International Journal of
Molecular Sciences

MDPI

Review

Synapse Dysfunctions in Multiple Sclerosis

Karin Schwarz * and Frank Schmitz *

Department of Neuroanatomy, Institute of Anatomy and Cell Biology, Medical School, Saarland University, 66421 Homburg, Germany; karin.schwarz@uks.eu (K.S.); frank.schmitz@uks.eu (F.S.)
Academic Editor: Andreas Grabrucker
Received: 22 December 2022; Revised: 11 January 2023; Accepted: 12 January 2023; Published: 13 January 2023

Abstract: Multiple sclerosis (MS) is a chronic neuroinflammatory disease of the central nervous system (CNS) affecting nearly three million humans worldwide. In MS, cells of an auto-reactive immune system invade the brain and cause neuroinflammation. Neuroinflammation triggers a complex, multi-faceted harmful process not only in the white matter but also in the grey matter of the brain. In the grey matter, neuroinflammation causes synapse dysfunctions. Synapse dysfunctions in MS occur early and independent from white matter demyelination and are likely correlates of cognitive and mental symptoms in MS. Disturbed synapse/glia interactions and elevated neuroinflammatory signals play a central role. Glutamatergic excitotoxic synapse damage emerges as a major mechanism. We review synapse/glia communication under normal conditions and summarize how this communication becomes malfunctional during neuroinflammation in MS. We discuss mechanisms of how disturbed glia/synapse communication can lead to synapse dysfunctions, signaling dysbalance, and neurodegeneration in MS.

Keywords: multiple sclerosis; synapse; astrocyte; microglia; glutamate; ionotropic glutamate receptors; synaptopathy; glutamate excitotoxicity

1. Primer on Multiple Sclerosis (MS): Multi-Faceted Neuroinflammatory Autoimmune Disease with Pathologies in the White and Grey Matter of the Brain

Multiple sclerosis (MS) is a chronic neuroinflammatory autoimmune disease of the human central nervous system (CNS). Almost three million people worldwide suffer from MS [1]. Among those, young adults (in particular women) are the preferentially affected disease group [2–7]. Although the cause of the disease remains elusive, it has become evident that environmental factors and multiple gene loci are risk factors for disease susceptibility [3,8–16]. Viral infections, particularly those with the Epstein–Barr virus, have also been proposed to enhance the likelihood of developing MS [17–19]. In a longitudinal study, Bjornevik et al. [20] provided evidence that infection with the Epstein–Barr virus is indeed the main trigger for the development of MS, leading to a 32-fold increase in disease susceptibility. In MS, brain-reactive, encephalitogenic T cells (particularly T_H-cells) from the body periphery invade the brain [21] and induce an auto-destructive immune response that leads to alterations both in the white and grey matter. These auto-reactive T-lymphocytes are the key drivers of the disease [22]. However, also abnormally activated glial cells [23,24] and B-lymphocytes play an important role [22,25–31]. Long-term depletion of B-lymphocytes by targeting CD20 with monoclonal antibodies can attenuate disease progression in relapsing-remitting but also primary progressive multiple sclerosis [32–35], emphasizing the role of different components of the immune system in establishing and maintaining the disease.

MS patients suffer from a plethora of clinical symptoms that mirror the sites of lesion. The symptoms include, for example, visual impairments/optic neuritis, central motor paresis, sensory dysfunctions (numbness/paresthesia), and sensory ataxia [36–41]. These

clinical symptoms are considered "white matter" symptoms resulting from demyelination and axonal damage of the respective fiber tracts in the white matter. In the CNS, the axonal myelin sheath is produced by oligodendrocytes (OL). Oligodendrocyte precursor cells can differentiate into OL and play an important role in the disease course [42]. In the most frequent form of MS, classified as relapsing/remitting multiple sclerosis (RRMS), the disease is characterized by acute inflammatory episodes that improve to some extent before symptoms become progressively chronic and worse with no or only incomplete remission (progressive forms of MS) [16,43,44]. Brain auto-reactive, T-lymphocytes (mainly $CD4^+$ T-helper cells) that enter the brain (either via the blood-brain-barrier or passage through the meninges) play a central role in white matter changes and axonal demyelination [16,22,45–47]. Auto-antibodies that cross-react with brain epitopes [48–54] and hyper-activated glial cells [55–57] also significantly contribute to the disease. Demyelination and neuro-axonal damage in the white matter have been extensively investigated [16,43,58–66] and represent the most appreciated, best-characterized part of MS.

More recently, also alterations in the grey matter of MS patients have been discovered and recognized as an important contributor to the disease [59,67–74]. The novel focus on the grey matter was motivated by the observation that MS patients often show cognitive and psychic symptoms like memory dysfunctions, fatigue, and mood disorders (e.g., depression) [74–84]. These cortical dysfunctions occur even at the early stages of the disease [76,77,85], independent from demyelination in the white matter and are difficult to reconcile with changes only in the white matter. In support of involvement of the grey matter in MS, MRI analyses found lesions in distinct cortical areas, e.g., the hippocampus, temporal cortex, and deep grey matter [70,71,80,84,86–91]. In line with the MRI data, analyses of post-mortem brains from MS patients revealed morphological and molecular synapse alterations [66,68,70,71,80,84,86–89,92–95]. These data pointed to synapse dysfunctions [66,68,70,71,80,84,86–89,92–94]. Similar alterations were observed in rodent models of multiple sclerosis [70,71,84,93,95–97]. These animal models mimic important aspects of the human disease [22,98–100] and are important to make the alterations observed in human MS patients accessible for systematic analyses and basic research. A frequently used and well-validated animal model of MS is the experimental autoimmune encephalomyelitis (EAE) mouse model, in which the autoimmune disease is induced by active immunization with an encephalitogenic peptide (e.g., $MOG_{35–55}$) from the myelin oligodendrocyte glycoprotein (MOG) [101–103]. In C57BL/6J mice, MOG-induced EAE resembles a model for chronic progressive MS [98,100]. After a defined pre-clinical period, the EAE mice develop characteristic clinical symptoms in a reproducible manner, starting ≈10 days after initial immunization [102,103]. The onset of synaptic changes in this EAE rodent model occurred early before the onset of clinical symptoms and independent of demyelination, arguing that the synaptic changes are not secondary to demyelination but independent or primary events [70,84,87,93].

Neuroinflammation strongly contributes to grey matter changes [69,70,74,85,104,105]. Neuroinflammation involves abnormal glial cell activation and an excessive release of inflammatory cytokines that cause excitotoxic synapse damage [69,106–108]. Excitotoxic synapse damage can cause cortical network dysfunctions, cognitive disabilities, neurodegeneration, and neuronal cell death that could lead to irreversible disease progression. Clearly, the pathogenesis of grey matter is complex and not completely understood. However, a general picture of MS-related changes in the grey matter is gradually emerging, which we attempt to summarize in the present review.

2. Primer on Brain Synapses: Communication Nano-Machines with Multiple Adjustment "Screws"

The remarkable capabilities of the human brain are enabled by neuronal networks formed by about 100 billion neurons that are connected by more than 100 trillion chemical synapses (10^{14} synapses). Recent evidence revealed that neuronal synapses, the key devices of intercellular communication in the grey matter of the brain, are compromised in

MS. Synaptic dysfunction and subsequent neurodegeneration likely account for the cognitive changes and for disease progression in MS. Before reviewing synapse alterations and dysfunctions in MS, we will summarize key aspects of synapse structure, function, and plasticity under healthy conditions. In MS, glutamatergic synaptic signaling is particularly altered. Therefore, we will focus mainly on glutamatergic synapses in this review.

Neuronal synapses were traditionally considered to be composed of only two basal morphological units, i.e., a presynaptic terminal and a postsynaptic compartment (Figure 1). The presynaptic terminal contains synaptic vesicles that are filled with neurotransmitters. After appropriate stimulation, synaptic vesicles fuse with the presynaptic plasma membrane and release the neurotransmitter contents into the synaptic cleft. Synaptic vesicle fusion is triggered by Ca^{2+} entry through voltage-gated Ca^{2+} (Cav) channels and subsequent activation of members of the synaptotagmin Ca^{2+} sensor protein family [109,110]. Fast synaptic vesicle fusion is mediated by SNARE proteins and preferentially occurs at the active zone (Figure 1). Active zone proteins recruit the vesicle fusion/priming machinery near voltage-gated Cav channels [111,112]. The distance between Cav channels and the vesicle release machinery is relevant for synaptic vesicle release probability [113]. Different types of voltage-gated Ca^{2+} channels endow the synapse with characteristic signaling properties [114,115]. P-/Q-/N-type of Ca^{2+} channels are found in the active zones of most CNS synapses. Retinal and inner ear ribbon synapses contain presynaptic L-type Cav channels [116,117]. Some synapses even contain multiple types of Cav channels [118]. Following synaptic vesicle fusion, retrieval of fused synaptic vesicle membrane and vesicle proteins are recovered via different types of endocytosis [119].

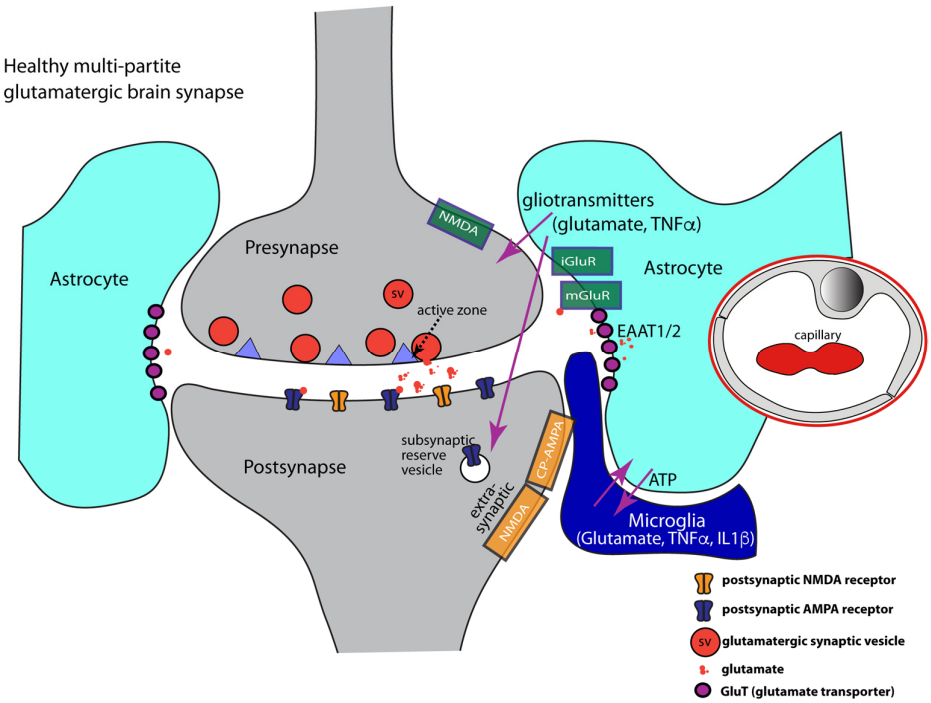

Figure 1. Glutamatergic brain synapses. It schematically depicts the composition of a healthy, glutamatergic tetrapartite brain synapse consisting of pre- and postsynaptic terminals and perisynaptic processes of astrocytes and microglia. At the presynaptic terminal, synaptic communication occurs via exocytosis of glutamatergic synaptic vesicles at the active zone. The active zone is a protein-rich compartment at which the synaptic vesicle fusion machinery is linked by active zone proteins close to voltage-gated Cav-channels. Influx of Ca^{2+} through Cav-channels triggers exocytosis. The postsynaptic membrane contains ionotropic glutamate receptors. AMPA and NMDA receptors are depicted. Perisynaptic processes of astrocytes contain glutamate transporters that remove synaptically released glutamate to prevent spillover of glutamate to neighboring synapses. Perisynaptic processes from astrocytes communicate with microglia processes (magenta arrows). Astrocytes

sense synaptic activity via various receptors, including metabotropic glutamate receptors, and modulate synaptic activity via release of "gliotransmitters", e.g., glutamate, TNFα and IL1β (magenta arrows). Furthermore, astrocytes control cerebral blood flow and the integrity of the blood-brain barrier. An exemplary capillary is shown with endothelial cell contacts sealed by tight junctions. Arrows in magenta show interactions between components of the multipartite synapse. Abbreviations: CP-AMPA, Ca^{2+}-permeable AMPA receptors, iGluR, ionotropic glutamate receptor, mGluR, metabotropic glutamate receptor, EAAT, excitatory amino acid transporter.

After release into the synaptic cleft, the neurotransmitter (e.g., glutamate) binds to postsynaptic neurotransmitter receptors. The neurotransmitter receptors are enriched in the postsynaptic density (PSD) that is located directly opposite to the active zone. In the PSD, neurotransmitter receptors are immobilized by a dense protein network of scaffold proteins [120,121]. These scaffold proteins include MAGUK family proteins, e.g., PSD-95, SAP-97, SAP-102, in excitatory synapses. Inhibitory synapses contain scaffold proteins such as gephyrin and collybistin [122]. PSD-95 of excitatory synapses is a particularly relevant PSD scaffold protein of excitatory synapses because it links AMPA- and NMDA-type glutamate receptors to each other [120,121]. These glutamate receptors are important for synaptic plasticity and for excitotoxic synapse damage (see below).

The synaptic cleft contains synaptic adhesion protein complexes that align pre- and postsynaptic signaling complexes into functionally connected transsynaptic nanocolumns required for synchronous, efficient information transfer [123–125]. An important synaptic adhesion complex consists of presynaptic neurexins and postsynaptic neuroligins and functions as transsynaptic organizers [123,124,126]. Neurexin genes generate large numbers of splice variants relevant for guiding connectivity between distinct, individual neurons. Dysfunctions of neurexin-neuroligin synaptic complexes were correlated with cognitive disturbances and neuropsychiatric diseases [123,124]. Other synaptic adhesion complexes, in part, also interact with the neurexin-neuroligin trans-synaptic adhesion axis [123,126].

3. Communication at Glutamatergic Synapses

Excitatory glutamatergic synaptic signaling appears to be strongly enhanced in MS and mouse models of MS [78,84,85,87,127–130]. Glutamate is the major excitatory neurotransmitter of the central nervous system (CNS) [131–134] and is of particular relevance in MS. The levels of glutamate in the cerebrospinal fluid (CSF) of MS patients and EAE mice are increased [70,129,135–140], pointing to the particular importance of glutamatergic signaling dysfunctions in MS.

Exocytosis of glutamatergic synaptic vesicles at the active zone is the prime mechanism for glutamate release at the synapse. Following presynaptic release, glutamate exerts its action at the postsynapse by binding to different types of glutamate receptors [131–133] (Figure 1). Glutamate receptors are classified into ionotropic and metabotropic glutamate receptors (iGluR, mGluR) [133,141]. iGluRs are sub-divided into AMPA-, Kainate, and NMDA-type receptors based on their molecular composition, physiological properties, and preferential agonists. For fast synaptic transmission, the postsynapse mainly employs iGluRs. All iGluR receptors are composed of several subunits. In the CNS, 2-Amino-3-(3-hydroxy-5-methylisooxazol-4-yl)proprionate (AMPA) receptors are the most abundant glutamate iGluRs. AMPA receptors assemble from four different subunits (GluA1-GluA4). These form homo- or hetero-tetramers [133,142,143]. Glutamate-gated opening of AMPA receptors depolarizes the postsynaptic compartment. AMPA receptors are permeable to Na^+, K^+ and, depending upon subunit composition, also to Ca^{2+}. If the GluA2 subunit is absent from AMPA receptors, the resulting AMPA channels are permeable to Ca^{2+} [133,142]. AMPA receptors containing GluA2 are not Ca^{2+} permeable. N-methyl-D-aspartate (NMDA)-type iGluRs also play an important role for synaptopathy in MS. NMDA receptors are hetero-tetramers that consist of GluN1, GluN2 (GluN2A, GluN2B, GluN2C, GluN2D), and GluN3(A,B) subunits [144,145]. Two GluN1 subunits combine with two

GluN2 or GluN3 subunits to form the NMDA channel. AMPA and NMDA receptors functionally interact. Strong depolarization of the postsynaptic compartment obtained by many AMPA-channel openings relieves the Mg^{2+} block of NMDA receptors and enables the opening of NMDA receptor channels [141,145,146]. Only strong depolarizations that typically result from multiple simultaneous presynaptic vesicle fusion events lift the block of NMDA glutamate receptors by expulsing Mg^{2+} from the channel pore. The influx of Ca^{2+} through the NMDA receptor induces early and late phases of LTP (Long-Term Potentiation) through CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) and cAMP/PKA/pCREB-dependent mechanisms [147–156]. Influx of Ca^{2+} also triggers increased surface expression of AMPA receptors via fusion of AMPA receptor-containing subsynaptic vesicles with the postsynaptic plasma membrane [147,157,158]. Elevated surface expression of AMPA receptors increases the efficacy of this individual synapse at which the NMDA receptor was activated and makes it more sensitive to the subsequent release of glutamate by the connected presynaptic terminal. The adjustment of synaptic efficacy based on previous activity is part of a phenomenon called "synaptic plasticity". It is considered the basis for learning, memory, and experience-based behavior [159]. Heavily used synapses become more efficient by this mechanism. Vice versa, the efficacy of less active synapses decreases. These positive feedback mechanisms belong to the Hebbian-type of synaptic plasticity and include short-term and long-term effects [147,157,160]. The Ca^{2+} permeability of iGluRs (GluA2-lacking AMPA- and NMDA receptors) is central to this process [142,161–163]. Further Ca^{2+}-dependent events also support synaptic plasticity. Ca^{2+} regulates the metabolic activity of mitochondria in order to synchronize energy production with synaptic activity [164–166]. Ca^{2+} also controls intracellular signaling cascades, such as the Ca^{2+}/Calmodulin/CaMKII system and the Ras/Raf/MAP-kinase pathway that control the activity of phosphorylation-regulated transcription factors (e.g., CREB, NF-kB). These transcription factors control transcriptional programs needed for the long-term remodeling of synaptic components (e.g., dendritic spines) and/or neuronal survival (e.g., secretion of BDNF [167]). Pre-synaptic mechanisms can also contribute to synaptic plasticity [112,150,168]. Presynaptic mechanisms include modulation of synaptic vesicle release probability, e.g., by modification of active zone components/Cav-channel number/distance/opening properties [112,113]. A second form of synaptic plasticity, homeostatic synaptic plasticity (HSP), prevents over-activation/saturation of active synapses and complete silencing of less frequently used synapses [169–174]. HSP is based on negative-feedback mechanisms that lead to counter-acting, compensatory adjustments, and a re-setting of the synaptic signaling range. HSP prevents saturation and unresponsiveness of synaptic connections and maintains synaptic activity in a functional range [169,170]. Interestingly, synaptic plasticity and adaptational changes of synapses are strongly influenced by inflammatory cytokines, such as TNFα and IL1β.

4. A More Extended View on Brain Synapses: Contribution of Glial Cells

In the brain, pro-inflammatory cytokines, such as TNFα and IL1β, are physiologically secreted in small amounts by glial cells, mainly by astrocytes and microglia. These glial cells establish close contacts with synapses and modulate synaptic communication. Glia-synapse interactions are important to adjust synaptic activity under normal conditions but are also relevant for synaptopathy as it occurs in MS.

5. Primer on Astrocytes: A Network of Guardians of Brain Homeostasis with Strong Impact on Synapses

The human brain contains about 86 billions of neurons and a similar number (85 billions) of glial cells [175]. Within the population of glial cells, astrocytes are the most abundant type of glial cells in the human brain. Astrocytes are multi-branched stellate cells that intensively communicate with each other via gap junctions [176–178]. Astrocytes also establish close contact with neurons. At a functional level, astrocytes execute many pivotal homeostatic functions. Some important functions include the maintenance of extracellular

ion and fluid balance, provision of metabolites (e.g., glutamine, see below) to neurons, control of blood flow, and maintenance of the blood-brain barrier [176,179–185]. Astrocytes are functionally very diverse, as also confirmed by single-cell sequencing [178]. Based on the molecular heterogeneity, a nomenclature has been proposed for astrocytes in which resting astrocytes and various types of "reactive" astrocytes have been discriminated [178].

Astrocytes are also relevant for synapses in the brain. Astrocytes form processes that wrap around synapses, thus establishing close perisynaptic contacts with pre- and postsynaptic compartments [83,177,186–188] (Figure 1). A single astrocyte can ensheath more than 100,000 synapses [189–191]. The degree of ensheathment of synapses by perisynaptic processes varies between brain regions [192,193]. Perisynaptic processes of astrocytes have a strong impact on synapse function. Therefore, astrocytes have been considered an integral part of chemical brain synapses, which has been coined "tripartite" synapse [194]. The "tripartite" synapse consists of presynapse, postsynapse, and perisynaptic astrocytic process according to this terminology [177,190,195–197] (Figure 1). Synapse-associated perisynaptic processes of astrocytes, sometimes also called "astrocytic cradle", are important for several aspects of synaptic function [83,177,194,197]:

(1) Astrocytes play an important role in synapse development [177,198]. Astrocytes secrete synaptogenic factors that promote synapse formation and maturation, e.g., synapse organizing molecules, such as thrombospondin, hevin, or trophic factors that promote presynaptic differentiation [177,199–208]. Astrocytes also secrete glypicans that increase the surface expression of postsynaptic AMPA receptors [209,210].

(2) At glutamatergic synapses, the perisynaptic processes of astrocytes contribute to the uptake of synaptically released glutamate [186,189,192,211–219]. Glutamate is taken up by various glutamate transporters [220–222]. Glutamate transporters (GluTs), also called excitatory amino acid transporters (EAATs), belong to the solute carrier 1 family (SLC1). Five sodium-dependent glutamate transporters (GluT) of the SLC1 family have been cloned: EAAT1/GLAST1, GLT1/EAAT2, EAAT3/EAAC1, EAAT4, and EAAT5/SLC1A7 [221,223–226]. GluTs have been localized to different localizations at the synapse. In general, GluTs are present either in the plasma membrane of the presynaptic terminal or in the plasma membrane of perisynaptic astroglial processes [222,227–232]. In this way, presynaptic neuronal and glial (astrocytic) glutamate uptake mechanisms collaborate to maintain low resting concentrations of extracellular glutamate and to prevent excitatory over-stimulation/excitatory synapse damage [84,190,216,220,233].

GLT1/EAAT2 accounts for most of the glutamate uptake in the brain [222,231,234]. GLT1/EAAT1 is expressed predominantly, although not exclusively, in astrocytes [222,231,234]. GLT1/EAAT2 is enriched in perisynaptic astrocytic processes [187,216,230]. Splice variants of GLT1/EAAT1 and EAAT5 are localized in presynaptic terminals close to the presynaptic release sites [235–238]. Moreover, GLAST/EAAT1 is localized to astroglia in perisynaptic processes. Glutamatergic ribbon synapses are organized in a similar manner (Figure 2). Ribbon synapses of the retina are strongly affected in mouse models of MS [239–241], and their early dysfunction might contribute to optic neuritis, a frequent symptom in MS [242]. In the retina, EAAT1/2 is mostly found in the perisynaptic processes of Müller glial cells (Figure 2) [243–251]. At a perisynaptic location, astrocytic GluTs are strategically well placed to remove glutamate spillovers and to prevent crosstalk to neighboring synapses. In astrocytes or astrocyte-related radial glial cells (Müller cells of the retina, Bergmann glia of the cerebellum), glutamate is metabolized into glutamine via glutamine synthetase. Glutamine, a metabolically inert form of glutamate, is re-provided to the neuron in order to replenish the neuronal glutamate stocks (glutamate-glutamine cycle [132,222,252]. EAAT5 has been localized in presynaptic terminals of retinal photoreceptors and retinal bipolar cells close to presynaptic release sites [228,253–255].

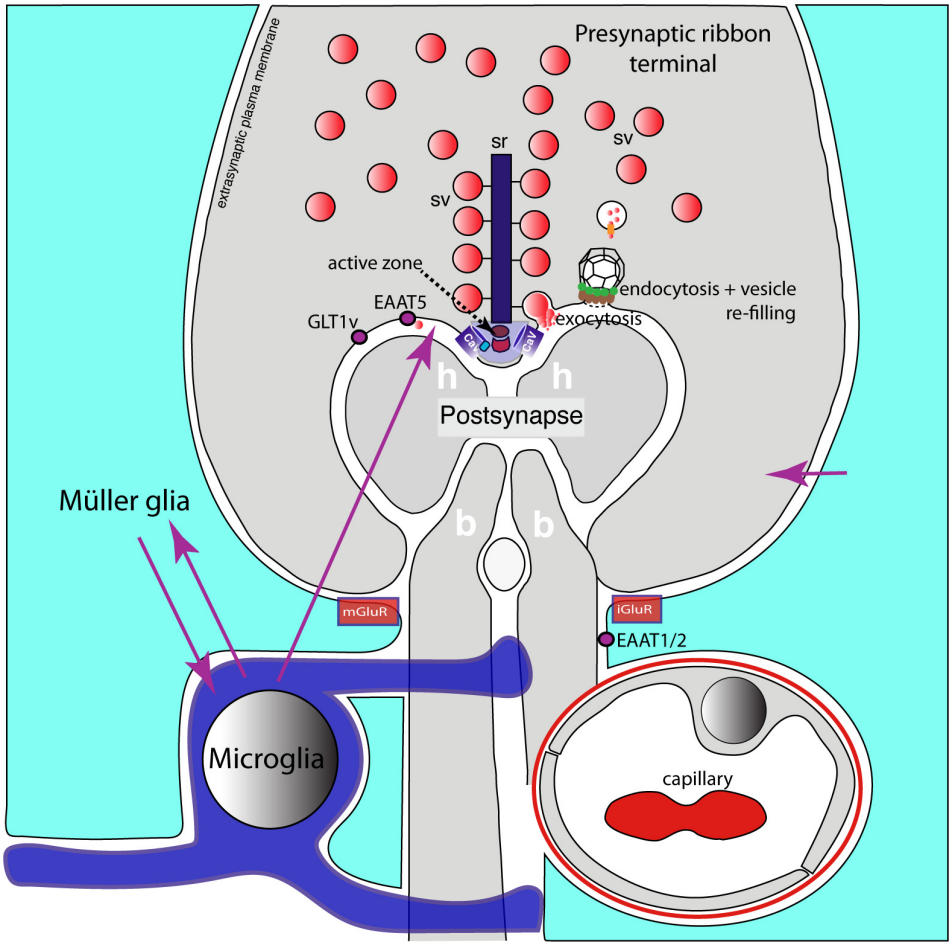

Figure 2. Glutamatergic retinal ribbon synapses. It schematically depicts a glutamatergic ribbon synapse of the retina. A photoreceptor ribbon synapse is shown. The functional and molecular composition of the presynaptic ribbon terminal is like that of the brain synapse shown in Figure 1. However, the presynaptic terminals of ribbon synapses possess eponymous synaptic ribbons that provide the active zone with additional synaptic vesicles to enable continuous synaptic transmission at this synapse. The active zone is the site at which exocytosis of synaptic vesicles occurs close to voltage-gated L-type Cav-channels. Endocytosis of fused vesicle membrane occurs in the periactive zone, followed by a refilling process of endocytosed vesicles with glutamate. The postsynapse is composed of the dendrites of horizontal and bipolar cells. The postsynaptic dendrites contain ionotropic and metabotropic glutamate receptors (not shown). Müller glial cells form perisynaptic processes that are enriched in glutamate transporters (EAAT1, EAAT2). The presynaptic terminal contains additional glutamate transporters (GLT1v, EAAT5) in the periactive zone. Retinal ramified microglial cells frequently contact synapses and likely communicate with Müller glial cells (magenta arrows). Retinal ribbon synapses are very sensitive to neuroinflammatory changes. Neuroinflammatory changes strongly affect presynaptic terminal functions (for details, see text). Active zone composition, presynaptic Ca^{2+} homeostasis and exo- and endocytic vesicle cycling in these synapses are disturbed in EAE. The underlying mechanisms are not yet fully elucidated but might involve simar pathways as described for brain synapses (see text). Arrows in magenta indicate possible interactions between Müller cells, microglia and the photoreceptor synapse. Abbreviations: sv, synaptic vesicles; sr, synaptic ribbon; Cav, voltage-gated Ca^{2+}-channel; mGluR, metabotropic glutamate receptor at Müller glial cells; iGluR, ionotropic glutamate receptor at Müller glial cells; h, horizontal cell postsynaptic dendrite; b, bipolar cell postsynaptic dendrite; GLT1v, glutamate transporter 1 splice variant; EAAT1/2, excitatory amino acid transporter 1/2.

Of note, glutamate transporters (GluTs) can also revert the transport direction of glutamate and secrete glutamate. This can occur during pathological conditions/diseases. The

physiological basis for this phenomenon is the fact that GluTs are secondary active transporters that depend upon the transcellular Na^+ gradient [221]. In this electrogenic transport, one glutamate molecule is co-transported with 3 Na^+ and 1 H^+. In the regular "forward" mode, this import is coupled with counter-transport (export) of a K^+ ion into the extracellular space. Disease conditions that dissipate the electrochemical Na^+ gradient can drive glutamate transport into the opposite direction, i.e., release of glutamate into the extracellular space (reverse mode of transporter activity [256,257]). Reverse efflux of glutamate through GluTs happens during ischemia and inflammation [257–259]. Such a mechanism could also be relevant for glutamate excitotoxicity in MS (see below). Further mechanisms that could contribute to the elevation of extrasynaptic glutamate include glutamate release through the cystine-glutamate antiporter xCT (cystine/glutamate antiporter) [260,261], release through bestrophin-1 anion channel [262–265], TREK-1 channels [264,265], and volume-regulated anion channels/volume-sensitive organic anion channels (VRACs/VSOACs) [266–268]. Moreover, vesicular release of glutamate by astrocytes and microglia could lead to elevated levels of extrasynaptic glutamate and contribute to glutamate excitotoxicity in MS (see below).

(3) Perisynaptic astrocytes possess different types of neurotransmitter receptors, e.g., metabotropic glutamate receptors (mGluR2, mGluR3, mGluR5), AMPA-type ionotropic glutamate receptors, GABA receptors, and purinoreceptors to sense synaptic activity [177,196,197,269–274]. Astrocytes are capable of secreting TNFα and also possess TNFα receptors that serve autocrine effects. TNFα receptors are also important for communication with microglia [82,162,177,275–277] and neurons [162,163,173,278–280].

Activation of astrocytic neurotransmitter receptors leads to changes in intracellular Ca^{2+} in astrocytes and to the release of "gliotransmitters" [195,208,272,281–286]. The source of these intracellular Ca^{2+} changes is controversially discussed [287,288]. Gliotransmitters are neuroactive molecules, such as glutamate, ATP/adenosine, GABA, NPY, D-serine (a co-agonist of NMDA-type of glutamate receptors), IL1β, and TNF-α [286]. Astrocytes release synapse-active components that affect synaptic performance [208,218,283–285,289]. Gliotransmitters released by astrocytes influence pre- and postsynaptic functions [193,195,276,278,290,291]. Important signaling cascades have been identified. Glutamatergic synapses that show only little activity secrete less glutamate. Decreased levels of synaptically released glutamate are sensed by neurotransmitter receptors of perisynaptic astrocytes in hippocampal synapses and induce secretion of TNFα (by astrocytes and microglia via astrocyte/microglia communication). These elevated, non-toxic levels of TNFα (≈100 picomolar TNFα) enhance pre- and postsynaptic glutamatergic signaling [162,163,173,278,292–294]. TNFα induces glutamate release by astrocytes that, in turn, stimulate presynaptic glutamate release at hippocampal synapses (i.e., entorhinal cortex/dentate gyrus synapses) via binding to presynaptic NMDA receptors [162,163,269,275,277,278,290,295]. Of note, the effect of astrocytic glutamate on presynaptic release depends on the expression of distinct neurotransmitter receptors. The binding of glutamate to metabotropic glutamate receptors (mGluR2/3) at the presynapse was reported to inhibit glutamate release from the presynaptic terminal [296–298]. At the postsynapse, glial TNFα leads to an increased surface expression of AMPA receptors to scale up synaptic activity and synaptic responsiveness [162,163]. In conclusion, the pro-inflammatory cytokine TNFα at physiological concentrations is an important positive regulator of synaptic activity in the healthy brain. Modulation of TNFα secretion in this physiological range serves homeostatic scaling of synapse activity (HSP, see above). Typically, astrocyte-mediated modulation of synaptic transmission occurs at a slower timescale as fast synaptic communication between the pre- and postsynaptic compartment due to the signal integration in the glial compartment [197,272,278]. At the systems level, physiologically elevated levels of pro-inflammatory cytokines have been shown to be important for

memory formation in freely moving animals reflecting their effect on synapses also in-situ [299].

Astrocytes establish intimate contacts with microglia at synapses and exchange important mutual signals with microglia. Astrocytes provide microglia with cues on synaptic activity. Microglia vice versa, provide signals for the differentiation of astrocytes into distinct sub-types, i.e., either into a beneficial, homeostatic, and activity-maintaining sub-type (initially denoted as "A2" astrocytes [217,284,300]) or into a neurotoxic, neuroinflammatory subtype ("A1" astrocytes [208]) whose activity is detrimental to the CNS [208,217,284,300]. C1q, IL-1α, and TNFα promote differentiation of resting astrocytes into the A1 neuro-destructive state [208], whereas co-stimulation with TNFα and IL1β promotes differentiation towards the neuro-supportive A2 phenotype in astrocytes [217,284,300,301].

As mentioned, the A1/A2 dichotomy of astrocytes is too simplified based on single-cell sequencing data but still useful as a simplified working model. Transcript analyses revealed markers common to all reactive astrocytes (e.g., GFAP [178,302]). The expression of complement protein C3 is a marker for inflammatory "A1" astrocytes [178,208,284,303,304]. Complement proteins were found to be highly elevated in the brain of MS patients, particularly in cortical grey matter lesions [305–308]. The complement system is likely involved in synapse dysfunctions in the MS brain based on its well-known function of synapse removal during brain development [309,310]. Astrocyte-microglia interactions are highly relevant for neuroinflammatory disease in multiple sclerosis and the resulting synaptic changes (see below).

6. Primer on Microglia: Never-Resting Brain "Police" with the Mission to Survey and to Take (Strong) Action

Microglia are the main resident immune cells of the brain, comprising ≈10% of total CNS brain cells with some regional differences [311–315]. Microglial cells develop from monocyte-like precursor cells of the bone marrow and yolk sac [316,317]. During embryonic development, they invade the brain, in which they mature and proliferate [216,318,319]. Cell surface markers, such as TMEM119, allow to discriminate microglia from blood-borne macrophages invading from capillaries [320,321]. A few years ago, microglia were believed to be active only during disease conditions. Recent investigations demonstrated that microglia perform important functions already in the healthy, non-injured brain. The range of functions performed by microglia, both in the healthy and injured brain, is broad [216,285,322–324].

Morphologically, microglia are very diverse and dynamic [325]. In the healthy brain, microglial cells often display a highly ramified morphology with many processes. Ramified microglia were previously considered "resting", i.e., inactive. This old view is not correct. Novel technologies, particularly live imaging analyses with genetically engineered fluorescent microglia, demonstrated that "resting" ramified microglial cells are indeed highly active already under physiological conditions in the healthy brain [322,326–331]. Live imaging experiments with genetically tagged microglia revealed that microglial processes are highly mobile and frequently expand and retract [322,326]. These processes continuously scan and monitor the extracellular environment of the CNS for a broad range of signals [216,285,322,323]. Thus, the term "resting" microglia should be replaced by the term "surveying" microglia [323].

Live-Imaging with these genetically engineered mice possessing fluorescent microglia revealed that ramified microglia use their processes to contact synapses [322,326]. The soma of the microglia typically stays stationary in this process, whereas the processes expand and retract continuously. A sub-type of ramified microglia that is positive for a 5D4 keratan-epitope and rich in IL1β is particularly active in this process [332]. The close relationship between microglial processes to both pre- and postsynaptic compartments, as well as to perisynaptic astrocytes has been referred to as tetra-partite synapse [285,333].

The interaction between ramified microglia processes and synapses is complex and depends upon synaptic activity [327,328]. Synapses and microglial synaptic processes influence each other in a mutual manner. On the one hand, synaptic activity regulates the contact properties between microglial processes and synapses (e.g., process motility, duration, and frequency of synaptic contacts) in a differential manner [334]. On the other hand, ramified microglia signal back to synapses and lead to changes in glutamatergic synaptic transmission [276,334]. The contact between ramified microglial processes and synapses was reported to increase synaptic activity [335]. This feedback from microglia to synapses is predominantly indirect and mediated via astrocytes that secrete gliotransmitters [276,335]. Similarly, synaptic activity also influences the motility of microglial processes in the retina [336]. In the retina, glutamatergic neurotransmission enhances microglia process motility, whereas GABAergic transmission inhibits microglial process motility [336].

The precise mechanisms of synapse-microglia interactions are complex and not fully understood. As mentioned, the effects of synaptically released glutamate on microglia are likely indirect because ramified surveying microglia do not express glutamate receptors (in contrast to "activated" microglia, see below). In the retina, the neurotransmitter effects of glutamate on microglia motility were reported to be mediated via ATP release from Müller glial cells/astrocytes [336]. Thus, synaptic neurotransmitter release likely does not signal directly to ramified microglial cells but indirectly via signals from perisynaptic astrocytes [326,335–338]. ATP binds to microglial ionotropic P2X7 receptors to induce the release of IL1β [339]. IL1β is a powerful modulator of synapse function (see below). ATP can also bind to microglial metabotropic purinergic receptors (P2Y12/13) that are relevant for chemotactic guiding of microglia [340–342]. Released ATP can also directly affect the postsynaptic terminal by activation of postsynaptic P2X receptors [343,344].

Of note, ramified microglia secrete trophic factors (e.g., BDNF, NGF, FGF, and IGF-1) that promote synapse function and synaptic plasticity [167,216,330,333,342,345–349].

7. Multivalent Microglia: Potentiator of Inflammatory Signals with Strong Impact on Synapses

Any kind of homeostatic disturbance in the brain can activate microglia and lead to a transformation into a reactive, particularly alerted state [216,285,318,319,323]. Microglia activation is often associated with de-ramification or even loss of microglial processes. A process-lacking amoeboid shape promotes the movement of the activated microglia towards the area in which a potential threat has been detected. The character and degree of microglia activation differ broadly [216,285,323,326–328,336,350]. Two extreme forms of activated microglia sub-types have been previously discriminated and denoted as M1- and M2-microglia [284,323,351–353]. "M1"-type microglia are pro-inflammatory and neurotoxic with low phagocytic activity. They show surface expression of MHC-II proteins, CD11b, CD16, CD68, TREM2, and release large quantities of glutamate (and glutamate-like toxic kynurenines) as well as pro-inflammatory cytokines, such as IL1β, TNFα, IL-6, IL-12, and IFNγ [216,284,323,342,354,355]. "M2"-type microglia are anti-inflammatory, neuroprotective with high phagocytic activity, express distinct surface markers such as CD163 and CD206, and secrete IGF-1 and TGF-β [216,284,323,342,354,355]. Single-cell sequencing revealed that the classification of activated microglia in only two classes is simplified. Activated microglia are functionally more diverse [302,356,357]. The dichotomic M1/M2 category still serves as a simplified model.

Microglial cells are equipped with various receptors for detecting homeostasis-threatening signals [358–364]. Large amounts of ATP released from damaged or dead cells are a strong attracting and activation signal for microglia [285,326,365,366]. Complement proteins (e.g., complement proteins C1, C3) are also detected by microglial cells via cell surface complement receptors [177,185,285,309,329]. During development, complement proteins tag excess or dysfunctional synapses and mark these for subsequent elimination by microglia, a process called "synapse stripping". Synapse stripping is important for the

development and refinement of functional neuronal circuits during development [216,309,329]. In the mature brain, less active synapses also contain increased levels of C1q that promote their removal by microglial cells, thus allowing activity-dependent refinement of neuronal circuits in the healthy, postnatal brain [327–329,345,367–369]. Astrocytes are also involved in synapse stripping of silenced or dysfunctional synapses together with the microglia [177,370].

As mentioned, the activation of microglia can be strong, particularly if the inflammatory event stays unresolved and remains to continuously activate the microglia. Under these conditions, i.e., when microglia are strongly and permanently activated, microglia become harmful to the host brain and promote disease progression/aggravation by secreting large amounts of reactive oxygen species and biologically active cytokines that cause neuroinflammation [216,284,285,348,353,371,372]. Inflammatory over-activation of microglia, as it occurs in active, progressive MS, can lead to significantly elevated release of the pro-inflammatory cytokines, e.g., TNFα, IL1β [70,84,373], that adversely affect synapse functions (see below). As mentioned, microglia also communicate with astrocytes and influence the differentiation of astrocytes. Pathologically activated microglia of the "M1" subtype activate astrocytes towards a harmful "A1" sub-type by the secretion of IL1α, TNFα, and C1q [162,177,208,216,276]. A1 astrocytes, together with the activated M1 microglia, represent the major source of the pro-inflammatory cytokines IL1β and TNFα in the brain [69,162,177,216,276,284]. The large amount of secreted IL1β and TNFα can lead to synapse damage in MS by multiple mechanisms and produce the observed grey matter dysfunctions in MS (see below).

8. Neuroinflammation-Induced Synapse Dysfunctions in MS

The levels of the pro-inflammatory cytokines TNFα and IL1β can severely increase in MS, particularly in the active, progressive stages of MS [69,70,78,84,85,128,373–377]. During persistent strong inflammation, activated microglia potentiate inflammatory signals leading to excessive pathological TNFα values up to the mM range [275,278]. A growing body of evidence indicates that the highly elevated levels of these pro-inflammatory cytokines (TNFα, IL1β), as it can occur in MS [378,379], are the main reason for early dysfunctions of synaptic transmission. These lead to glutamatergic excitotoxicity, neurodegeneration, and ultimately, neuronal cell death. Several mechanisms contribute to neuroinflammation-induced glutamatergic synapse dysfunction and glutamatergic excitotoxicity.

(1) TNFα regulates AMPA- and GABA- receptor trafficking in an antagonistic manner. The highly elevated levels of inflammatory cytokines released by activated microglia, astrocytes, and inflammatory $CD3^+$ T-cells in MS, inhibit the expression of glial glutamate transporters (EAAT1/2), resulting in a decreased clearance of glutamate from the synaptic cleft [85,128,129,380–385] (Figure 3). The decreased glutamate clearance results in increased levels of extrasynaptic glutamate. Extrasynaptic glutamate binds to extrasynaptic glutamate receptors, including Ca^{2+}-permeable NMDA receptors and Ca^{2+}-permeable AMPA receptors. Stimulation of these extrasynaptic glutamate receptors is considered the central mechanism causing glutamate excitotoxicity, neurodegeneration, and neuronal cell death [386–389]. Many of these mechanisms involve elevated levels of Ca^{2+}. Extrasynaptic NMDA receptor activation will trigger a deleterious signaling cascade that includes structural degeneration of the synapse, mitochondrial damage, and transcriptional shut-off of neuroprotective pathways [386–389]. Paradoxically, increased extrasynaptic glutamate can further inhibit the expression of astrocytic glutamate transporters [390], thus fostering a vicious cycle that leads to glutamate excitotoxicity.

(2) Inflammatory cytokines (TNFα, IL1β) induce an increased surface expression of AMPA receptors [85,127,129,162,163,391,392] (Figure 3). Increased surface expression of AMPA receptors was observed in animal models of MS as well as in MS patients

[127]. Of note, the significantly increased levels of TNFα/IL1β in MS/EAE, lead to an increased surface expression of the Ca^{2+}-permeable AMPA receptors that lack the GluA2 subunit and thus lead to an enhancement of excitatory synaptic signaling [85,129,142,162,163,173,292–294,392,393]. As mentioned above, the Ca^{2+}-permeability of glutamate-gated receptors is of particular importance for excitotoxic effects. High concentrations of TNFα increase not only synaptic but also non-synaptic AMPA receptor expression that further contributes to inflammation-induced glutamate excitotoxicity [127,278,373,392,394]. NMDA glutamate receptors could also be affected [138,139,395–403]. Increased surface expression of synaptic or extrasynaptic NMDA receptors in response to TNFα [397,404,405] aggravates glutamate excitotoxicity. This could occur either via Ca^{2+} overload of the postsynaptic compartment (Figure 3) or the formation of pathological glutamate receptor complexes [389] that lead to neurodegeneration and neuronal cell death [386–388].

(3) Inflammatory cytokines (IL1β, TNFα) induce decreased surface expression of GABA receptors resulting in an imbalance between excitatory and inhibitory signaling [292,406–409]. TNFα promotes endocytosis of inhibitory GABA receptors thus leading to a decrease in GABA receptor surface expression [292,408]. In the EAE model of multiple sclerosis, inhibitory GABAergic signaling is diminished [84,85,87,128–130,407–409]. The TNFα effects on AMPA and GABA receptor trafficking are mediated by neuronal TNFR1 receptors [177,292]. IL1β is also involved in the downregulation of synaptic GABA receptors [128,129,407,408,410–412]. On the other hand, IL-1β enhances the surface expression of GABA transporters (GATs), thus promoting increased GABA clearance from the synaptic cleft [413–415]. In MS patients, GABA levels are significantly reduced and correlated with increasing physical disability in progressive multiple sclerosis [416].

(4) Elevated levels of TNFα increase glutaminase activity in microglia and induce significant release of glutamate from microglia [108,417–419]. Activated astrocytes and invading T cells also contribute to increased levels of glutamate in neuroinflammation [259]. These mechanisms will lead to strong activation of extrasynaptic N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors. Activation of extrasynaptic glutamate receptors results in neurotoxic effects and ultimately leads to neuronal cell death via various mechanisms [386–389]. The underlying mechanisms are still under intense investigation, and likely include dysfunctional Ca^{2+} homeostasis, molecular and structural alterations of the synapse, malfunctional pre- and postsynaptic signaling cascades, mitochondrial dysfunctions, and dysregulation of synapse-dependent transcriptional programs [386–389].

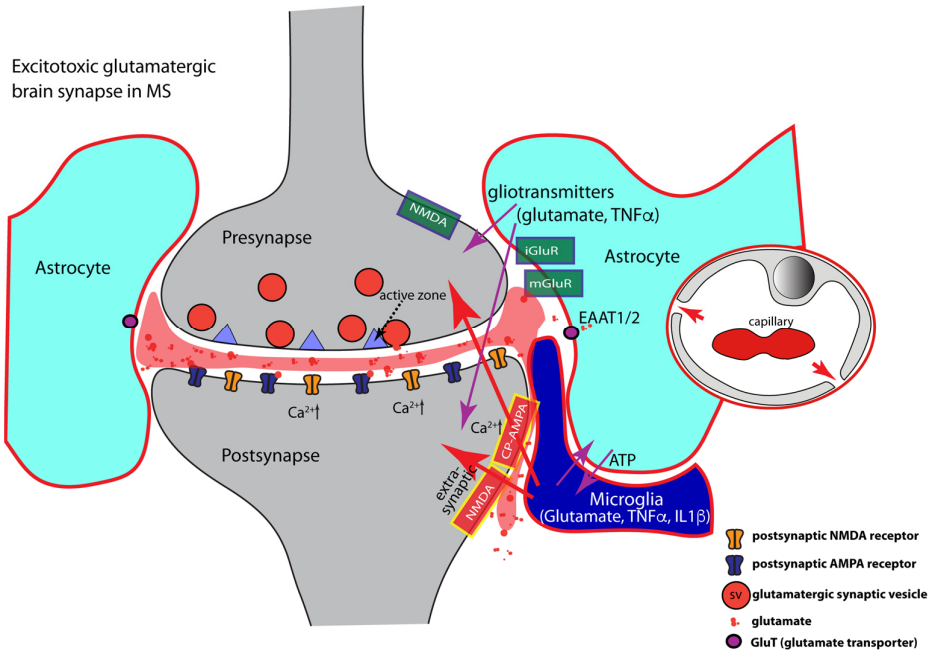

Figure 3. schematically depicts a brain synapse, as shown in Figure 1, but under neuroinflammatory conditions as in multiple sclerosis (MS). Perisynaptic astrocytes and microglia are strongly activated (encircled in red) and secrete large amounts of inflammatory cytokines. Inflammatory cytokines produce glutamatergic excitotoxicity (see text). Neuroinflammation leads to decreased expression of astrocytic glutamate transporters and to elevated levels of extracellular glutamate (colored in red). Increased extracellular glutamate binds to extrasynaptic glutamate receptors. This initiates a series of deleterious events at the synapse consisting of structural synapse damage, mitochondrial dysfunctions and transcriptional down-regulation of neuroprotective pathways. Synaptic excitotoxicity is further aggravated by increased incorporation of AMPA and NMDA receptors into the postsynaptic membrane, together with a concomitant decrease of inhibitory synaptic transmission (not shown). During neuroinflammation, the integrity of the blood-brain-barrier is compromised and inter-endothelial cell contacts become leaky (indicated by red arrows in the depicted capillary) allowing the entry of blood-borne immune cells into the CNS. Arrows in magenta show interactions between components of the multipartite synapse. Arrows in red denote pathologically activated signaling events during neuroinflammation. Abbreviations: CP-AMPA, Ca^{2+}-permeable AMPA receptors; iGluR, ionotropic glutamate receptor; mGluR, metabotropic glutamate receptor; EAAT, excitatory amino acid transporter.

Collectively, early synapse changes in MS (and mouse models of MS) appear to result from increased levels of inflammatory cytokines. Synapse dysfunctions are likely correlates of the known cognitive disabilities and memory dysfunctions in MS patients [68,71,76,92,279,280,420–429]. Signals from glial cells, particularly microglia, play a prominent role in synaptic pathology. In support of this suggestion, paralysis of microglia ameliorates EAE [430]. Clearly, the role of microglia in this process is complex. As mentioned, pro-inflammatory microglia ("M1" microglia) can generate pathologically elevated levels of inflammatory cytokines in active MS. M2 microglia can counteract these events and disease pathology. Thus, influencing the differentiation behavior of activated microglia toward the anti-inflammatory M2 microglia subtype will likely provide potential for the development of novel therapeutic strategies in MS. Interestingly, MS susceptibility genes are more frequently associated with microglia functions than with neuronal or astrocyte functions emphasizing the central role of microglia for MS [431,432].

Many of the described synaptic alterations in MS/mouse models of MS can be assigned to the postsynaptic compartment. In glutamatergic ribbon synapses of the retina, also strong alterations of presynaptic events have been observed in EAE [239–241]. These alterations included changes in the molecular composition of components of the active

zone, presynaptic Ca^{2+} homeostasis, and decreased exocytic and endocytic synaptic vesicle cycling. The detailed underlying mechanisms for these presynaptic changes remain to be elucidated but might possibly also involve glutamatergic excitotoxicity. As mentioned, glutamate excitotoxicity can also affect presynaptic events via presynaptic glutamate receptors [275,276]. Gliotransmitter like IL1β and TNFα could also exert effects on such presynaptic events based on the presence of receptors for IL1β and TNFα at the presynaptic terminal [342]. Disorders of the visual system are frequent symptoms of multiple sclerosis, and the early dysfunctions of retinal ribbon synapses observed in the EAE mouse model of MS [239–241] could contribute to these symptoms.

9. Conclusions and Outlook

Glial cells play an important role in modulating synaptic activity under normal, healthy conditions. Glial cells are targets and amplifiers of neuroinflammatory signals that if secreted in excessive amounts, damage brain synapses and lead to progressive neurodegeneration and brain dysfunctions. The underlying mechanisms and signaling cascades are not fully understood despite enormous recent scientific advancement. Further analyses will likely provide not only an improved understanding of synaptopathy in MS but will also help in the development of novel therapeutic strategies.

Author Contributions: K.S. and F.S. performed literature searches, designed and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: The work of the authors was supported by the Dr. Rolf M. Schwiete Foundation (2021-022) and Deutsche Forschungsgemeinschaft DFG (FOR2289).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availabilty Statement: Not applicable.

Acknowledgments: The work of the authors was supported by Dr. Rolf M. Schwiete Foundation (2021-022) and Deutsche Forschungsgemeinschaft DFG (FOR2289). We apologize to our colleagues that not all relevant studies/original work could be mentioned in the review due to limitations of space.

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

Abbreviations

MS	multiple sclerosis
EAE	experimental autoimmune encephalo-myelitis
CNS	central nervous system
OL	oligodendrocyte
GluT	glutamate transporter
Cav-channel	voltage-gated Ca^{2+}-channels
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
PKA	protein kinase A
CREB	cAMP response element-binding protein
pCREB	phospho-CREB
PSD	postsynaptic density
mGluR	metabotropic glutamate receptor
iGluR	ionotropic glutamate receptor

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