IL-10 and IL-12p40 in secondary progressive multiple sclerosis. *J. Neuroimmunol.* 2004, 146, 209–215. [CrossRef] [PubMed]
7. Wedmore, C.V.; Williams, T.J. Control of vascular permeability by polymorphonuclear leukocytes in inflammation. *Nature* 1981, 289, 646–650. [CrossRef] [PubMed]
8. Sun, X.; Ma, S.F.; Wade, M.S.; Acosta-Herrera, M.; Villar, J.; Pino-Yanes, M.; Zhou, T.; Liu, B.; Belvitch, P.; Moitra, J.; et al. Functional promoter variants in sphingosine 1-phosphate receptor 3 associate with susceptibility to sepsis-associated acute respiratory distress syndrome. *Am. J. Physiol. Lung Cell Mol. Physiol.* 2013, 305, L467–L477. [CrossRef] [PubMed]
9. Tiruppathi, C.; Minshall, R.D.; Paria, B.C.; Vogel, S.M.; Malik, A.B. Role of Ca2+ signaling in the regulation of endothelial permeability. *Vascul. Pharmacol.* 2002, 39, 173–185. [CrossRef]
10. Vigl, B.; Aebischer, D.; Nitschke, M.; Iolyeva, M.; Rothlin, T.; Antsiferova, O.; Halin, C. Tissue inflammation modulates gene expression of lymphatic endothelial cells and dendritic cell migration in a stimulus-dependent manner. *Blood* 2011, 118, 205–215. [CrossRef]
11. Heidland, A.; Klassen, A.; Rutkowski, P.; Bahner, U. The contribution of Rudolf Virchow to the concept of inflammation: What is still of importance? J. Nephrol. 2006, 19 (Suppl. 10), S102–S109. [CrossRef] [PubMed]

12. Liu, M.; Kalbasi, A.; Beatty, G.L. Funkto Laesa: Cancer Inflammation and Therapeutic Resistance. J. Oncol. Pract. 2017, 13, 173–180. [CrossRef] [PubMed]

13. Sierra, A.; de Castro, F.; Del Rio-Hortega, J.; Rafael Iglesias-Rozas, J.; Garrosa, M.; Kettenmann, H. The “Big-Bang” for modern glial biology: Translation and comments on Pio del Rio-Hortega 1919 series of papers on microglia. Glia 2016, 64, 1801–1840. [CrossRef]

14. Tremblay, M.E.; Lecours, C.; Samson, L.; Sanchez-Zafra, V.; Sierra, A. From the Cajal alumni Achucarro and Rio-Hortega to the rediscovery of never-resting microglia. Front. Neuroanat. 2015, 9, 45. [CrossRef] [PubMed]

15. Webster, H.; Armstrong, K.E. Gliogenesis: Historical perspectives, 1839–1985. Adv. Anat. Embryol. Cell Biol. 2009, 202, 1–109.

16. Penfield, W. Microglia and the Process of Phagocytosis in Gliomas. Am. J. Pathol. 1925, 1, 77–90.

17. Sierra, A.; Paolicelli, R.C.; Kettenmann, H. Cien Anos de Microglia: Milestones in a Century of Microglial Research. Trends Neurosci. 2019, 42, 778–792. [CrossRef] [PubMed]

18. Suter, T.; Biollaz, G.; Gatto, D.; Bernasconi, L.; Herren, T.; Reith, W.; Fontana, A. The brain as an immune privileged site: Dendritic cells of the central nervous system inhibit T cell activation. Eur. J. Immunol. 2003, 33, 2998–3006. [CrossRef]

19. Obermeier, B.; Verma, A.; Ransohoff, R.M. The blood-brain barrier. Handb. Clin. Neurol. 2016, 133, 39–59. [CrossRef] [PubMed]

20. Banks, W.A.; Gray, A.M.; Erickson, M.A.; Salameh, T.S.; Damodarasamy, M.; Sheibani, N.; Meabon, J.S.; Wing, E.E.; Morofuji, Y.; Cook, D.G.; et al. Lipopolysaccharide-induced blood-brain barrier disruption: Roles of cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit. J. Neuroinflammation 2015, 12, 223. [CrossRef] [PubMed]

21. Halliday, M.R.; Rege, S.V.; Ma, Q.; Zhao, Z.; Miller, C.A.; Winkler, E.A.; Zlokovic, B.V. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E carriers with Alzheimer’s disease. J. Cereb. Blood Flow Metab. 2016, 36, 216–227. [CrossRef]

22. Hammer, C.; Stepniak, B.; Schneider, A.; Papiol, S.; Tantra, M.; Begemann, M.; Siren, A.L.; Pardo, L.A.; Mohd Jofrry, Y.; et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. Mol. Psychiatry 2014, 19, 1143–1149. [CrossRef] [PubMed]

23. Louveau, A.; Herz, J.; Alme, M.N.; Salvador, A.E.; Dong, M.Q.; Viar, K.E.; Herod, S.G.; Knopp, J.; Setliuf, J.C.; Lupi, A.L.; et al. The lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. Nat. Neurosci. 2018, 21, 1380–1391. [CrossRef] [PubMed]

24. Heidland, A.; Klassen, A.; Rutkowski, P.; Bahner, U. The contribution of Rudolf Virchow to the concept of inflammation: What is still of importance? J. Nephrol. 2006, 19 (Suppl. 10), S102–S109. [CrossRef] [PubMed]

25. Salter, M.W.; Stevens, B. Microglia emerge as central players in brain disease. Nat. Med. 2017, 23, 1018–1027. [CrossRef]

26. Wu, Y.; Dissing-Olesen, L.; MacVicar, B.A.; Stevens, B. Microglia: Dynamic Mediators of Synapse Development and Plasticity. Trends Immunol. 2015, 36, 605–613. [CrossRef] [PubMed]

27. Carpentier, P.A.; Palmer, T.D. Immune influence on adult neural stem cell regulation and function. Neuro 2009, 64, 79–92. [CrossRef] [PubMed]

28. Gardoni, F.; Boraso, M.; Ziani, E.; Corsini, E.; Galli, C.L.; Cattabeni, F.; Marinovich, M.; Di Luca, M.; Viviani, B. Distribution of interleukin-1 receptor complex at the synaptic membrane driven by interleukin-1β and NMDA stimulation. J. Neuroinflamm. 2015, 11, 8. [CrossRef] [PubMed]

29. Becker, D.; Deller, T.; Vlachos, A. Tumor necrosis factor (TNF)-receptor 1 and 2 mediate homeostatic synaptic plasticity of denervated mouse dentate granule cells. Sci. Rep. 2015, 5, 12726. [CrossRef]

30. Habbas, S.; Santello, M.; Becker, D.; Stubbe, H.; Zappia, G.; Liaudet, N.; Klaus, F.R.; Kollias, G.; Fontana, A.; Pryce, C.R.; et al. Neurinflammatory TNFalpha Impairs Memory via Astrocyte Signaling. Cell 2015, 163, 1730–1741. [CrossRef]

31. Heir, R.; Stellwagen, D. TNF-Mediated Homeostatic Synaptic Plasticity: From in vitro to in vivo Models. Front. Cell Neurosci. 2020, 14, 565841. [CrossRef]

32. Stellwagen, D.; Malenka, R.C. Synaptic scaling mediated by glial TNF-alpha. Nature 2006, 440, 1054–1059. [CrossRef]

33. Gonzalez, Y.; Herrera, M.T.; Soldevila, G.; Garcia-Garcia, L.; Fabian, G.; Perez-Arnendariz, E.M.; Bobadilla, K.; Guzman-Beltran, S.; Sada, E.; Torres, M. High glucose concentrations induce TNF-alpha production through the down-regulation of CD33 expression in primary human monocytes. BMC Immunol. 2009, 10, E197–E205. [CrossRef] [PubMed]

34. Lenz, M.; Eicher, A.; Kruse, P.; Strehl, A.; Rodriguez-Rozada, S.; Goren, I.; Yogeve, N.; Frank, S.; Waisman, A.; Deller, T.; et al. Interleukin 10 Restores Lipopolysaccharide-Induced Alterations in Synaptic Plasticity Probed by Repetitive Magnetic Stimulation. Front. Immunol. 2020, 11, 614509. [CrossRef]

35. Sawada, M.; Kondo, N.; Suzumura, A.; Marunouchi, T. Production of tumor necrosis factor-alpha by microglia and astrocytes in culture. Brain Res. 1989, 491, 394–397. [CrossRef]

36. Maggio, N.; Vlachos, A. Tumor necrosis factor (TNF) modulates synaptic plasticity in a concentration-dependent manner through intracellular calcium stores. J. Mol. Med. 2018, 96, 1039–1047. [CrossRef]

37. Paolicelli, R.C.; Bolasco, G.; Pagani, F.; Maggi, L.; Scannell, P.; Panzani, P.; Giustetto, M.; Ferreira, T.A.; Guiducci, E.; Dumas, L.; et al. Synaptic pruning by microglia is necessary for normal brain development. Science 2011, 333, 1456–1458. [CrossRef] [PubMed]
38. Merlini, M.; Rafalski, V.A.; Ma, K.; Kim, K.Y.; Bushong, E.A.; Rios Coronado, P.E.; Yan, Z.; Mendiola, A.S.; Sozmen, E.G.; Ryu, J.K.; et al. Microglial Gi-dependent dynamics regulate brain network hyperexcitability. Nat. Neurosci. 2021, 24, 19–23. [CrossRef]

39. Shemer, A.; Scheyltjens, I.; Frumer, G.R.; Kim, J.S.; Grozovsky, J.; Ayanaw, S.; Dassa, B.; Van Hove, H.; Chappell-Maar, L.; Boura-Hallion, S.; et al. Interleukin-10 Prevents Pathological Microglia Hyperactivation following Peripheral Endotoxin Challenge. Immunity 2020, 53, 1033–1049 e1037. [CrossRef] [PubMed]

40. Santello, M.; Bezzi, P.; Volterra, A. TNFα controls glutamatergic gliotransmission in the hippocampal dentate gyrus. Neuron 2011, 69, 988–1001. [CrossRef] [PubMed]

41. Chen, Y.H.; Kuo, T.T.; Chu, M.T.; Ma, H.L.; Chiang, Y.H.; Huang, E.Y. Postnatal systemic inflammation exacerbates impairment of hippocampal synaptic plasticity in an animal seizure model. Neuroimmunomodulation 2013, 20, 223–232. [CrossRef] [PubMed]

42. Commins, S.; O’Neill, L.A.; O’Mara, S.M. The effects of the bacterial endotoxin lipopolysaccharide on synaptic transmission and plasticity in the CA1-subiculum pathway in vivo. Neuroscience 2001, 102, 273–280. [CrossRef]

43. Maggio, N.; Shavit-Stein, E.; Dori, A.; Blatt, I.; Chapman, J. Prolonged systemic inflammation persistently modifies synaptic plasticity in the hippocampus: Modulation by the stress hormones. Front. Mol. Neurosci. 2013, 6, 46. [CrossRef]

44. Strehl, A.; Lenz, M.; Itsokson-Hayosh, Z.; Becker, D.; Chapman, J.; Deller, T.; Maggio, N.; Vlachos, A. Systemic inflammation is associated with a reduction in Synaptophysin expression in the mouse hippocampus. Exp. Neurol. 2014, 261, 230–235. [CrossRef]

45. Nistico, R.; Mori, F.; Feligioni, M.; Nicoletti, F.; Centonze, D. Synaptic plasticity in multiple sclerosis and in experimental autoimmune encephalomyelitis. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2014, 369, 20130162. [CrossRef] [PubMed]

46. Nistico, R.; Mango, D.; Mandolesi, G.; Piccinin, S.; Berretta, N.; Pignatelli, M.; Feligioni, M.; Musella, A.; Gentile, A.; Mori, F.; et al. Inflammation subverts hippocampal synaptic plasticity in experimental multiple sclerosis. PLoS ONE 2013, 8, e54666. [CrossRef] [PubMed]

47. Lenz, M.; Vlachos, A. The neuroimmunological synapse: From synaptic homeostasis to brain disease. Neuroforum 2019, 25, 163–172. [CrossRef]

48. Charrad, R.; Berraias, A.; Hamdi, B.; Ammar, J.; Hamzaoui, K.; Hamzaoui, A. Anti-inflammatory activity of IL-37 in asthmatic children: Correlation with inflammatory cytokines TNF-alpha, IL-6 and IL-17A. Immunobiology 2016, 221, 182–187. [CrossRef]

49. Neurath, M.F. Cytokines in inflammatory bowel disease. Nat. Rev. Immunol. 2014, 14, 329–342. [CrossRef] [PubMed]

50. Su, D.L.; Lu, Z.M.; Shen, M.N.; Li, X.; Sun, L.Y. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. J. Biomed. Biotechnol. 2012, 2012, 347141. [CrossRef] [PubMed]

51. D’Andrea, A.; Aste-Amezaga, M.; Valiante, N.M.; Ma, X.; Kubin, M.; Trinchieri, G. Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. J. Exp. Med. 1993, 178, 1041–1048. [CrossRef] [PubMed]

52. Gruber, M.F.; Williams, C.C.; Gerrard, T.L. Macrophage-colony-stimulating factor expression by anti-CD45 stimulated human monocytes is transcriptionally up-regulated by IL-1 beta and inhibited by IL-4 and IL-10. J. Immunol. 1994, 152, 1354–1361. [CrossRef]

53. Lobo-Silva, D.; Carriche, G.M.; Castro, A.G.; Roque, S.; Saraiva, M. Balancing the immune response in the brain: IL-10 and its regulation of interleukin-10 and interleukin-10 receptor in rat astroglial and microglial cells. Eur. J. Neurosci. 2002, 16, 1175–1185. [CrossRef]

54. Moran, C.J.; Walters, T.D.; Guo, C.H.; Kugathasan, S.; Klein, C.; Turner, D.; Wolters, V.M.; Bandsma, R.H.; Mouzaki, M.; Zachos, M.; et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. Inflamm. Bowel. Dis. 2013, 19, 115–123. [CrossRef] [PubMed]

55. Moore, K.W.; de Waal Malefyt, R.; Coffman, R.L.; O’Garra, A. Interleukin-10 and the interleukin-10 receptor. Annu. Rev. Immunol. 2001, 19, 683–765. [CrossRef]

56. Nenov, M.N.; Konakov, M.V.; Teplov, I.Y.; Levin, S.G. Interleukin-10 Facilitates Glutamatergic Synaptic Transmission and Homeostatic Plasticity in Cultured Hippocampal Neurons. Int. J. Mol. Sci. 2019, 20, 3375. [CrossRef] [PubMed]

57. Suryanarayanan, A.; Carter, J.M.; Landin, J.D.; Morrow, A.L.; Werner, D.F.; Spigelman, I. Role of interleukin-10 (IL-10) in regulation of GABAergic function and the acute response to ethanol. Neuropsychopharmacology 2016, 41, 181–188. [CrossRef]

58. Woiciechowsky, C.; Asadullah, K.; Nestler, D.; Eberhardt, B.; Platzer, C.; Schoning, B.; Glockner, F.; Lanksch, W.R.; Volk, H.D.; Docke, W.D. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. Nat. Med. 1998, 4, 808–813. [CrossRef] [PubMed]

59. Ledeboer, A.; Breve, J.J.; Wierinckx, A.; van der Jagt, S.; Dassa, B.; Van Hove, H.; Chappell-Maar, L.; Boura-Hallion, S.; et al. Interleukin-10 Prevents Pathological Microglia Hyperactivation following Peripheral Endotoxin Challenge. Immunity 2020, 53, 1033–1049 e1037. [CrossRef] [PubMed]

60. Williams, K.; Dooley, N.; Ulvestad, E.; Becher, B.; Antel, J.P. IL-10 production by adult human derived microglial cells. Neurochem. Int. 1996, 29, 55–64. [CrossRef]

61. Bohlen, C.J.; Bennett, F.C.; Tucker, A.F.; Collins, H.Y.; Mulinyawe, S.B.; Barres, B.A. Diverse Requirements for Microglial Survival, Specification, and Function Revealed by Defined-Medium Cultures. Neuron 2017, 94, 759–773.e758. [CrossRef]

62. mosselin, D.; Link, V.M.; Romanowski, C.E.; Fonseca, C.G.; Eichenfield, D.Z.; Spann, N.J.; Stender, J.D.; Chun, H.B.; Garner, H.; Geissmann, F.; et al. Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. Cell 2014, 159, 1327–1340. [CrossRef] [PubMed]
63. Delbridge, A.R.D.; Huh, D.; Brickelmaier, M.; Burns, J.C.; Roberts, C.; Challa, R.; Raymond, N.; Cullen, P.; Carlile, T.M.; Ennis, K.A.; et al. Organotypic Brain Slice Culture Microglia Exhibit Molecular Similarity to Acutely-Isolated Adult Microglia and Provide a Platform to Study Neuroinflammation. Front. Cell. Neurosci. 2020, 392005. [CrossRef] [PubMed]

64. Lefaucheux, J.P.; Aleman, A.; Baeken, C.; Benningter, D.H.; Brunelin, J.; Di Lazzaro, V.; Filipovic, S.R.; Greifkes, C.; Hasan, A.; Hummel, F.C.; et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clin. Neurophysiol. 2020, 131, 474–528. [CrossRef] [PubMed]

65. Di Lazzaro, V.; Profice, P.; Pilato, F.; Dileo, M.; Oliviero, A.; Ziemann, U. The effects of motor cortex rTMS on corticospinal descending activity. Clin. Neurophysiol. 2012, 121, 464–473. [CrossRef]

66. Rossini, P.M.; Burke, D.; Chen, R.; Cohen, L.G.; Daskalakis, Z.; Di Iorio, R.; Di Lazzaro, V.; Ferreri, F.; Fitzgerald, P.B.; George, M.S.; et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin. Neurophysiol. 2015, 126, 1071–1017. [CrossRef] [PubMed]

67. Ziemann, U. Thirty years of transcranial magnetic stimulation: Where do we stand? Exp. Brain Res. 2017, 235, 973–984. [CrossRef]

68. Blumberger, D.M.; Vila-Rodriguez, F.; Thorpe, K.E.; Feffer, K.; Noda, Y.; Giacobbe, P.; Knyaznytska, Y.; Kennedy, S.H.; Lam, R.W.; Daskalakis, Z.J.; et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): A randomised non-inferiority trial. Lancet 2018, 391, 1683–1692. [CrossRef]

69. Gerster, R.; Kravetz, E.; Feil, J.; Pell, G.; Zangen, A. Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: Differential outcomes in anesthetized and awake animals. J. Neurosci. 2011, 31, 7521–7526. [CrossRef] [PubMed]

70. Lenz, M.; Platschek, S.; Priesemann, V.; Becker, D.; Willems, L.M.; Ziemann, U.; Deller, T.; Muller-Dahlhaus, F.; Jedlicka, P.; Vlachos, A. Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse CA1 pyramidal neurons. Brain Struct. Function. 2015, 220, 3323–3337. [CrossRef] [PubMed]

71. Vlachos, A.; Muller-Dahlhaus, F.; Rosskopp, J.; Lenz, M.; Ziemann, U.; Deller, T. Repetitive magnetic stimulation induces functional and structural plasticity of excitatory postsynapses in mouse organotypic hippocampal slice cultures. J. Neurosci. 2012, 32, 17514–17523. [CrossRef] [PubMed]

72. Maeda, F.; Keenan, J.P.; Tormos, J.M.; Topka, H.; Pascual-Leone, A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin. Neurophysiol. 2000, 111, 800–805. [CrossRef]

73. Lenz, M.; Vlachos, A. Releasing the Cortical Brake by Non-Invasive Electromagnetic Stimulation? rTMS Induces LTD of GABAergic Neurotransmission. Front. Neural Circuits 2016, 10, 96. [CrossRef]

74. Clarke, D.; Penrose, M.A.; Penstone, T.; Fuller-Carter, P.I.; Hool, L.C.; Harvey, A.R.; Rodger, J.; Bates, K.A. Frequency-specific effects of repetitive magnetic stimulation on primary astrocyte cultures. Restor. Neurol. Neurosci. 2017, 35, 557–569. [CrossRef]

75. Badimon, A.; Strasburger, H.J.; Ayata, P.; Chen, X.; Nair, A.; Ikegami, A.; Hwang, P.; Chan, A.T.; Graves, S.M.; Uweru, J.O.; et al. Negative feedback control of neuronal activity by microglia. Nature 2020, 586, 417–423. [CrossRef]

76. Becker, D.; Zahn, N.; Deller, T.; Vlachos, A. Tumor necrosis factor alpha maintains denervation-induced homeostatic synaptic plasticity of mouse dentate granule cells. Front. Cell. Neurosci. 2013, 7, 257. [CrossRef] [PubMed]

77. Steinmetz, C.C.; Turrigiano, G.G. Tumor necrosis factor-alpha signaling maintains the ability of cortical synapses to express synaptic scaling. J. Neurosci. 2010, 30, 14685–14690. [CrossRef]

78. Vazana, U.; Schori, L.; Monsonego, U.; Swissa, E.; Pell, G.S.; Rohy, Y.; Brodt, P.; Friedman, A.; Prager, O. TMS-Induced Controlled BBB Opening: Preclinical Characterization and Implications for Treatment of Brain Cancer. Pharmaceutics 2020, 12, 946. [CrossRef]

79. Li, X.; Nahas, Z.; Lomarev, M.; Denslow, S.; Shastri, A.; Bohning, D.E.; George, M.S. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: A magnetic resonance imaging study in patients with depression. Cogn. Behav. Neurol. 2003, 16, 128–135. [CrossRef] [PubMed]

80. Ravnborg, M.; Knudsen, G.M.; Blinkenberg, M. No effect of pulsed magnetic stimulation on the blood-brain barrier in rats. Neuroscienc 1990, 38, 277–280. [CrossRef]

81. Ruber, T.; David, B.; Luchters, G.; Nass, R.D.; Friedman, A.; Surges, R.; Stocker, T.; Weber, B.; Deichmann, R.; Schlau, G.; et al. Evidence for peri-ictal blood-brain barrier dysfunction in patients with epilepsy. Brain 2018, 141, 2952–2965. [CrossRef]

82. Vazana, U.; Veksler, R.; Pell, G.S.; Prager, O.; Fassler, M.; Chassidim, Y.; Roth, Y.; Shahar, H.; Zangen, A.; Raccah, R.; et al. Glutamate-Mediated Blood-Brain Barrier Opening: Implications for Neuroprotection and Drug Delivery. J. Neurosci. 2011, 36, 7727–7739. [CrossRef]

83. Schafer, D.P.; Lehman, E.K.; Stevens, B. The ”quadr-partite” synapse: Microglia-synapse interactions in the developing and mature CNS. Glia 2013, 61, 24–36. [CrossRef]

84. Del Turco, D.; Deller, T. Organotypic entorhino-hippocampal slice cultures—a tool to study the molecular and cellular regulation of axonal regeneration and collateral sprouting in vitro. Methods Mol. Biol. 2007, 399, 55–66. [CrossRef] [PubMed]

85. Humpel, C. Organotypic Brain Slices of ADULT Transgenic Mice: A Tool to Study Alzheimer’s Disease. Curr. Alzheimer Res. 2019, 16, 172–181. [CrossRef] [PubMed]

86. Ravi, V.M.; Joseph, K.; Wurm, J.; Behringer, S.; Garrelfs, N.; d’Errico, P.; Naseri, Y.; Franco, P.; Meyer-Luehmann, M.; Sankowski, R.; et al. Human organotypic brain slice culture: A novel framework for environmental research in neuro-oncology. Life Sci. Alliance 2019, 2. [CrossRef] [PubMed]