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Review

Deciphering the Enigma of Neuron-Glial Interactions in Neurological Disorders

S Rehan Ahmad[1,*], Md. Zeyaullah[2,*], Abdullah M. AlShahrani[2], Adam Dawria[3], Haroon Ali[3], Ali Mohieldin[3], Abdelrhman AG Altijani[3], Ufaq Razi[4], Munzila Mehdi[5], Sabika Akram[5], Ejaz Rizvi Hussain[5]

[1]Hiralal Mazumdar Memorial College for Women, West Bengal State University, 700035 Kolkata, West Bengal, India
[2]Department of Basic Medical Science, College of Applied Medical Sciences, Khamis Mushait Campus, King Khalid University (KKU), 62561 Abha, Saudi Arabia
[3]Department of Public Health, College of Applied Medical Sciences, Khamis Mushait Campus, King Khalid University (KKU), 62561 Abha, Saudi Arabia
[4]Department of Biosciences, Jamia Millia Islamia, 110025 New Delhi, India
[5]Department of Botany, Aligarh Muslim University, 202001 Aligarh, India
*Correspondence: professor.rehaan@gmail.com (S Rehan Ahmad); mdhafed@kku.edu.sa (Md. Zeyaullah)
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Abstract

Innate lymphocytes, including microglial cells, astrocytes, and oligodendrocytes, play a crucial role in initiating neuroinflammatory reactions inside the central nervous system (CNS). The prime focus of this paper is on the involvement and interplay of neurons and glial cells in neurological disorders such as Alzheimer's Disease (AD), Autism Spectrum Disorder (ASD), epilepsy, and multiple sclerosis (MS). In this review, we explore the specific contributions of microglia and astrocytes and analyzes multiple pathways implicated in neuroinflammation and disturbances in excitatory and inhibitory processes. Firstly, we elucidate the mechanisms through which toxic protein accumulation in AD results in synaptic dysfunction and deregulation of the immune system and examines the roles of microglia, astrocytes, and hereditary factors in the pathogenesis of the disease. Secondly, we focus on ASD and the involvement of glial cells in the development of the nervous system and the formation of connections between neurons and investigates the genetic connections associated with these processes. Lastly, we also address the participation of glial cells in epilepsy and MS, providing insights into their pivotal functions in both conditions. We also tried to give an overview of seven different pathways like toll-like receptor signalling pathway, MyD88-dependent and independent pathway, etc and its relevance in the context with these neurological disorders. In this review, we also explore the role of activated glial cells in AD, ASD, epilepsy, and MS which lead to neuroinflammation. Even we focus on excitatory and inhibitory imbalance in all four neurological disorders as imbalance affect the proper functioning of neuronal circuits. Finally, this review concludes that there is necessity for additional investigation on glial cells and their involvement in neurological illnesses.

Keywords: microglia; astrocytes; Alzheimer's Disease; autism spectrum disorder; epilepsy; multiple sclerosis; neuroinflammation; excitatory and inhibitory imbalance

1. Introduction

Glial cells consist of microglia, astrocytes, oligodendrocytes and their progenitors NG2-glia which constitute between 33 and 66% of the total mass brain [1]. Glial cells play role in the release of gliotransmitters and cytokines, as well as the induction of synaptic modifications and even play a crucial role in initiating neuroinflammatory reactions [2]. Astrocytes play a crucial role in maintaining physiological equilibrium and regulating synaptic transmission, while microglia primarily serve an immunological function [2]. The primary cause of the inflammatory response in the central nervous system (CNS) is mostly attributed to factors such as infection, toxins, trauma, and ischemia. These factors trigger the activation of microglia and astrocytes, leading to an upregulation in the production of pro-inflammatory cytokines, chemokines, secondary messengers, and reactive oxygen species (ROS) [1–3]. On the other hand, the chronic inflammatory response has negative effects on neurodegenerative diseases and is associated with functional deficits resulting from oxidative stress, the accumulation of misfolded proteins, and inflammation in peripheral tissues [4]. Glia has the potential to either facilitate or impede the central nervous system's capacity for recovery following inflammation. A1 and A2 astrocyte phenotypes, as well as M1 and M2 microglia states are simplifications of a more complex reality. However, these classifications are not unique and there may be more phenotypes to study [5]. The reactive astrocyte exhibits two distinct phenotypes, namely the detrimental "A1" and the beneficial "A2", which are triggered by inflammatory

processes and ischemic conditions. The A1 phenotype is elicited by the NF-κB pathway and by activated microglia via the secretion of IL-1α, TNF, and C1q. Simultaneously, reactive astrocytes caused by ischemia contribute to CNS recovery and repair through the activation of the transcription 3 (STAT3) pathway [5,6]. The induction of A1-activated astrocytes results in a reduction in synapse formation by downregulating the expression of genes involved in the creation of excitatory synapses, specifically glypicans (GPC4 and GPC6). A1 is characterized by a deficiency in phagocytic activity, which can be attributed to a decrease in the messenger RNA (mRNA) levels of the phagocytic receptors Mertk and Megf10 [7]. Additionally, it has been observed that the A1 phenotype exhibits toxicity towards cortical neurons, spinal motor neurons, and differentiated oligodendrocytes. Furthermore, in the context of neurodegenerative eye illness, the presence of A1 astrocytes has been found to result in the death of retinal ganglion cells following axotomy, primarily due to the production of toxic signals. A1 astrocytes have been observed in various neurodegenerative disorders, such as Alzheimer's Disease (AD) and Multiple Sclerosis (MS), resulting in the demise of neuronal and oligodendrocyte cells [6]. Escartin *et al.* [8], 2021 introduced the updated concept of A1 and A2 astrocytes in which reactive astrocytes can be classified into binary divisions based on their characteristics, such as being either good or harmful, neurotoxic or neuroprotective, or falling into the A1 or A2 category. Reactive astrocytes are evaluated by examining various molecular and functional characteristics, preferably in living organisms, using statistical analysis that considers numerous variables [8]. Reactive astrocytes contribute to the development of pathogenic features in relevant models. Reactive astrocyte-derived biomarkers, along with medicines that specifically target astrocytes, can counteract the harmful effects of reactive astrocytes and enhance their protective actions on neurons and glial cells. These interventions can also help restore or enhance the astrocytes' normal tasks related to maintaining balance, regulating activity, and providing defence [8]. Likewise, microglia display two phenotypes that resemble macrophages: the pro-inflammatory phenotype known as "M1" and the anti-inflammatory phenotype referred to as "M2". Despite the emergence of conflicting evidence, the M1-M2 dichotomy continues to be largely acknowledged as a model for characterizing the beneficial or detrimental impacts of microglia [9,10]. Based on the recent study conducted by Kim *et al.* [11], 2021 microglia and astrocytes could be polarized to M2 microglia and A2 astrocytes. It is noteworthy that microglia exhibit a wide range of morphological variations that can be related to the specific characteristics of brain diseases, such as their location, stage, quantity, and severity [12]. For instance, significant alterations in the morphology of microglia have been observed in brains classified as Braak stage V-VI, which exhibit extensive involvement of the neocortex, as compared to previous stages. The observed alterations in microglia phenotypes lead to the impairment of microglial disease progression and the compromised functionality of immunosurveillance [13]. Microglia can detect and identify foreign entities and pathogens by means of pattern recognition receptors (PRRs) located on their plasma membrane. This encompasses toll-like receptors (TLR), triggering receptor expressed on myeloid cells (TREM), nucleotide-binding oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene I-like receptors (RLRs), among other receptor types [14]. Several inflammatory mediators, such as IL-1, IL-6, TNF, ROS, and potent proteins like PTX3, are generated because of the interaction between protein-ligand [15]. Extracellular vesicles (EVs) are secreted by microglia and astrocytes, exerting a significant impact on several physiological processes such as neuro-glial communication, myelination maintenance, and synaptic plasticity [16,17]. However, in the presence of inflammatory stimuli, active microglia and astrocytes can release EVs that contain pro-inflammatory cytokines. EVs have been found to contribute to the development of neuroinflammation, which is a characteristic feature of various neurological disorders and neurodegenerative conditions. In addition, recent studies have demonstrated that EVs possess an abundance of micro-RNA (miRNA) cargos, which are non-coding RNA molecules that regulate gene expression in the target cell [17,18]. The delivery of EVs to neurons occurs by a transitory fusion process, whereby the EVs release their contents directly into the neuron. This process leads to the induction of translational inhibition of mRNA through complementary base-pairing, as previously documented [19]. Certain microRNAs (miRNAs) play a role in the pathogenesis of various neurological diseases, such as AD, MS, epilepsy, and Autism Spectrum Disorder (ASD). An example of this is the presence of a pro-inflammatory microRNA, specifically miR-146a-5p, which has been reported in MS to inhibit the translation process of presynaptic synaptotagmin1 (Syt1) and post-synaptic neuroligin1 (Nlg1). The study conducted by Lukiw *et al.* [20], 2018 demonstrates that the decrease in levels of *Syt1* and *Nig1* proteins leads to a notable decline in both dendritic spine density and excitatory synapses inside hippocampus neurons, both *in vivo* and *in vitro*. Furthermore, the M1 phenotype, which is stimulated by lipopolysaccharide (LPS), induces the release of EVs containing miR-155. This miRNA promotes the expression of inflammatory genes such as *NOS2*, *TNF-*α, and *IL-1*β, thereby contributing to pro-inflammatory signaling [21]. Finally, we added the list of miRNAs related to different disorders in form of table which is depicted in Table 1 (Ref. [22–39]). In addition, glial cells, particularly activated astrocytes and microglia, play a crucial role in the development of neuroinflammatory and neurodegenerative diseases through the activation of various inflammatory mediators and pathways. The focus of this review is primarily on four neurological disorders, namely AD, MS, epilepsy,

Table 1. miRNAs in different neurological disorders.

Name of miRNA	Name of disorder	Target and role	References
miR-16	Alzheimer's Disease	Target APP and reduce Aβ	[22]
miR-128	Alzheimer's Disease	Target BAG2 and reduce tau	[23]
miR-9	Alzheimer's Disease	Target SIRT1and reduce tau	[24]
miR-7	Alzheimer's Disease	Target NLRP3 and reduce neuroinflammation	[25]
miR-34a	Alzheimer's Disease	Target tau and reduce tau	[26]
miR-125b	Autism Spectrum Disorder	Regulates the expression of FMR1 and contributes to the alteration of synaptic plasticity as in FXS	[27]
miR-132	Autism Spectrum Disorder	Involved in synaptic plasticity	[28]
miR-137	Autism Spectrum Disorder	miRNA-137 is downregulated, it influences the expression of many genes implicated in neurodevelopment	[29]
miR-134	Autism Spectrum Disorder	Regulates synaptic plasticity	[30]
miR-181c	Autism Spectrum Disorder	miRNA-181c is upregulated in the amygdala of ASD patients; its function is associated with the development of the nervous system	[31]
miR-146a	Epilepsy	Target IL-1β, upregulated and target inflammation pathways	[32]
miR-155	Epilepsy	Target TNF-α, upregulated and target inflammation and blood brain barrier pathways	[33]
miR-98	Epilepsy	Target CCL2, CCL5, downregulated and target inflammation and blood brain barrier pathways	[34]
miR-218	Epilepsy	Target GRM1, SLC1A2, ROBO1, GNAI2, downregulated and target synaptic plasticity	[35]
miR-21	Epilepsy	Target NT-3, upregulated and neutrite growth pathways	[36]
miR-155	Multiple Sclerosis	Upregulated and promotes microglial inflammation	[37]
miR-145	Multiple Sclerosis	Downregulated and promotes microglial inflammation	[38]
miR-125b	Multiple Sclerosis	Upregulated and promotes microglial inflammation	[38]
miR-222	Multiple Sclerosis	Upregulated and promotes microglial inflammation	[39]
miR-32	Multiple Sclerosis	Upregulated and promotes microglial inflammation	[37]

miRNA, micro-RNA; APP, Amyloid Precursor Protein; Aβ, amyloid-beta; BAG2, Bcl-2-associated athanogene; SIRT1, Sirtuin 1; NLRP3, nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain containing 3; FMR1, Fragile X Mental Retardaton 1; FXS, Fragile X Syndrome; ASD, Autism spectrum disorder; IL-1β, Interleukin-1β; TNF-α, Tumour Necrosis Factor – alpha; CCL2, Chemokine (C-C motif) ligand 2; GRM1, Metabotropic Glutamate Receptor 1; SLC1A2, Solute Carrier Family 1 Member 2; ROBO1, Roundabout Guidance Receptor 1; GNAI2, G Protein Subunit Alpha I2; NT-3, Neurotrophin-3.

and ASD. In this review, we focus on the role of neuron glial interaction in four different disorders and then explore different pathways associated with these disorders followed by role of glial cells in neuroinflammation in all four disorders and at last we highlight the presence of an excitatory/inhibitory (E/I) imbalance in all four different disorders.

2. Understanding the Action of Astrocytes

The terms 'astrocytosis', 'astrogliosis', 'reactive gliosis', 'astrocyte activation', 'astrocyte reactivity', 'astrocyte re-activation', and 'astrocyte reaction' have all been employed to characterize the responses of astrocytes to abnormal occurrences in the CNS, such as neurodegenerative and demyelinating diseases, epilepsy, trauma, ischemia, infection, and cancer [40]. Astrocyte reactivity can occur in several pathogenic situations, which can differ significantly. These contexts can be either spontaneous or genetically determined, acute or chronic, resulting from a systemic illness (such as sepsis), a specific injury or disease of the CNS, or a harmful experimental manipulation [40]. Astrocyte reactivity, as defined, is a response that occurs in response to an external signal. This response can change over time and, in many cases, can be reversed [41]. Astrocytes can also experience cell-autonomous disruptions, which occur in astrocytopathies caused by mutated versions of astrocytic genes (such as *GFAP* in Alexander disease), as well as from direct viral infections or exposure to toxic substances that precisely harm astrocytes (such as ammonium in hepatic encephalopathy) [41]. Reactive astrocytes experience structural, molecular, and functional alterations in reaction to abnormal conditions in the nearby tissue, such as central nervous system diseases, injuries, or harmful experimental interventions [41]. Astrocytes carrying genetic alterations that cause disease are astrocytes that originate or contribute to pathology. These astrocytes later become reactive in a manner that may differ from the typical response of astrocytes to external stimuli. Genetic variations associated with CNS disorders can also impact the functioning of astrocytes and prepare them to adopt specific reactive

states [42]. There is no typical reactive astrocyte; reactive astrocytes do not divide into essential opposing characteristics, such as beneficial-harmful, toxic-protective, A1–A2, etc. Reactive astrocytes can assume several states depending on the situation, with just a tiny portion of shared alterations across distinct states [43]. Simultaneous loss of certain homeostatic functions and acquisition of certain protective or harmful functions is possible. The ultimate effect on disease, whether advantageous or harmful, will depend on the equilibrium and characteristics of impaired and acquired functions and the varying prevalence of distinct astrocyte subgroups [43]. Astrocytes affected by the disease are the primary initiators and may subsequently develop a reactive phenotype that influences the progression of the disease. Genetic mutations in genes expressed in all cells of the body, such as those seen in familial neurodegenerative disorders, or variations in genes highly expressed in astrocytes (such as *APOE* in AD), can result in dysfunctional astrocytes [44]. While astrocytes may not be the leading cause of the disease, their dysfunction can negatively affect the progression and outcome of the condition [41].

3. Different Glial Inflammatory Pathways

Glial cells, namely astrocytes and microglia, play a crucial role in the pathogenesis of neuroinflammatory and neurodegenerative disorders by means of several inflammatory mediators and pathways. In this review we have discussed seven different pathways.

3.1 Toll-Like Receptor Signaling Pathway

The immune system can be classified into two main components, namely the cellular and humoral systems. In general, the cellular immune system is composed of macrophages, neutrophils, natural killer cells, and dendritic cells [45]. On the other hand, within the CNS, the primary components of the cellular immune system consist of glia and macrophages [46]. Glia cells have been proposed to fulfill many functions inside the CNS, including serving as a cellular repair mechanism, facilitating the removal of deceased cells, and contributing to neuroinflammatory processes [47]. Microglia and astrocytes are essential components in the preservation of neuronal integrity. Microglial cells contribute to the neuroinflammatory response in the CNS by releasing chemokines and cytokines with pro-inflammatory properties, including IL-1β, IL-6, and TNF-α. Additionally, they have a role in modulating the response of T-lymphocytes to pathogens [48–52]. It has been proposed that the biological function of astrocytes may have an impact on the blood-brain barrier, perhaps leading to an increase in T-cell permeability [53]. Glia cells have been observed to be prevalent in several neurological conditions, including neurodegenerative illnesses and cerebral ischemia [54]. TLRs interact as pattern recognition receptors with exogenous ligands and endogenous molecules or danger associated molecular patterns (DAMPs) that are released upon tissue injury and cellular stress [55]. In humans, the total number of *TLRs* is 11, and these receptors can be categorized according to their capacity to identify specific infections. For instance, it has been observed that TLR1 and TLR2 exhibit recognition capabilities for distinct lipopeptides, TLR3 demonstrates recognition of viral RNA, and TLR4 is responsible for recognizing bacterial lipopolysaccharides. It is worth noting that TLR activation can also occur through endogenous chemicals released by damaged cells [56]. Upon activation of TLRs on microglia and astrocytes, it triggers the production of pro-inflammatory mediators, which in turn promotes the synthesis of inflammatory cytokines through the activation of various signaling pathways. These pathways include NF-kB, mitogen-activated protein kinase (MAPK), p38 extracellular signal-regulated kinase (ERK), and interferon regulatory factor 3 (IRF3) [57]. The stimulation of brain inflammatory markers is ultimately achieved through the involvement of many signaling pathways [58]. The activation of TLRs has been proposed to trigger a specific signaling pathway that is contingent upon the cell type, the unique environment, or the cellular adaptors involved. Hence, it has been proposed that the activation of TLRs could exhibit either neuroprotective or pathogenic effects, contingent upon the specific circumstance being considered. In the context of ischemia illnesses affecting the CNS, such as acute ischemic stroke [59], intracerebral hemorrhage [60], cerebral palsy [61], and epilepsy [61], the activation of TLRs has been observed to initiate an inflammatory cascade that may exacerbate the ischemic injury [60,61]. However, it has been emphasized that the TLR plays a significant role in the regulation of glial cells phagocytic function. Studies have shown that TLRs work as receptors that facilitate communication with endogenous dying neuronal ligands, hence priming glial cells for their role in neuronal death [60]. It has been proposed that dysfunctions in the functional TLR signaling pathway may contribute to the development of neurodegeneration, as evidenced by the presence of brain lesions [61].

3.2 MyD88-Dependent Pathway

MYD88 refers to Myeloid Differentiation Primary Response 88, commonly known as *MyD*. This protein is associated with myeloid differentiation. Simultaneously, the numerical value “88” denotes the position of the activated gene within a list of five adaptors that interact with downstream signaling proteins associated with IL-1 and TLRs [62,63]. Type I transmembrane receptors known as TLRs possess external leucine-rich repeats, a transmembrane helix, and an internal Toll/IL-1 receptor domain (TIR) [63]. TLRs are a subset of pattern recognition receptors (PRRs) that are typically triggered by pathogen-associated molecular pattern molecules (PAMPs) and damage-associated molecular pattern molecules (DAMPs). Each TLR can identify certain components of pathogens. For instance,

TLR4 can recognize the LPS found in the outer membrane of bacteria, whereas TLR5 can identify flagellin, a protein present in bacterial flagella [64,65]. Hence, TLRs play a crucial role in the activation of innate immunity, leading to the initiation of inflammatory reactions and the development of antigen-specific adaptive immunity [66]. In general, TLR signaling pathways can be categorized into two main groups: MyD88-dependent pathways and MyD88-independent pathways, which are distinguished by the recruitment of certain adaptors. In relation to the MyD88-dependent pathway, it is noteworthy that all Toll-like receptors (except for TLR3) rely on MYD88 for the activation of downstream signaling. This process, known as "Myddosome", is responsible for activating *NF-κB* and *AP-1* [67]. MyD88 consists of three primary domains: a death domain (DD), an intermediary domain (*INT*), and a Toll/interleukin-1 receptor (TIR) domain. The N-terminal DD is responsible for binding to IRAK4 (IL-1R-associated kinase), while the C-terminal TIR domain binds to the receptor's TIR domain. It has been observed that the absence of the INT domain is correlated with the inability of MyD88 to facilitate signaling [68,69]. In addition, *TIRAP* (Toll/IL-1 receptor domain-containing adapter protein), alternatively referred to as *Mal* (MyD88 adapter-like), serves as an intermediary for certain Toll-like receptors (TLRs) in the recruitment of MyD88 [70,71]. The contact between a ligand and its corresponding receptor leads to the formation of receptor dimers. These dimers then bind MYD88, resulting in the activation of *IRAK1* or *IRAK2* through *the kinase IRAK4*, which has a death domain [72]. After undergoing auto-phosphorylation, *IRAK1/IRAK2* dissociates from the receptor complex and interacts with E3 ubiquitin ligase TRAF6 (TNF receptor-associated factor 6), leading to the process of ubiquitination and subsequent activation of *TAK1* (transforming growth factor-β-activated kinase 1) [73]. The activation of TAK1 leads to its binding with the IKK complex, resulting in the activation of the complex through ubiquitination via phosphorylation of the *IKKβ* subunit [74]. The IKK complex, which consists of two catalytic subunits, namely *IKKα* (*IKK1*) and *IKKβ* (*IKK2*), together with a regulatory subunit known as IKKγ or *NEMO* (NF-κB essential modulator), is involved in various cellular processes. The activation of IKK leads to the phosphorylation of IκBα, which serves as an inhibitor of nuclear factor-kappa Bα. This phosphorylation event occurs when *NF-κB* is in an inactive state and confined inside the cytoplasm [75]. The process of phosphorylation of IκBα leads to its destruction by the proteasome, resulting in the subsequent translocation of NF-κB into the nucleus [76]. The NF-κB protein then interacts with DNA, leading to the activation of specific genes and, as a result, initiating the process of transcription [76]. Intracellular TLRs, namely *TLR7*, facilitate the activation of Interferon regulatory factor 7 (*IRF7*) through the recruitment of *TRAF3* and *IKKα*, in addition to NF-κB activation, by the protein MyD88. The transcription factor known as IRF7 is responsible for the production of type-1 Interferon [77]. Simultaneously, TAK1 initiates the activation of members belonging to the *MAP3K* family, namely *p38*, *ERK*, and *JNK*, which in turn activate AP-1 [78]. Therefore, it can be inferred that TAK1 is responsible for the activation of both the NF-κB and MAP3K signaling pathways [79]. The MyD88-dependent pathway is responsible for the initiation of pro-inflammatory cytokine production, highlighting the crucial role of MyD88 in immune signaling. Previous pre-clinical investigations have documented that MyD88-knock out mice exhibit resistance to fatal septic shock caused by LPS. Furthermore, MyD88-deficient macrophages were seen to lack the ability to generate pro-inflammatory cytokines upon LPS stimulation, despite the activation of MAPK and NF-κB signaling pathways [80]. Additionally, comparable outcomes were observed in mice that lacked *TIRAP* and *IRAK4*, as reported in previous studies [81,82]. These results were repeated with anti-inflammatory medications that target the MyD88-dependent pathway. Hence, MyD88 has been identified as a promising therapeutic target due to its ability to mitigate inflammatory reactions mediated by MyD88. Recent studies have demonstrated that MyD88 exhibits beneficial effects in various pathological conditions, such as cancers, Ischemia-Reperfusion Injury, inflammatory diseases, blood-brain barrier dysfunction, and inflammatory lung diseases, including chronic obstructive pulmonary disease (COPD). Additionally, it has been identified as a potential antiviral therapy by activating IRF3/IRF7 and facilitating the type-I-IFN response [83–90].

3.3 MyD88-Independent Pathway

The TIR-domain-containing adapter-inducing interferon-β (TRIF), also known as TICAM1, is an additional adaptor protein associated with TLRs that facilitates the MyD88-independent signaling pathway [91]. The synthesis of interferon-related genes is mediated by TRIF-dependent signaling. The *TRIF-related adaptor molecule* (TRAM), also known as *TICAM2*, functions as an intermediary adapter to facilitate the recruitment of *TIRF* to *TLR4*. In contrast, TIRF is attracted to TLR3 in a direct manner, without the use of an adaptor protein [92]. Following the binding of a ligand, the ubiquitin ligase TRAF3 is recruited. Consequently, the activation of *TBK1* and *IKKi kinases* is triggered, resulting in the phosphorylation of IRF3. This event facilitates the translocation of *IRF3* to the nucleus, ultimately leading to the expression of *type-I-IFN* genes. In addition, it should be noted that TRIF plays a crucial role in the recruitment of *TRAF6*, hence triggering a subsequent activation of NF-κB and MAPK signaling pathways during the late phase. This activation is facilitated by the *kinase protein RIP1*, also known as receptor-interacting protein [93]. The sterile α and armadillo-motif-containing protein (*SARM*) has been recognized as an additional adaptor protein involved in

the signaling of *TLRs*. *SARM* functions as an inhibitor of TRIF-mediated signaling specifically for *TLR3* and *TLR4* [94].

3.4 IL-6-Grp130/JAK-STAT Signaling Pathway

Interleukin-6 (*IL-6*) is a cytokine that has pleiotropic effects and has gained significant recognition for its pivotal involvement in maintaining the pathophysiological equilibrium of the central nervous system and regulating glial function [95]. In the brain, under typical physiological circumstances, there exists a diminished concentration of *IL-6* [95]. Nevertheless, the protein expression and release of this particular entity exhibited a favorable correlation with several neurological illnesses, including brain cancer, AD, PD, MS, and brain ischemia [96]. The pleiotropic biological effects of *IL-6* on target cells are facilitated by its contact with the non-signaling membrane-bound receptor, *IL6R* [97]. In comparison to the receptor for Lipocalin-2 (*LCN2*), the expression of the receptor specific to *IL6R* was observed to be relatively restricted inside nervous tissue. Specifically, IL6R was mostly detected in microglia, while its presence was not observed in oligodendrocytes or astrocytes [98]. The IL6R is also present in a soluble form, which is produced through either alternate splicing of its mRNA or proteolytic cleavage from the cell membrane [99]. At the molecular level, it can be observed that IL6R does not possess the inherent ability to transmit signals downstream. Therefore, it elicits its chemical cascades via two distinct signaling channels, namely the canonical signaling pathway and the trans-signaling pathway. In the conventional signaling pathway, the cytokine IL6 engages in interaction with a particular glycoprotein receptor called IL-6 receptor-α (*IL-6R*, *CD126*), resulting in the formation of a high-affinity complex between *IL-6* and *IL-6R* [98]. The complex then interacts with a transmembrane signal-transducing glycoprotein known as gp130, facilitating its dimerization and subsequent activation of intracellular signaling pathways. These pathways include JAK/STAT, ERK, and PI3K, which ultimately result in the expression of genes dependent on IL-6 and various cellular responses such as proliferation, migration, and metabolic alterations [99]. The trans-signaling route involves the interaction between the soluble *IL6 receptor* (*sIL6-R*) and *IL-6*, leading to the activation of distant cells expressing gb130. These cells are commonly found in neuronal cells, endothelial cells, and oligodendrocytes [100].

3.5 Chemokine Signaling Pathway

Chemokines are a group of extracellular pro-inflammatory proteins that function as chemotactic agents, stimulating cellular communication within the immune response. Additionally, they have a role in the establishment of neuronal networks, synapse development, and the regulation of cognitive function [101]. The classification of chemokine subfamilies can be determined by analyzing the structural motifs of the N-terminal cysteine residues. These subfamilies are categorized as *CC*-, *CXC*-, *XC*-, and *CX3C* [102]. Multiple chemokines can bind to either one receptor or multiple receptors. These receptors can be categorized based on their ligands into chemokine receptors *CCR* (*1-10*), *CXCR* (*1-7*), *XCR1*, and *CX3CR1* [103]. Therefore, chemokines have the potential to serve as chemotactic mediators in various biological processes [104]. The CNS possesses a distinct anatomical arrangement, which is delineated from other bodily organs by the presence of colony- stimulating factor (CSF). The CNS has cellular compartments, including T cells, which exhibit a deficiency in humoral immunity to uphold an immunosuppressive milieu. During instances of neuronal damage, glial cells become activated and initiate inflammation in the CNS by releasing chemokines. These chemokines serve to attract T-lymphocytes, which infiltrate the affected area. Additionally, glial cells facilitate communication between neurons to maintain proper brain function. However, it is worth noting that the levels of these chemokines have been found to be linked to the development of many CNS diseases [105]. The activation mechanism of glia cells involves the activation of various signaling pathways through trans-membrane G protein-coupled receptors. These pathways include the activation of mitogen-activated protein kinases (*MAPKs*) and phospholipase C, which leads to the release of intracellular Ca ions. This release of Ca ions plays a role in modulating gene regulation, among other pathways [106–108]. Chemokines are observed within the CNS in the form of pro-inflammatory cells, serving a protective function against neuronal injury. Nevertheless, it has been documented that chemokines also contribute to the development of many neurological illnesses [109]. *CX3CL1*, a chemokine of considerable interest in scientific research, has a distinctive characteristic by selectively binding to a singular receptor, *CX3CR1*. The central CNS concentrations of this chemokine are subject to conflicting interpretations and opinions among the academic community. The CX3CL1-CX3CR1 signaling pathway has the potential to stimulate microglia, leading to the release of inflammatory substances and exacerbating the pathological condition in various neurological illnesses, including mesial temporal lobe epilepsy (MTLE), AD, PD, and amyotrophic lateral sclerosis (ALS). During the occurrence of MTLE, which is distinguished by an intense inflammatory reaction, the activation of microglia was found to be linked to the recurrent initiation of seizures, heightened neurogenesis, and synaptic remodeling [110,111]. Elevated concentrations of CX3CL1 were observed in both blood and CSF of individuals diagnosed with mesial temporal lobe epilepsy (MTLE). Experimental studies have indicated that the absence of the CX3CR1 receptor leads to a decline in microglial activation and a decrease in the quantity of degenerated neurons [111]. The CX3CL1-CX3CR1 signalling route has been implicated

in the pathogenesis of neurodegenerative illnesses. It has been observed that dysfunction of this signalling system tends to augment the activation of microglia. The chemokine signalling system has been proposed to undergo modifications in AD, resulting in an elevated population of activated microglia and the subsequent production of inflammatory markers, including IL6. Thus, it was discovered that modifying the signalling route will lead to an increasing amount of amyloid-β, which creates neurotoxicity that impacts cognitive dysfunction that is known as AD [112,113]. In contrast, a number of studies have examined the CX3CL1-CX3CR1 signaling pathway in the context of cerebral ischemia. These studies have indicated that elevated levels of *CX3CL1* have the potential to inhibit the activation of microglia cells. Consequently, this inhibition may result in neuroprotective effects by reducing the expression of inflammatory markers, including *IB-1* and *TNF-*α [114–116]. In addition, the disruption of the signaling pathway through the deletion of *CX3CR1* resulted in an elevated production of IL-1β and exacerbated cerebral ischemia. The CX3CL1-CX3CR1 signaling pathway exhibits a dualistic nature, capable of exerting either neurotoxic or neuroprotective effects. The influence of pathological conditions inside the CNS on *CX3CL1* levels and its receptor is contingent upon the specific type of illness.

3.6 Lipocalin2-LCN2R Signaling Pathway

Lipocalin-2 (*LCN2*) is classified as a low molecular weight acute phase protein that is a member of the lipocalin superfamily. This superfamily encompasses a total of 20 soluble proteins [117]. The substance referred to as neutrophil gelatinase-associated lipocalin (*NGAL*) or *24p3* is primarily synthesized and released by astrocytes, serving as a robust indicator of reactive astrocytes. Like other proteins implicated in inflammation, *LCN2* is upregulated in reaction to diverse inflammatory and harmful stimuli, including as infection and damage [118]. Furthermore, the release of *LCN2* by glial cells in response to various inflammatory stimuli enhances and controls neuroinflammation by activating the transcriptional processes of inflammatory chemokines and subsequently attracting immune cells [119]. Nevertheless, the function of *LCN2* is facilitated by its interaction with hydrophobic ligands known as *LCN2R,* which enables the regulation of several cellular processes either by autocrine or paracrine mechanisms. The cellular processes may include cellular proliferation, differentiation, migration, and survival. Furthermore, the expression profile of *LCNR2* exhibits significant upregulation in several neurological tissues, including neurons, microglia, and astrocytes. Thus, *LCN2* is acknowledged to be elevated in numerous clinical disorders linked with the central nervous system, such as brain injury [52,120,121]. At the molecular level, it has been observed that the activation of *LCN2* elicits the initiation of many inflammatory signaling pathways, the majority of which are facilitated by *NF-Kb*, *MAPK*, *STATs*, *C/EBP*, and *HIF-1* [122]. Furthermore, the engagement between *Lcn2 and LCN2R* leads to the enhancement of the molecular signaling pathways involving *JAK-STAT3* and *IKK/NF-kB*. This, in turn, triggers the transcriptional activities of various genes associated with the maintenance of glial cell integrity, including *CXCL10*, *GFAP* (glial fibrillary acidic protein, a constituent of the cytoskeleton), and *ITGB3* (integrin beta chain beta 3).

3.7 IL-6-Grp130/JAK-STAT Signaling Pathway

IL-6 is a cytokine with pleiotropic effects that has gained significant recognition for its pivotal involvement in the pathophysiological regulation of the central nervous system and glial function [123]. In the brain, there exists a basal level of IL-6 under typical physiological circumstances [124]. Nevertheless, previous studies have established a favorable association between the production and release of this protein and several neurological illnesses, including brain cancer, AD, PD, MS, and brain ischemia [94]. The pleiotropic biological effects of IL-6 on target cells are facilitated by its contact with the non-signaling membrane-bound receptor, *IL6R* [95]. In comparison to the receptor for LCN2, the expression of the receptor specific to *IL-6* (*IL6R*) was observed to be relatively restricted inside nervous tissue. Specifically, IL6R was predominantly detected in microglia, whereas its presence was not identified in oligodendrocytes or astrocytes [96]. The IL6R can also be detected in a soluble state, which is produced through two mechanisms: alternate splicing of its mRNA or proteolytic cleavage from the cell membrane [97]. At the molecular level, it can be observed that IL6R exhibits a deficiency in its ability to generate intrinsic downstream signals. Therefore, it initiates its molecular cascades by either the traditional or trans-signaling pathways. In the conventional signaling pathway, the cytokine IL6 engages in interaction with a particular glycoprotein receptor called IL-6 receptor-α (*IL-6R*, *CD126*), resulting in the formation of a high-affinity complex between IL-6 and IL-6R [98]. The complex interacts with a transmembrane signal-transducing glycoprotein known as gp130, which facilitates its dimerization and subsequently activates intracellular signaling pathways, including JAK/STAT, ERK, and PI3K. This activation leads to the expression of genes dependent on IL-6 and various cellular responses such as proliferation, migration, and metabolic changes [99]. In the trans-signaling pathway, the soluble IL6 receptor (sIL6-R), which is not bound to the cell surface, can form a complex with IL-6 and stimulate distant cells expressing gb130. These cells are often found in neuronal cells, endothelial cells, and oligodendrocytes [100].

4. The Role of Glial Cells in Neuroinflammation

Neuroinflammation, an often-observed symptom in inflammatory and degenerative disorders, serves as a distinguishing feature of both acute and chronic neurological conditions. The aforementioned problem primarily arises from chronically activated glial cells inside the cerebral region. Pro-inflammatory cytokines are a subset of neuroexcitatory substances that are generated by activated glial cells and have the ability to promote the release of neurotransmitters. One potential use involves the utilization of this method to inhibit glial activity as a means of effectively managing neuropathic pain.

4.1 Neuroinflammation in Alzheimer's Disease

Dementia is the term used to describe the decline in cognitive functioning that impairs an individual's ability to carry out typical daily activities [125]. Neurological illnesses such as brain vascular diseases, brain damage, and dementia with Lewy's bodies have been identified as contributing factors to its development [126]. Around 60% to 70% of dementia instances were detected in patients diagnosed with AD [125]. AD is a neurodegenerative disorder characterized by progressive cognitive decline and is recognized as the primary contributor to memory impairment [125]. In certain instances, the use of AD medication has been associated with the development of psychological problems, including schizophrenia. The etiology of AD remains elusive; nevertheless, a prominent clinical characteristic is the development of senile plaques inside the cerebral tissue [126]. The aforementioned plagues played a role in the initiation of neuroinflammation within the brain tissue [126]. The presence of neuroinflammation in AD was initially observed during the early 20th century through postmortem brain examinations conducted by Alois Alzheimer, a neuropathologist from Germany. Subsequently, there has been a comprehensive investigation into the neuroinflammation process in patients and models of AD [127]. This section aims to elucidate the involvement of inflammatory mediators in the interaction between neurons and glial cells in AD. In the context of axonal sprouting, synaptogenesis, and nervous tissue regeneration, it is crucial to acknowledge the significant role played by chemokines, which are inflammatory mediators produced by supporting cells and glial cells within the nervous system [128]. During instances of brain tissue injury, the pro-inflammatory neurotoxic cytokines, namely *TNF*-α, initiate a response in astrocytes and microglial cells subsequent to the neural cells being harmed by nitric oxide free radicals [129,130]. From a physiological standpoint, it has been seen that microglial cells and other cells within neural tissue have the ability to secrete chemokines. These chemokines are tiny proteins that possess chemoattractant properties and bind to heparin. This information has been documented in a study [131–133]. The chemokines in question exhibit the ability to bind to their respective receptors, thereby promoting cellular migration towards the site of inflammation through interactions with cell membrane proteins, namely integrin and laminin, via their extracellular matrix ligands [133,134]. Under typical circumstances, microglial cells and astrocytes possess the ability to eliminate the pathogenic stimuli and facilitate tissue regeneration. Nevertheless, it has been observed that the cytokines released by glial cells in AD are unable to eliminate the harmful Aβ amyloid plaques [135–137]. The procedure, which did not achieve its intended outcome, elicits a response from microglial cells and astrocytes, resulting in an increased release of cytokines. This, in turn, leads to damage in brain tissue, subsequently subjecting the brain tissue to repeated episodes of inflammation. Furthermore, microglial cells play a crucial role in the maintenance of the neural network and synapse function through the release of brain-derived neurotrophic factor (BDNF) [138,139]. Therefore, it is proposed that the malfunction of microglial cells is responsible for axonal degradation and the inability of axonal regeneration in AD [140–142]. Microglial cells directly affect the brain tissue in AD, whilst astrocytes effect the blood-brain barrier (BBB). Astrocytes, which constitute the predominant neuronal population in the brain, play a crucial role in regulating the permeability of the BBB [143–145]. During instances of brain damage, astrocytes exhibit an augmented permeability of the BBB, facilitating the entry of pro-inflammatory mediators that launch the inflammatory process. Nevertheless, in the case of AD, the BBB permeability becomes excessively heightened because of recurrent cycles of inflammation inside the brain tissue [146–150]. As a result, neurotoxins can infiltrate the brain tissue, leading to additional harm to the tissue [151]. It is worth noting that there was a correlation observed between astrogliosis and cognitive impairment [152]. Non-steroidal anti-inflammatory medications (NSAIDs) have been widely employed in AD research as therapeutic interventions due to the prevalent involvement of neuroinflammation as a pathogenic mechanism in both AD patients and models. Regrettably, although demonstrating favorable outcomes in pre-clinical investigations, non-steroidal anti-inflammatory drugs (NSAIDs) did not yield substantial protective effects in clinical trials [153]. Currently, individuals diagnosed with AD are prescribed medication that targets symptoms associated with the disease, such as anti-epileptic and antidepressant drugs, based on the specific issues experienced by the patient.

4.2 Neuroinflammation in Autism Spectrum Disorder

ASD is distinguished by enduring impairments in both verbal and nonverbal communication, as well as repeated behavioral patterns, hobbies, or activities [154,155]. According to recent research, the prevalence of ASD is approximately 1 in 100 children, with a significantly higher occurrence in boys compared to females, with a ratio of 4–5 to 1 [156]. The etiology of ASD is multifaceted and may

involve a combination of genetic and environmental influences [157]. Several environmental factors related to ASD have been found, including the presence of an inflammatory reaction [158]. The interaction between the CNS and the immune system, encompassing both innate and adaptive immunity, occurs continuously throughout an individual's lifespan and developmental stages. This dynamic relationship is commonly referred to as neuroimmunity [159]. The influence of the maternal immune system on fetal brain development is believed to have a significant impact on the occurrence of ASD [160]. There are other variables that contribute to the dysregulation of maternal immunity, including viral and bacterial infections [161]. The correlation between prenatal ASD and maternal infection is contingent upon the specific pathogen involved as well as the timing of the infection. Research has indicated a correlation between the occurrence of bacterial infection during the second trimester of pregnancy and the development of ASD. Conversely, viral infection has been found to relate to the first trimester of pregnancy in relation to ASD [162]. It is noteworthy that the virus does not manifest in the fetal brain, indicating that the materials associated with the maternal immune response hold greater significance compared to the infection itself. One piece of evidence that supports the link between maternal immune response and fetal ASD is the detection of cytokines in the blood of the fetus. The transmission of cytokines from the mother to the fetus can occur via the placental barrier, or alternatively, fetal cytokines may be generated because of maternal cytokine activity [163]. The impact of cytokines on prenatal brain development is shown regardless of whether they originate from the maternal or fetal source [164]. An excessive production of pro-inflammatory cytokines, including tumour necrosis factor-α (*TNF-*α), interleukin-6 (*IL-6*), and *IL-17*, was observed in children diagnosed with ASD as compared to a control group of individuals of the same age [165]. In addition, the Childhood Autism Rating Scale (CARS) was employed to discern the varying degrees of ASD severity by measuring plasma cytokine levels. Elevated levels of *IL-12p40* were shown to be correlated with a less severe manifestation of ASD, whereas increased levels of *TNF-*α were observed in cases of moderate severity [166]. A prior investigation conducted on deceased individuals' brains revealed elevated levels of IL-6 in brain samples obtained from patients diagnosed with ASD [167]. The cytokine mentioned in reference [168] exerts an influence on synapse development, impulse transmission, and the morphology of dendritic spines. Prior research has indicated that a specific immune cell known as CNS microglia, which originates from the monocyte/macrophage lineage, not only participates in inflammatory responses but also contributes to neurological development. This immune cell has been implicated in the development of ASD [169]. It is worth noting that activated microglial cells were observed in the dorsolateral prefrontal cortex and other brain regions of individuals diagnosed with ASD [170]. Additionally, a study conducted postmortem revealed a notable augmentation in both the quantity and functionality of microglial cells within the cerebellum and midfrontal regions of individuals diagnosedss with ASD [171]. Within the cerebral cortex, microglial cells that have been stimulated create nitric oxide (NO), resulting in a reduction and deactivation of natural killer (NK) cells [172]. A prior investigation demonstrated a decrease in NK cell activity among individuals diagnosed with ASD [173]. In the context of autoimmune illnesses, it has been observed that maternal IgG can traverse the placenta, engage with fetal brain proteins, and thus heighten the likelihood of ASD in the developing fetus [174]. The microbiota presents in the gut, also known as normal flora, can activate the immune system in the initial year of an individual's existence, as well as influence the activity of microglial cells [175]. The prevalence of dysbiosis, characterized by an imbalance in the composition of microbiota, was found to be elevated in individuals diagnosed with ASD [176]. Bacteroides and Clostridia are widely recognized as the predominant gut microbiota. The administration of these species as a probiotic to individuals with ASD has been found to promote communication and mitigate repetitive behaviors in this population [177]. To be more precise, the activation of the maternal immune system by antigens has been found to result in fetal brain malformation, which has been associated with the development of ASD.

4.3 Neuroinflammation in Epilepsy

Seizures refer to the occurrence of abnormal neuronal excitation or inhibition inside the brain, resulting in the development of abnormal hypertonic or hypotonic states [178]. The exact cause of seizures remains uncertain; however, several risk factors have been identified as contributors to aberrant brain activity, including but not limited to high-grade fever, head trauma, and metabolic illnesses [179]. Epilepsy is characterized by the occurrence of recurrent unstimulated seizures [180]. There exist various clinical manifestations of this condition, each exhibiting distinct levels of severity and prognosis. Examples include absence epilepsy, generalized tonic-clonic epilepsy, and benign newborn convulsions. The etiology of epilepsy often involves brain tissue injury, with neuroinflammation being a commonly reported pathogenic mechanism in this disorder. The signs of inflammation, brain tissue damage and enhanced glial cell activities have been identified in several brain locations in epilepsy [181]. Previous research has documented a notable increase in microglial activity, with the presence of cytokines being identified in brain tissue as soon as 4 hours after the occurrence of status epilepticus [182]. Elevated levels of inflammatory mediators, such as *IL-1*β, *IL-6*, and *TNF-*α, were observed in the cerebrospinal fluid of patients experiencing febrile seizures [183]. The presence of increased levels of *IL-1*β, *IL-6*, and *TNF-*α in the hippocampal areas of the brain has been observed in

studies conducted on seizures [184–186]. The histological examination of deceased individuals experiencing seizures revealed a notable augmentation in the microglial response, together with their corresponding antigens, in the *CA3 region* (3-fold increase) and *CA1 region* (11-fold increase) of the hippocampus, as compared to the control group [177]. The observations provide empirical evidence that lends support to the hypothesis positing that the permeability of the BBB is enhanced because of inflammatory mechanisms occurring within the brain during epileptic convulsions. The regulation of the blood-brain barrier is primarily governed by astrocytes. Research has demonstrated that the activity of astrocytes and the production of nitric oxide can be enhanced by *IL-1*β. Additionally, it has been observed that prostaglandin disrupts the structure of the blood-brain barrier and leads to an increase in its permeability [176]. As a result, leukocytes can penetrate the hippocampus of the brain and initiate an inflammatory response. The activation of microglia cells is a consequence of neuroinflammation [184]. The aforementioned cells are responsible for regulating neurological activity, with the relationship between neurons and glial cells mostly governed by fractalkine signaling pathways [178]. Prior research has documented dysregulation in synaptic, neurogenesis, and behavioral functions in animals with a deficit in fractalkine [179,181]. The development of synaptic plasticity is facilitated by the production of BDNF by microglia. This process leads to the induction of LTP and the subsequent generation of learning behaviors [187]. Both activated microglia and astrocytes are known to secrete cytokines, including as *IL-1*β, *TNF-*α, and *IL-6* [188]. The presence of *IL-1*β has been found to play a role in the induction of hyper-excitability in individuals with temporal lobe epilepsy. This effect is achieved by the reduction of the inhibitory neurotransmitter, GABA (gamma-aminobutyric acid), inside the brain tissue of affected individuals [182,183]. Furthermore, there is evidence suggesting a connection between it and deficiencies in long-term potentiation, as seizures caused by interleukin have been found to affect the expression of post-synaptic N-methyl-D-aspartate (NMDA) receptors [183,184]. Moreover, it should be noted that tumor necrosis factor-alpha (TNF-α) is also secreted by glial cells in the context of ongoing inflammation. From a physiological standpoint, it has been seen that *TNF-*α has a role in promoting the release of glutamate by microglial cells and also leads to an increase in the expression of AMPA receptors. Conversely, *TNF-*α has been found to induce the internalization of GABA receptors. As a result, the presence of *TNF-*α leads to an augmentation of brain excitatory transmission and a reduction in neural inhibition [185,186,189,190]. Hence, the presence of excessively increased levels of *TNF-*α plays a role in the induction of synaptic over-excitability in the context of seizures. Epilepsy has been found to be associated not only with inflammation of brain tissue, but also with the presence of systemic inflammatory illnesses, which can also trigger the onset of epilepsy. The prevalence of epilepsy in individuals diagnosed with systemic lupus erythematosus (SLE) was found to be nearly three times higher when compared to the control group, as reported in a study [188]. SLE is known to induce brain vasculitis, leading to structural disruption to the BBB and subsequent infiltration of inflammatory mediators into the brain tissue [191]. The prevalence of epilepsy was found to be elevated in several systemic inflammatory disorders, such as rheumatoid arthritis (with a 1.27-fold increase) [192] and type I diabetes mellitus (with a 2.2-fold increase) [193]. The co-occurrence of neuroinflammation and systemic inflammation disorders has been found to be linked to the development of epilepsy.

4.4 Neuroinflammation in Multiple Sclerosis

MS is a complex neurodegenerative and inflammatory disorder that is characterized by recurrent inflammatory episodes leading to demyelination and damage to axons [194]. MS is characterized by three distinct patterns, namely relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). RRMS is distinguished by the occurrence of recurring episodes that are followed by periods of remission. These remission periods have the potential to develop into SPMS. On the other hand, it is plausible that it could manifest as PPMS. The manifestation of MS symptoms is contingent upon the location of demyelination and might manifest as cognitive, motor, or sensory dysfunction [195–199]. The CNS lesions manifest as demyelination plaques located in both the white and grey matter [200]. Historically, MS has been widely acknowledged as a T-cell-mediated immunological disorder [201]. The involvement of B-cells and innate immunity in the pathophysiology of MS has been widely recognized [202]. The detection of B-cells and macrophages in MS lesions has been substantiated [202]. The process of pathogenesis begins with the invasion of CD4+ cells in the white matter, facilitated by the compromised integrity of the BBB. The expansion of CD4+ cells is facilitated by the presence of *IL-1*, *IL-6*, *IL-12*, and *IL-23*, which are produced by dendritic cells, microglia, and macrophages derived from monocytes. These cytokines facilitate the recruitment of extra macrophages produced from monocytes into the CNS, resulting in the rupture of the BBB [203]. The enlarged T-cells can be categorized into two distinct kinds, namely T helper 1 (Th1) and T helper 17 (Th17) cells. The cells are responsible for the secretion of IL-17 and IL-12, which in turn contribute to the amplification of the Th17 cell through a feedback mechanism. Furthermore, Th1 and Th17 produce granulocyte-macrophage colony-stimulating factor (GM-CSF), INF-γ, and TNF-α, which stimulate microglial cells to create *IL-8*. This cytokine serves the purpose of attracting neutrophils to the specific location of inflammation, while also stimulating their synthesis of metalloproteinases and chemokines. The process of demyelination and axonal injury is initiated by

the combined action of *INF-γ*, *IL-17*, chemokines, and metalloproteinases [200]. A previous study has demonstrated that the inhibition or neutralization of *IL-17* and *INF-γ* leads to a reduction in the production of lesions in the CNS of patients with MS [204]. The CD8+ cell plays a prominent role in the pathogenesis of MS lesion formation. In the observed lesions, astrocytes, neurons, and axons exhibited a significant upregulation of MHC class I expression, rendering them susceptible to the lethal impact of CD8+ cells [205]. The CD8+ cell is responsible for the induction of multiple sclerosis MS lesions by the augmentation of granzyme secretion, as well as the synthesis of *INF-γ* and *IL-17* [206,207]. On the contrary, the alternative subset of T-cells known as T regulatory (Treg) cells played a role in inhibiting the establishment of MS lesions. The suppressive effects of Treg cells on autoimmune and their role in tissue regeneration have been demonstrated [208]. The frequency and activity of these cells were found to be inadequate in patients with multiple sclerosis [209]. In addition, the presence of B-cells was seen in the CSF and brain of individuals diagnosed with MS [210]. During the initial phase of the disease, the presence of the lesion was detected, however in the later stages, there was a prevalence of plasma cells [211]. B-cells have a role in the pathogenesis of MS through various mechanisms. These processes include the formation of ectopic lymphoid follicles inside the CNS, antigen presentation to CD4+ and CD8+ cells, secretion of cytokines, and generation of antibodies [202]. A study conducted *in vitro* demonstrated that the B-cells of individuals with MS are responsible for causing CNS demyelination and neurodegeneration [212]. The utilization of oligoclonal bands of IgG as biomarkers for MS has been previously documented, but the identification of IgM oligoclonal bands has been associated with the presence of aggressive MS [213,214]. Meningeal and grey matter inflammation are widely recognized as the primary causative mechanisms that give rise to MS lesions, hence contributing to the development of all three clinical manifestations of the disease.

5. Excitatory/Inhibitory Imbalance in Different Neurological Disorders

Excitatory and inhibitory (E/I) imbalance is regarded to be critical for the proper functioning and integrity of neural circuits and is illustrated in Fig. 1. This section covers the concept of the E/I imbalance in AD, ASD, MS, and Epilepsy.

5.1 Impaired E/I Imbalance in Alzheimer's Disease

Research show that amyloid-beta (Aβ) and its associated proteins have a substantial impact on the disruption of the balance between E/I neuronal activity in the initial phases of AD [214]. Alterations in excitatory synaptic transmission are crucial in the manifestation of hyperactivity and hypersynchrony, hence leading to the onset and spread of epileptic seizures. The administration of soluble Aβ, both *in vivo* and *in vitro*, lead to hyperactivation of neurons in the hippocampus [215,216]. The hyperactivation is facilitated by various mechanisms associated with the transmission of glutamate at synaptic sites. Soluble Aβ enhances N-Methyl-D-Aspartate receptor (NMDAR) currents in the hippocampus, directly influencing neuronal firing [217,218]. Furthermore, Aβ has been found to interfere with the process of glutamate absorption by directly modifying the functioning or expression of glutamate transporters, hence leading to an elevation in the extracellular concentration of glutamate. This phenomenon results in the occurrence of sudden stimulation of post-synaptic neurons and hindered long-term potentiation [218]. Nevertheless, a decrease in the expression of the glutamate transporter has been shown to hinder the beginning and spread of seizures in epilepsy [219,220]. The increase in APP elevation has been found to enhance the mRNA expression of NMDAR that contains GluN2B in the hippocampus [221,222]. The activation of the GluN2B NMDA receptor has been found to be correlated with the perturbation of calcium homeostasis. Apoptosis may occur because of the unregulated elevation of intracellular Na^{+} and Ca^{2+} levels, which is triggered by the release of the NMDAR Mg^{2+} blocker due to sustained depolarization of the neuron [223]. Conversely, it has been observed that inhibitory circuits are similarly impaired in AD [127,224]. Animal models of AD have demonstrated an imbalance between E/I neural activity following the injection of a GABAA antagonist (picrotoxin), resulting in the occurrence of seizures [128,129]. Tg2576 rat model, when administered with an alternative GABAA antagonist known as pentylenetetrazol, exhibited the manifestation of seizures [130,131]. These effects have the potential to lead to a decrease in the functionality of the inhibitory circuit. [132,133]. Downregulation of certain subunits within the receptor in distinct brain areas suggests that there is a remodeling of the GABAergic receptor [134,135]. In addition to the impact on the GABA receptor, it has been observed that the release of GABA is diminished in AD due to the presence of Aβ [136].

5.2 Impaired E/I Imbalance in Autism Spectrum Disorder

Neurons exhibit excitability and inhibition during neurodevelopment in the forebrain are produced in distinct regions and undergo migration to atypical locations which leads to the formation of heterotopias [137]. Heterotopias, disorganized cortical patches and focal cortical dysplasia, are abnormalities seen in ASD. However, E/I neocortical imbalance may be connected to pyramidal glutamatergic neurons and the inhibitory GABAergic parvalbumin-positive interneurons [138,139]. ASD show modifications in gene transcription, translation, and the degeneration of synaptic proteins known as neuroligins. This modification has an effect on ion channels, receptors, cell adhesion, and synaptic scaffolding proteins. Neuroligin is a

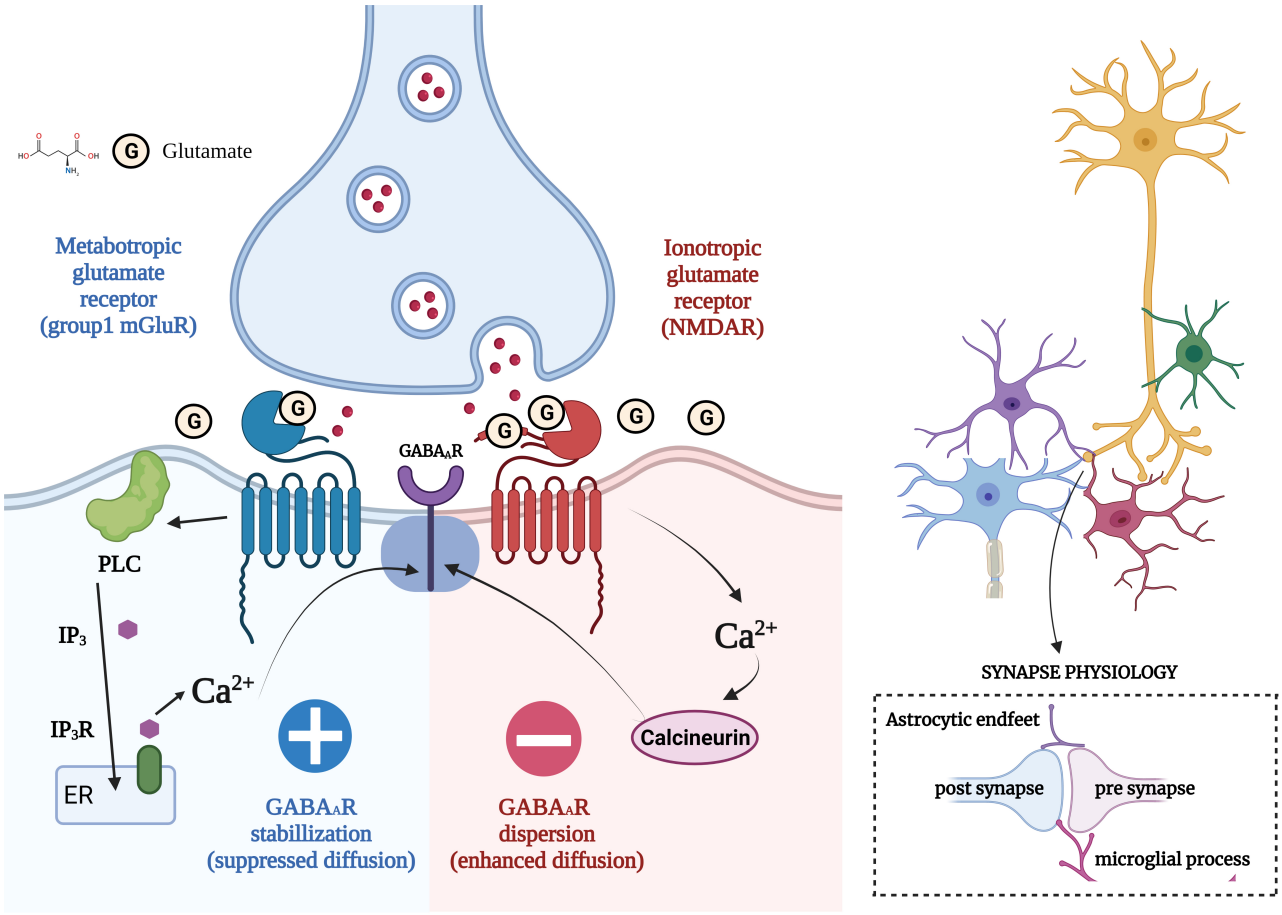

Fig. 1. Concept of Excitatory/Inhibitory Imbalance in Different Neurological Disorders. (Figures were created with BioRender.com). Regular neuronal stimulation of N-methyl-D-aspartate (NMDA) receptors by the neurotransmitter glutamate results above incoming calcium, eventually promoting the sensors to be more dispersed and reducing the amount of GABA that can suppress the neuron. GABAA synapses are generally grouped. The receptors are continuously re-clustered to counteract this action, maintaining the proper E/I equilibrium in the brain. In this route, glutamate interacts with the mGluR, causing Ca to be released from internal storage and released into the interior surroundings of the cell. This Ca interacts with protein kinase C to encourage the aggregation of GABAAR at the post-synaptic membrane, which has been shown using quantum dot-single particle monitoring. The same neurotransmitter that causes GABAAR scattering from the synaptic space also functions oppositely to stabilize GABAAR. It was also unexpected that the procedures utilizing various Ca ions in the signalling pathways of the cluster-forming passageway effectively prevented the distribution of GABAAR, which is generally caused by extremely high levels of glutamatergic input, as happens in epileptic seizures. Synapses are tri- or even quadripartite arrangements in which glial pathways come into touch with elements of the neuron. Additionally, the glial removes extra connections throughout maturation, adjusting the excitatory/inhibitory balance in growing neural networks. GABA, gamma-aminobutyric acid; GABAAR, γ-aminobutyric acid type A receptor; E/I, excitatory and inhibitory; mGluR, metabotropic glutamate receptor; ER, endoplasmic reticulum; PLC, Phospholipase C; IP_3R, inositol 1,4,5-trisphosphate receptor.

cell adhesion molecule which is specifically localized to excitatory synapses through the action of neuroligin one, or to inhibitory synapses through the action of neuroligin 2 [140]. Neuroligin 3 is present in both excitatory and inhibitory synapses, whereas neuroligin 4 has been observed to be specifically localized in glycinergic synapses [141]. During *in vivo* study, mutation in the neuroligin 4 genes, which differs from that of humans [142,143]. However, mice with a mutation in neuroligin 1–3 exhibited impaired transmission of GABAergic/glycinergic signals in the brainstem, both in response to external stimuli and spontaneously [144,145]. The regulation of synaptic function is influenced by neurexin, which acts as a binding partner for neuroligin, and regulation is dependent on the specific neurotransmitter involved [225]. The trans-synaptic adhesions formed by neuroligin and its binding proteins, neurexins (Nrxns), have been implicated in ASD by facilitating the recruitment of NMDARs and AMPARs to the synapse surface [226]. A mutation in contactin-associated protein-like 2 (*CNTNAP2*), a protein belonging to the neurexin superfamily, is identified as a cause of childhood epilepsy, hyperactivity, and Autism. The absence of CNTNAP2 re-

sults in impairments in the process of neuronal migration and the degradation of GABAergic cells [227]. Tuberous sclerosis complex (TSC) plays a vital role as an inhibitory element within the mTORC1 pathway, which is responsible for cellular growth and preserving the balance of synaptic activity. The activity of the mTORC1 pathway is increased in ASD because of mutations in the TSC gene. However, the functional examination of neurons with TSC mutations has show conflicting results. The presence of a loss-of-function mutation in the TSC gene has been linked to a multisystem illness is characterized by neurological symptoms which is associated with ASD [228,229]. Decrease in excitability of TSC2-/- stem cell-derived neurons reported an elevation in neuronal activity [230–232]. Significantly, the administration of rapamycin effectively rectified aberrant excitability by suppressing mTORC1 in instances when neuronal activity was heightened or diminished [233,234]. The occurrence of haploinsufficiency in the *ARID1B* gene, serves as a sequence-specific DNA-binding subunit within the chromatin complexes of mammalian *SWI/SNF* or Brg1-associated factors (*BAF*) and it contribute to the development of ASD [235]. The occurrence of haploinsufficiency in *ARID1B* is considered as a causative factor with decrease of total GABAergic interneurons in the cerebral cortex, but cortical pyramidal neurons do not show major alteration which is the concept of E/I [236] The cognitive impairment observed in Arid1b-deficient mouse models resembled the behavioral pattern associated with ASD [237]. Based on recent study, ARID1B regulatES Wnt/β-catenin signaling in HEK293T cells [237,238].

5.3 Impaired E/I Imbalance in Epilepsy

Epilepsy is distinguished by the occurrence of recurrent and unprovoked seizures [239]. Epilepsy has a global prevalence rate of 1% among the general population [238]. The equilibrium between E/I synapses is crucial for regulating synaptic activity. And Epilepsy is characterized by an imbalance in electrical activity, which arises due to a decrease in inhibitory GABA synaptic and voltage-gated conductance, as well as an increase in excitatory glutamate synaptic and voltage-gated conductance [239,240]. Glutamatergic neuronal activity is referred to as the glutamate hypothesis. And even basic anomaly in the pathogenesis of epilepsy [240,241]. The administration of Pilocarpine at a dosage of 40 mg/kg intraperitoneally shows persistent seizure-like behavior in mice which is through activation of the M1 receptor [242]. The resulting seizure-like behavior is primarily mediated by the activation of NMDA receptors, which subsequently leads to the development of temporal lobe epilepsy (TLE), secondarily generalized seizures, and status epilepticus [130–138]. The activation of receptors has a crucial role in the establishment of long-term synaptic plasticity and coordinated firing, although its significance in the preservation of epileptic convulsions is limited [139,243]. High influx of calcium ions (Ca^{2+}) into the neuron via NMDA-dependent calcium channels has been observed in cases of epilepsy [244]. This influx leads to the generation of ROS, which subsequently leads to an elevation in mitochondrial permeability transition [245,246]. This leads to swelling of the mitochondria and the hydrolysis of ATP, which ultimately result in the demise of the affected neurons [245,246]. The overexpression of mGluR group I/II has been observed in both epileptic individuals and animal models. The presence of these receptors has been observed in hippocampal neurons and astrocytes, and also associated with the regulation of glutamate and GABA neurotransmission as well as the interaction between astrocytes and neurons [247]. The release of Ca^{2+}-dependent glutamate from astrocytes in a spontaneous manner has the potential to enhance the activity of metabotropic glutamate receptors (mGluRs) by augmenting glutamatergic neurotransmission in the terminals of presynaptic neurons [248,249]. Multiple anticonvulsant medications effectively mitigate epileptic activity through the attenuating Ca^{2+} signaling inside astrocytes. Moreover, they exhibit antagonistic effects on NMDAR and AMPAR. Postmortem studies in patients with epilepsy have indicated substantial change in the expression and trafficking of GABAA receptors [244]. Nevertheless, epileptiform activity has been observed to induce changes in the intracellular concentration of Ca^{2+} and a role in the pathological processes associated with status epilepticus (SE) [245]. In addition, activation of calcineurin leads to GABAA receptors trafficking in neurons during epileptiform activity. The depletion of GABAergic interneurons can lead to a reduction in tonic inhibition in rat hippocampal neuronal cultures which were subjected to persistent epileptogenic stimulation [246]. In contrast, individuals with TLE have a disruption in the regulation of Cl^- levels and this disruption indicates show improper functioning of the Na-K-2Cl transporter (NKCC1) which is responsible for facilitating the influx of Cl- ions, K-Cl co-transporter (KCC2) and facilitating the efflux of Cl- ions [247]. The activation of flux leads to an increase in the excitability of granule cells and a decrease in the effectiveness of inhibitory synapses. In recent study the expression of NKCC1 in epileptic tissue was high, whereas the expression of KCC2 was shown to be diminished [244,248–250]. The reduction in the effectiveness of GABA inhibitory action can be attributed to the downregulation of KCC2, which is facilitated by the activation of the TrkB receptor through BDNF [251].

5.4 Impaired E/I Imbalance in Multiple Sclerosis

Still, intense research is needed to understand the importance of glutamatergic and GABAergic systems in MS [252]. MS involves glutamate-mediated excitotoxicity, wherein neuronal death occurs due to excessive activation of glutamate receptors and subsequent increase in intraneuronal calcium levels [253,254]. The extracellular level of glutamate is elevated due to the overproduction of

glutamate by macrophages and microglial cells [255] and decrease in the breakdown of glutamate by oligodendrocytes [256]. The increase in extracellular glutamate levels initiate the glutamate signaling pathway by activating glutamate receptors present in neurons, oligodendrocytes, and astrocytes [257]. Therefore, the increase in extracellular glutamate adversely affects all of these cellular populations. Furthermore, an excessive amount of glutamate stimulates both NMDA and non-NMDA receptors, causing an aberrant buildup of intracellular calcium ions, which ultimately leads to neuronal harm [258,259]. The utilization of magnetic resonance spectroscopy (MRS) imaging methods helps in identification of increased levels of glutamate in the active lesion located in the white matter. Conversely, individuals with MS exhibit a diminished concentration of glutamate in the grey matter when compared to individuals without the condition [260]. Based on findings, by decreasing the quantity of glutamate in the grey matter, it led to neuronal and synaptic degeneration [261,262]. Excitotoxicity can arise not only due to an excessive concentration of glutamate, but also due to an inadequate presence of GABA to counteract excitatory effect. Even reduction in the extracellular concentration of GABA has been observed in individuals diagnosed with MS which is linked to deficits in both motor and cognitive functioning [263,264]. The decrease in GABAergic neurotransmission is hypothesized to be facilitated by IL-1 in MS [265].

6. Role of Neuron Glial Interaction in Alzheimer's Disease

Proteinopathies, or the accumulation of toxic proteins, cause synaptic dysfunction, which is linked to AD [266]. The amyloid hypothesis posits that Aβ is the primary etiological factor of the disease. It suggests that the misfolding of the extracellular Aβ protein, which accumulates in senile plaques, and the intracellular deposition of misfolded tau protein in neurofibrillary tangles lead to memory loss, confusion, and gradual deterioration of personality and cognitive function [266,267]. Neurotransmitter release, synaptic plasticity—the capacity of synapses to alter and fortify their connections—and synaptic loss can all be hampered by them. Additionally, causing oxidative stress and inflammatory reactions, Aβ can also cause synaptic damage. When cytokine levels are high, the innate immune system is dysregulated, which leads to neuronal death [268]. Glutamate absorption by astrocytes protects neuronal cells, while glutamate alteration causes neuronal damage. Although the exact mechanism by which Aβ 42 material aggregates within stimulated astrocytes is unknown, it is thought to be caused either by phagocytosis or endocytosis [269]. Reactive astrogliosis could start releasing inflammatory mediators, leading to chronic inflammation and AD, aided by extracellular vesicles [270]. Sustained inflammatory cytokines released by microglia and astrocytes increase secretion of beta secretase-1, also known as beta-site amyloid precursor protein cleaving enzyme 1 (BACE 1) [268] and we hypothesize that BACE 1 may increase suppression of long-term potentiation (LTP). A cellular mechanism known as LTP is linked to synaptic plasticity, which is essential for memory and learning. Although persistent inflammation and elevated secretase activity have been linked to the impairment of synaptic plasticity in AD, research into the precise connection between inflammatory cytokines, secretase activity, and the suppression of LTP is still in progress [269]. The mechanisms behind AD are intricate and multifaceted and that research on the interactions between neuroinflammation, secretase activity, and synaptic dysfunction is ongoing. Additional research is required to understand the roles of inflammatory cytokines, secretase activity, and LTP suppression in AD development. Recently, it has been confirmed that nitration occurs in AD and nitride peptides play a dual role, in which nitride can cause amyloid formation and might prevent the formation of amyloid plaque [268]. The frontal and temporal lobes are highly vulnerable to neurodegeneration due to extensive myelination by oligodendrocytes [268]. Astrocytes and oligodendrocytes can produce brain cholesterol as well as the secretion of apolipoprotein E and apolipoprotein J, and secretion, especially by astrocytes, enhances phagocytic of microglial cells to clear amyloid protein [270]. The microglial function is altered when Apo E, produced by astrocytes, is absent. It has been established that amyloid plaques are linked to microglia as pro-inflammatory cells based on the downregulation of several homeostatic genes and anti-inflammatory types, and upregulation of AD and Protein Triggering receptor expressed on myeloid cells 2 (*TREM2*) receptor is considered as a microglial response controller [271]. One of the TREM2 signalling pathways controls microglia's phagocytotic ability to remove cell debris and amyloid plaques, which acts like a neuroprotective mechanism. On the other hand, other signalling pathways lead to *TREM2* abrogation, which causes cytokine secretion to be suppressed, resulting in inflammation response and neuronal loss [272]. The concept of neuron glial interaction in AD is shown in Fig. 2.

7. Role of Neuron Glial Interaction in Autism Spectrum Disorder

ASD is caused by a combination of genetic and environmental factors and there is no single cause of ASD and it is thought that both genetic and environmental factor contribute to development of ASD [273,274]. Glial cells even regulate and optimize several neurodevelopmental processes, including synaptic connectivity shaping [275]. The involvement of glial cells in the pathogenesis of ASD and the meticulous genetics in the etiology of ASD is unknown, as no solitary liable gene has been discovered thus far. Some of the genes linked to ASD risk perform a crucial part in brain development and thus are abundantly expressed in glial cells [275]. For instance, ASD has been

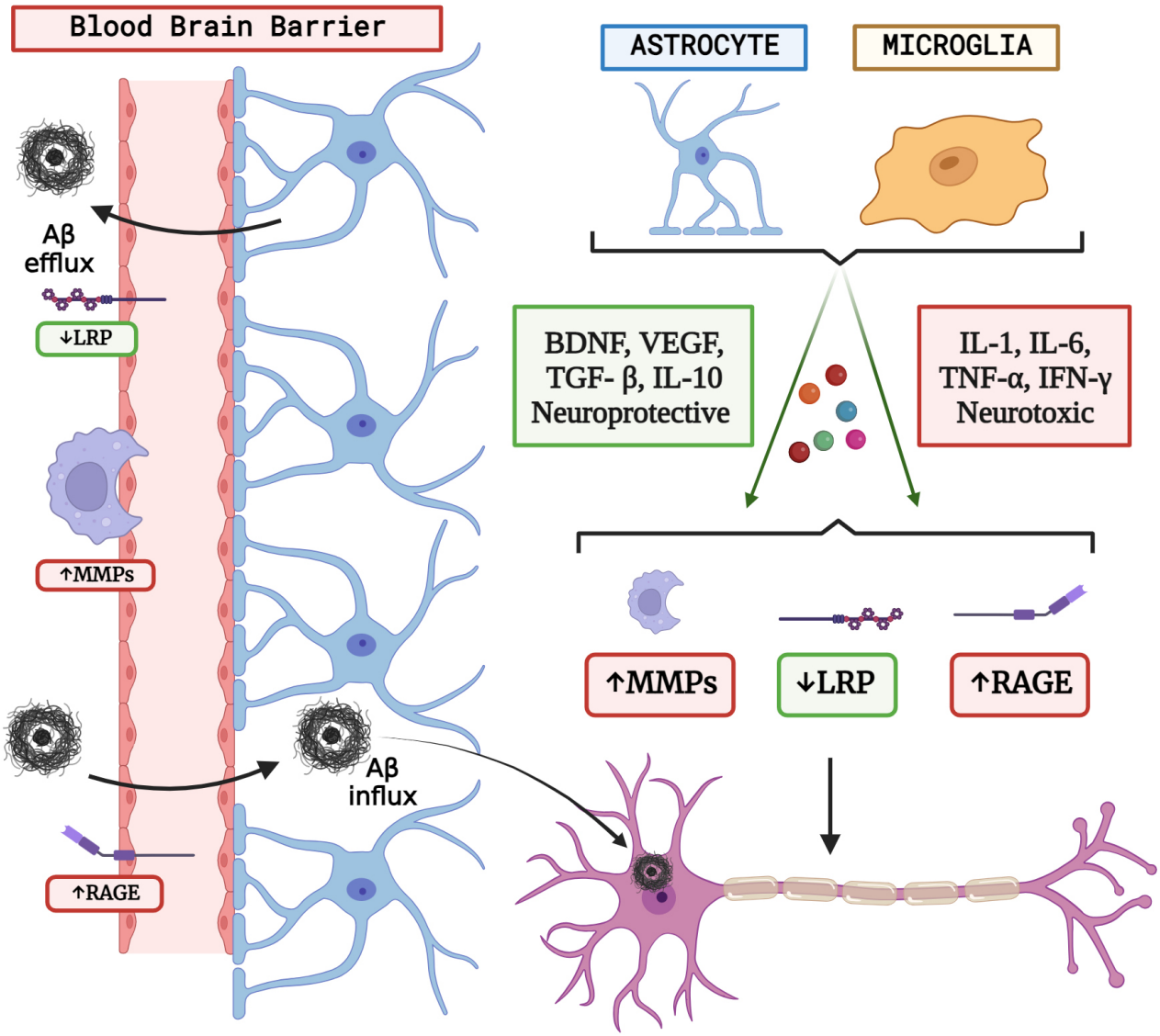

Fig. 2. The concept of neuron glial interaction in Alzheimer's Disease. (Figures were created with BioRender.com). Aβ deposition is carried on by elevated amyloidogenicity, blood-brain barrier (BBB) damage, downregulation of RAGE and decreased receptor expression. Astrocytes and microglia release pro-inflammatory mediators that encourage APP synthesis along the amyloid precursor protein route to Aβ. Glia mediated inflammation also induces vascular dysfunction involving dysregulated activation of MMPs and altered RAGE and LRP-1-dependent Aβ clearance from the brain. Nevertheless, when it takes on a hazardous form, it results in tau degeneration, the emission of neurotoxic agents, and subsequent activation of synaptic invagination. Bidirectionally activating either in a cytotoxic or restorative manner are microglia and astrocytes. MicroRNAs can influence glia's functionality transformation in addition to cytokines and toxins. A few ion channel expressions also influence the alteration. RAGE, receptor for advanced glycation end products; APP, amyloid precursor protein; MMPs, matrix metalloproteinases; LRP, low density lipoprotein receptor-related protein; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor; IFN, interferon; IL, interleukin.

linked to mutations in genes like *PTEN*, *TSC1*, *TSC2*, and *NF1*, linked to conditions like tuberous sclerosis and neurofibromatosis. These genes are essential for controlling the connection of neurons and the activity of glial cells. Gene changes that affect the ligand-binding molecules neuroligins (NL), for example, have been linked to ASD in humans. These NLs play critical roles in synaptic structure formation, maturation, and function. Indeed, genetic studies of rare ASD variants revealed a possible link to NL3 and NL4 mutations in humans. Transgenic mice with mutations like those found in ASD patients showed impaired social and stereotyping behaviours, indicating that

NLs play a conserved role in determining ASD phenotype across species [275–277]. Increasing data shows that inflammatory NLs are disrupted in Autism, although neuroligins were also generated exclusively in astrocytic glial and oligodendrocyte progenitor cells [276,277]. Enhanced soma, quick processes, extended filopodia, and elevated microglial cell density in the grey matter were all signs of activated microglia in ASD patients. Greater levels of pro-inflammatory cytokines/chemokines, such as *IL-1 alpha*, *IL-6 alpha*, *IL-8 alpha*, *INF*, and *TNF*, were identified that affect the ligand binding molecules to typically developing controls, confirming the neuroinflammatory status [277]. Glial cells are widely recognized as the primary contributor to the neuroinflammatory response mediated by *IL-1* signalling. ASD is linked to mutants in the *IL-1* cytokine receptor family. Individuals with Autism have both an uncommon mutant in the genome expressing for Interleukin-1 binding site accompanying associated protein, which is intensely concentrated in astrocytes, and a restriction fragment length polymorphism in the genes coding for Interleukin-1 binding site type 2, which is significantly concentrated in microglia [278]. Pre-clinical research has linked the mother's nutrition during maternity, nursing, and child behavioural modification, as such changes appear to be linked to changes in the inflammatory response; neuroglia is most likely involved in this mechanism. Still, glial cells are highly dynamic elements of the CNS, and their implication in ASD needs further research [279]. The concept of neuron glial interaction in ASD is shown in Fig. 3.

8. Role of Neuron Glial Interaction in Epilepsy

Based on previous studies, glial cells are linked to epilepsy pathogenesis, suggesting that targeting these cells could be used to supplement existing treatments [280]. Microglial involvement, as a major inflammatory cell in the epileptic brain and it may activate in response to the abnormal neuronal activity that occurs during epileptic seizures [281]. Neuroinflammation may result from releasing pro-inflammatory cytokines, chemokines, and other mediators by activated microglia. This neuroinflammatory response, in turn, can affect seizure activity and epileptic phenotypes in both favourable and unfavourable ways. Since microglia are central nervous system homeostasis controllers and convulsions and as seizures entwined with variations in neuronal functioning, microglial influences on epileptic phenotypes and repercussions are predicted [282]. On the one hand, epileptogenesis—the process of epileptic brain alterations and the shift from a single seizure to a chronic epileptic condition and the production of inflammatory chemicals by microglia can potentially worsen seizure activity [283–285]. On the contrary, microglia also contribute significantly to the control of synaptic connection, the promotion of tissue repair, and the resolution of inflammation. They have been demonstrated to participate in synaptic pruning, which removes extra or pointless synapses from the developing brain. Nevertheless, abnormal, or dysregulated microglial synaptic pruning may be a factor in the disruption of neuronal function in epilepsy. Microglial might well be able to manage neuronal processes in epilepsy [286]. Fractalkine receptor is expressed exclusively on microglial cells. Since chemokine (C-X3-C motif) ligand one is produced by brain cells, it is a fascinating and well-studied signalling pathway for interactions among microglial and nerve cells. Mice missing microglia ligands experience latency in the operational development of neural junctions, which disrupts neural activity [287]. The absence of postnatal excision reduced microglial colonization of the CNS, and a breakdown of the transition from Glutamate [NMDA] receptor subunit epsilon-2N to A N-methyl-D-aspartate subunits at the synaptic were all associated with chemokine signalling impairment. Impairment in anxiety, sensorimotor, and social behaviour has also been associated with chemokine receptor impairment and disturbances in neurogenesis, brain connection, and long-term stimulatory effects [288]. Microglia ablation techniques also raise concerns about local inflammation and astrogliosis. It is uncertain if additional glial purinergic channels are also implicated, even though microglial P2Y12 channels have been discovered as stimulators of epileptic movement morphologies. According to a new analysis, there was no discernible difference comparing wild-type and P2X4 defective rats undergoing abrupt convulsions, suggesting that glial P2X4 sensors do not influence rapid seizure behaviours. Finally, while P2X7 receptor function is thought to be neurotoxic during epilepsy, the evidence for the role of microglial-specific P2X7 receptors in epilepsy is currently being debated in addition to acute seizure phenotypes, ed. Microglia perform a crucial role in seizure-induced neurodegeneration [289,290]. According to these findings, microglia are crucial in controlling both the long-term and short-term aspects of sudden seizures and their effects on neuronal maintenance and growth. After CNS is affected, activated glia is essential for the recovery of neuropathological disorders. On the contrary, if left uncontrolled, severe reactive gliosis may significantly contribute to the neuropathology of epilepsy. Finally, more study is required to thoroughly understand and comprehend the role of microglia during acute seizures [291]. The concept of neuron glial interaction in epilepsy is shown in Fig. 4.

9. Role of Neuron Glial Interaction in Multiple Sclerosis

The brain has an immune system, which may encourage or block regeneration as a suitable reaction. In contrast, an inability in this response causes neuronal death, which is frequently found in MS [292,293]. The immune system incorrectly targets and assaults the myelin sheath, which serves as the central nervous system's safeguarding layer of nerve fibres, in MS. This immune reaction

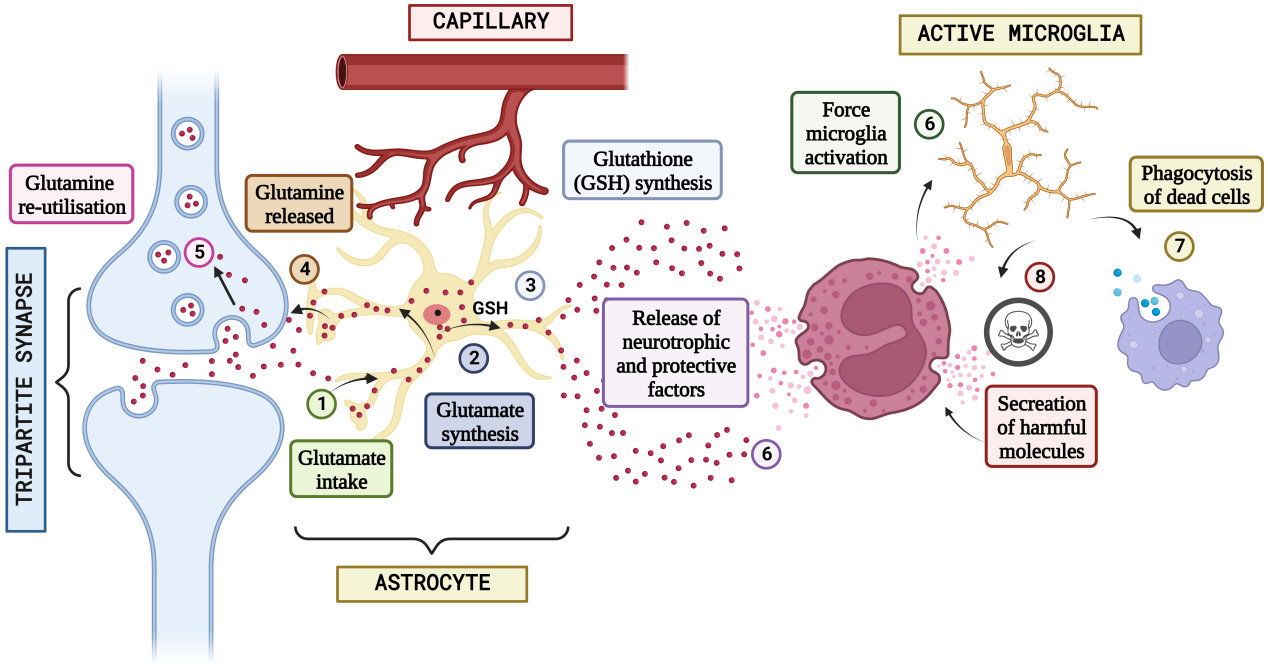

Fig. 3. Concept of neuron glial interaction in Autism Spectrum Disorder. (Figures were created with BioRender.com). Integrating neuron-glial connectivity and predicting glutamatergic transmission in the brain of patients having Autism. The pathogenesis of Autism is heavily influenced by glutamatergic communication. When glutamate is produced during neurotransmission in standard settings, astrocytes absorb it (1), which is often used to generate either glutamine (2) or glutathione (GSH) (3). After that, glutamine is liberated and used again by neural connections in the form of freshly produced glutamate (4 and 5), keeping the glutamatergic pathway. However, glial stimulation and increased astrocytic-mediated secretion of neurotrophic substances might result from epigenetic, hereditary, or environmental variables that impair neuronal propagation (6) and cause neuro-inflammatory processes that induce various amounts of stimulation in the microglia. It is hypothesized that activated microglia will scavenge cellular debris (7). In reaction to signs of neurotoxicity, the Central Nervous System (CNS) releases neuroprotective substances. Contrarily, the same microglial excitation might release potentially dangerous chemicals (8) such as NO, glutamate, pro-inflammatory mediators, free radicals, and others. The characteristic abnormal sociological phenomena seen in autistic individuals may be significantly influenced by a long-lasting interruption of neuron-glia connections and a defective release and action of neurotransmitter systems.

causes inflammation and demyelination, impairs nerve signal transmission and, in some cases, results in neuronal death. Microglia and invading immune cells release pro-inflammatory mediators and contribute to neuroinflammation when the neuroimmune response is dysregulated in MS. Myelin degeneration. Neuronalry potential consequences of this persistent neuroinflammation. Neurodegenerative illnesses of the CNS, such as MS, are characterized by leukocyte invasion with few T-lymphocytes and peripheral blood mononuclear cell (PBMC), as well as a significant glial activation of the CNS. Neuro-inflammatory mechanism stimulation phases cause the remyelination processes that characterize MS. There have been studies that back up the theory that the autoimmune response starts in the CNS [294,295]. Others, on the other hand, believe the initial activation takes place outside the CNS. To develop MS, a primary neuron disorder must exist within the CNS. In an operational setup with the inoculum of neural cells, even glia produces major histocompatibility complex-II molecules following activation with IFN- when substantially isolated from electroactive neurons. Glial cells expressed MHC-II throughout the crop culture after adding tetrodotoxin (TTX) to hinder the action potential of neurons. Treatment with TTX inhibited myelination, indicating that the production of MBP by oligodendrocytes depends on neuronal electrical activity. Numerous investigations have shown that myelination is regulated by neuronal electrical activity. In these investigations, TTX was utilized to decrease electrical activity in neurons and stop neuronal action potentials. The result was a reduction in MBP synthesis and subsequent myelination. Investigations are ongoing to determine the precise methods by which neuronal electrical activity affects myelination. However, it is thought that neuronal activity can affect the release of particular signaling molecules or elements that control oligodendrocyte activity and myelin synthesis. These elements could consist of neurotransmitters, growth factors, or other substances involved in cell-cell communication. The precise develop-

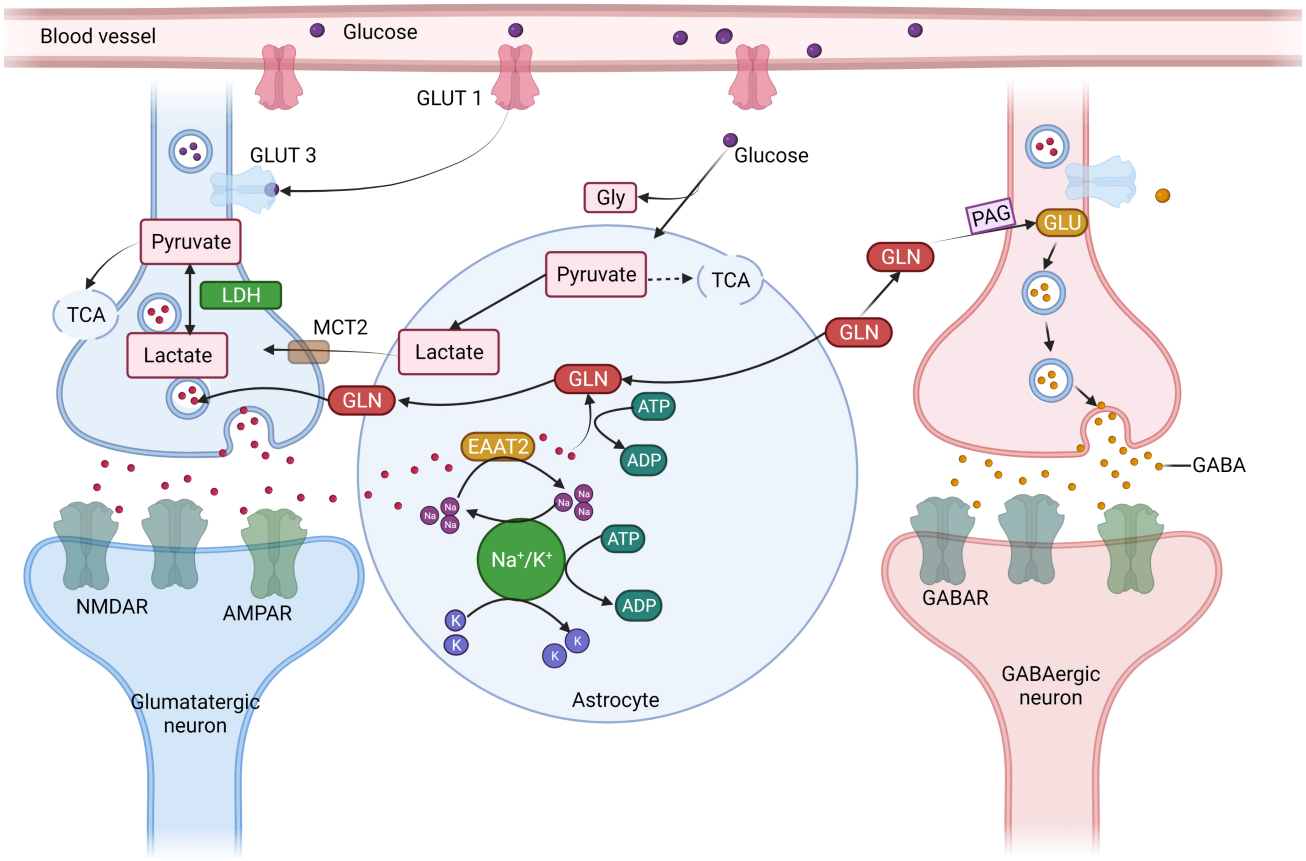

Fig. 4. The concept of neuron glial interaction in epilepsy. (Figures were created with BioRender.com). Astrocytes control the equilibrium of synaptic transmitters and active intermediates. Through the glutamate (GLU)-glutamine (GLN) cycle, astrocytes play a crucial role in preserving the ideal amount of extracellular Glu. Astrocytes take up (1) Excessive extracellular Glutamate via an excitable amino acid channel after the signal transduction. (2) GLN synthetase (GS) produces GLN, which is then transported to the nerve cells. (3) Phosphate-activated glutaminase (PAG) converts GLN to GLU, which is subsequently packed in synaptic vesicles in glutamatergic synapses. (4) GLU is further transformed by the enzyme Glu decarboxylase (GAD) in GABAergic neurons, producing GABA, which is secreted at the synapses during inhibiting neurotransmission due to the energy-intensive aspect of the process and the requirement of Adenosine triphosphate for both excitatory amino acid transporter two and GS, complete removal of extracellular Glu following enhanced synaptic transmission places energetic stress on astrocytes. (5) Energy mediator lactate and pyruvate are formed by the action of the glycolytic conversion of glucose that is enzyme-derived from astrocyte glycogen reserves and absorbed from the blood through glucose transporter 1 (GLUT1). (6) Because astrocytes have a limited ability to oxidize substances, lactate dehydrogenase 5 (LDH5) and other enzymes primarily turn pyruvate into lactic (7) transported by monocarboxylate transporters (MCT) into the neighborhood neurons. (8) Lactate dehydrogenase 1 catalyzes the process in neurons where lactate is transformed into pyruvate, which is then utilized as an energy source by the tricarboxylic acid (TCA) cycle. Astrocyte neuronal lactate shuttling, or ANLS, is an essential mechanism for generating power to neurons during intense neuronal transmission, such as during epilepsy (9). Furthermore, due to the cell's low glycogen synthesis capitals and the absence of glycogen reserves, neurons primarily get pyruvate from astrocytes via the ANLS route. Glucose is also absorbed by neurons from blood arteries using GLUT3. Inflammation which is driven by cytokines like IL-1 and TNF-α leads to neuronal hyperexcitability. The imbalance in the expression and function of KCC2 and NKCC1 can cause a shift from the traditional inhibitory effect of GABA to an excitatory one, contributing to hyperexcitability and seizure activity. Gly, glycine; EAAT2, excitatory amino acid transporter 2; ATP, adenosine triphosphate; ADP, adenosine diphosphate; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor; ANLS, astrocyte-neuron lactate shuttle; KCC2, K-Cl cotransporter; NKCC1, Na-K-2Cl transporter.

mental stage, brain location, and cell types can impact the link between neuronal activity and myelination, which is probably complex and can change. It is possible that the effects of TTX on myelination in experimental models do not completely replicate the physiological circumstances in the human brain. It has also been suggested that the first event in MS is an operational interference or damage to myelination's ability [296,297]. Initially, no morpholog-

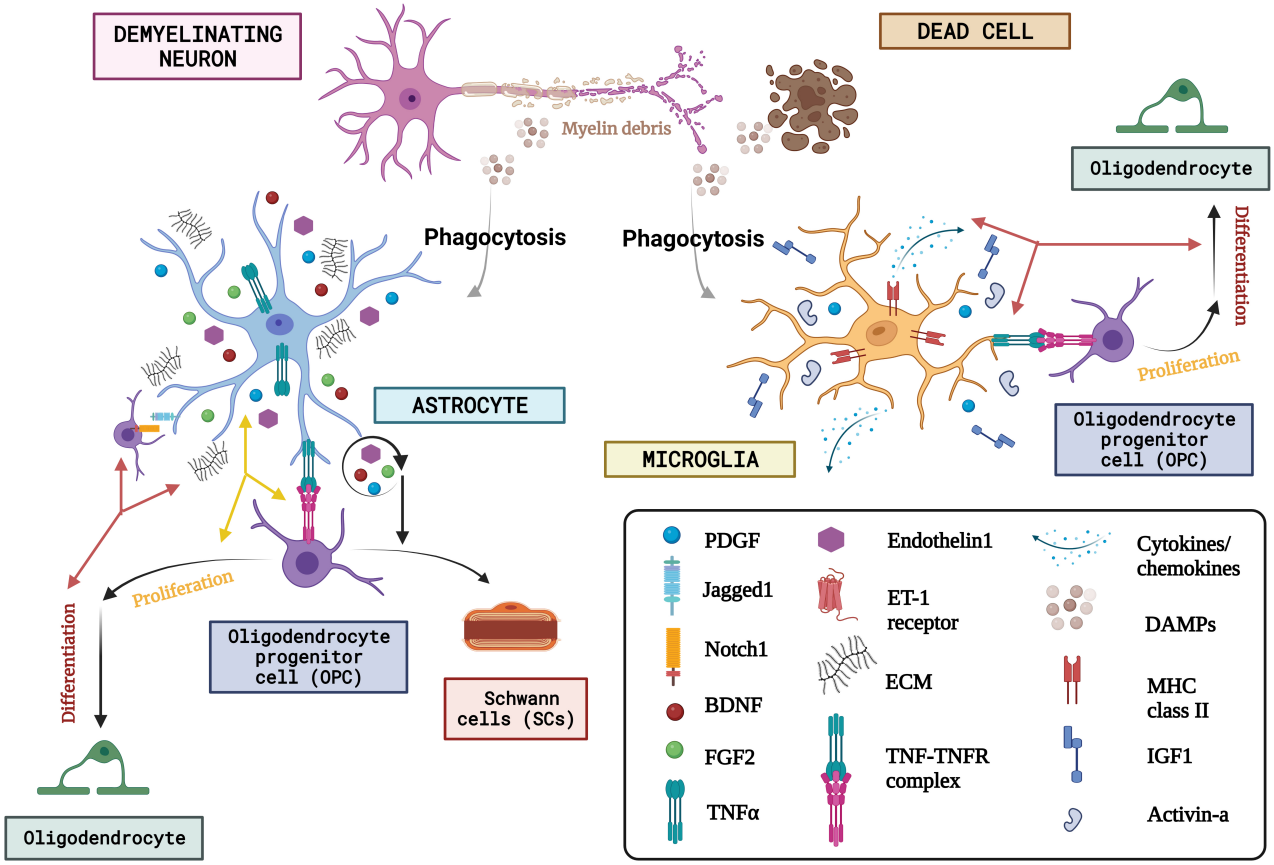

Fig. 5. The concept of neuron glial interaction in multiple sclerosis. (Figures were created with BioRender.com). Through the affirmation of extracellular matrix (ECM) compounds like chondroitin sulfate glycosaminoglycans (CSPGs), hyaluronan, fibronectin, and tenascin C, endothelin-1 and growth factor exudation including such Fibroblast growth factor-2 (FGF2), BDNF, and astrocytes, Oligodendrocyte progenitor cells behaviour is regulated after neurodegeneration. Microglia are discerned as DAMPs (damage-associated molecular patterns) via various receptor classes. Microglia recognize abnormalities in the aftermath of demyelination. Via paracrine and autocrine signalling, endothelin-1 increases the production of the notch ligand jagged. OPCs' destiny selection after demyelination is governed by astrocytes, who oppose their development into Schwann cells (SCs). On the other hand, astrocytes have only been shown to phagocytose myelin detritus in culture. Numerous actions are induced by DAMPS, one of which is the stimulation of microglia to phagocytose myelin and dead cells. Once energized, microglia also increase the expression of the utterance of a variety of immunologic molecules like MHC-II and cytokine release, chemokines, and growth regulators like *Activin-A*, platelet-derived growth factor (*PDGF*), *IL-1*, and *IGF-1* that control the lineage advancement of OPCs. Finally, they both produce tumour necrosis factor (*TNF*), which interacts with TNF receptor 2 (*TNFR2*) and encourages remyelination. ET-1, endothelin 1; DAMPs, danger associated molecular patterns; MHC-II, major histocompatibility complex class II; IGF1, insulin-like growth factor 1.

ical changes were associated with this, but later, myelin degeneration occurred. As a consequence, neurons, astrocytes, and endothelium may display allergenic epitopes that were initially inaccessible to the immune function in the setting of specific human leukocyte antigens molecules. Eventually, they penetrate the central nervous system, and T-lymphocytes that can recognize all of these hidden antigens start an immune condition [298,299]. The pathogenic mechanism is sped up by cytotoxic T cells, macrophages, and cytokines, which can impede bare axon activity. The CNS has previously been viewed as a specialized system in considerations of immunological irrespective of the CNS because it tends to lessen and restrict innate immunity reactivity. This is due to the possibility of permanent neuron death if the CNS has a significant inflammatory process. Low human leukocyte antigens-I&II expression, low signal transduction effectiveness, and the emergence of solubility substances in CSF that neutralize or reverse the actions of some pro-inflammatory mediators all contribute to this result [300,301]. Many writers propose that demyelination starts after active lymphocytes penetrate the CNS since, in this situation, the CNS would not be the ideal location to initiate an immune response that demands higher effectiveness. In this context, we found that MS individ-

uals' peripheral blood also began lymphocytes with phenotypically resembling encephalitogenic cells. It is suggested as a middle ground between the two possibilities that antigenic release through some (mainly olfactory) cranial nerves via lymphatics, where effective antigen-presenting would happen, happens due to an earlier engagement in the CNS. The theory proposes that lymphatic capillaries found in the meninges, the protective membranes enclosing the brain and spinal cord, may be able to trap antigenic material emitted by the olfactory nerve or other cranial nerves once it has entered the CNS. These lymphatic tubes are a component of the recently identified glymphatic system, which allows the interchange of fluid and molecules between the peripheral lymphatic system and the central nervous system, as well as the removal of waste materials. If meningeal lymphatics take in antigenic material from the CNS, it may be transferred to lymph nodes, home to antigen-presenting cells like dendritic cells. These antigen-presenting cells can process the antigens that have been collected and then deliver them to T cells to start an immune response. Excluding the target tissue, the CNS, and the existence of the BBB, the sequence of processes and components in an immune reaction are virtually the same in anybody else's non-autoimmune responses. Many researchers support this data, and each link in the circumstances is examined to pinpoint the comparative relevance of signalling pathways or mediators that suppress innate immunity as precisely as feasible [48–51]. Investigators now understand the ontogeny, diversity, and functioning of glial cell types in inflammation situations with concurrent demyelination because of recent advances in multiplexed and single-cell omics. Recent discoveries of sequences of gene activation and transcriptome tissue segmentation, which also included post-mortem MS tissues, have increased our understanding of glial subgroups throughout numerous CNS locations at various states of activation, but they have also brought new challenges. Contrary to the commonly held idea that the glial reaction is solely reactive, active microglia may also serve as effector cells, regulating and prolonging the immune system response and tissue damage [298–302]. Reactionary glial subcategories frequently deliver antigens via major histocompatibility complex I and II proteins, demonstrating that both reacting OL and astrocyte progenitor cells play significant roles in immune-related processes. Glial cells may phagocytose antigens and display them on major histocompatibility complex-II molecules, just as expert allergen cells like dendritic cells, which cause a particular immune system response. Oligodendrocyte progenitor cells (OPCs) that exhibit MHC class I are more susceptible to immune cell cytotoxicity during inflammation than microglia and DCs, which may not be as skilled at antigen-presenting via MHC class I as Dendritic cells. Another instance of improper immunological signalling is the release of neurotoxic substances like complementing cascade constituents, which can cause synaptic disease and accelerate neurodegeneration [297,298]. Additionally, it has been shown that a range of CNS glial subtypes exhibits several MS susceptibility gene variations in individuals that were assistive devices to peripheral immune responses, including some that control Nuclear factor-B in astrocytes. Different microglial types have different functions in the pathophysiology of MS, many of which are hostile. As indicated by abnormal immunological activation that can damage neurons through complementing mediators and self-destruction via primary histocompatibility complex class I recruitment and activation, these activities can be detrimental and, in certain circumstances, result in the development of a pro-inflammatory, tissue death, and CNS degeneration [295–299]. However, pro- and anti-inflammatory neuronal subgroups can be essential in removing waste and encouraging repair, as shown by pro-regenerative myeloid cells or astrocyte-mediated myelin phagocytosis. Because the single cell type is believed to play several functions, addressing these variants to slow neurodegenerative and boost healing will be challenging. Finding treatment targets unique to a specific glial subtype will need an awareness of the distinct molecular areas of glial subtypes in the pathogenesis of MS symptoms. This is where MS pathobiology varies from other predominantly aggressive or neurodegenerative illnesses, such as AD, which do not have repeated stages of inflammatory demyelinating lesions that can damage the whole CNS. The intrinsic transcriptional and operational distinctions of glial subtypes among anatomical categories and CNS regional groups must be considered to translate glial subtype variety and functioning in MS [298,302]. Given that MS is a relapsing-remitting disease, it is also possible that glial cells cycle between different subtypes depending on the stage of the inflammatory phase. Therefore, future studies must identify these subtype-specific crucial health regulators and develop therapeutic strategies to alter glial subtype-specific networks along spatial and temporal MS development pathways. This may also enable us to comprehend and promote anti-inflammatory and pro-regenerative cell subgroups, speeding up MS recovery. The Toll-like receptors- TRIF Interferon regulatory factor 3 pathways, which regulate caspase11 transcription, produce the pro-inflammatory mediator type I-IFN and Nuclear factor, which increase caspase11 synthesis. Recent research indicates that the non-canonical transit of the pro-inflammatory mediators, which contain Caspase11, is crucial for the beginning of seizures [299–302]. The concept of neuron glial interaction in Multiple Sclerosis is shown in Fig. 5.

10. Conclusion

Overall, this review has elucidated the inherent significance of glial cells, specifically microglia and astrocytes, in the etiology of diverse neurological disorders, such as AD, ASD, epilepsy, and MS. Our comprehension of the intricate interplay between neurons and glia, as well as its

involvement in neuroinflammation and neurodegeneration, has revealed potential targets for therapeutic intervention. Synaptic dysfunction may arise as a consequence of dysregulation in proteinopathies and innate immune function in AD, or as a result of neurodevelopmental processes and inflammation in ASD. An in-depth examination of epilepsy and multiple sclerosis MS has revealed the significant influence of microglia activation, leukocyte infiltration, and other inflammatory mechanisms on neurological functions. Therapeutic approaches may show potential by focusing on the targeting of neuroinflammation and inflammatory mediators. The presence of an imbalance between excitation and inhibition has been identified as a significant factor in the development of these disorders. It has been observed that changes in genes associated with neurotransmission can possibly result in either neurotoxicity or neuroprotection, depending on the specific pathway and characteristics of the disorder. The crucial involvement of GABAA receptors in the initiation of conditions such as AD and epilepsy has been firmly established. Nevertheless, further investigation is required in order to comprehensively comprehend the intricate molecular connections, imbalances, and inflammatory responses associated with various neurological disorders, with the ultimate goal of developing efficacious therapeutic interventions.

Abbreviations

CNS, Central Nervous System; AD, Alzheimer's Disease; ASD, Autism Spectrum Disorder; MS, Multiple Sclerosis; ROS, Reactive Oxygen Species; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; IL-1α, Interleukin-1 alpha; TNF, Tumour Necrosis Factor; C1q, Complement Component 1q; ALS, Amyotrophic Lateral Sclerosis; TREM2, Triggering Receptor Expressed On Myeloid Cells 2; TLR, Toll-Like Receptors; RIP1, Receptor-Interacting Protein Kinase 1; EV, Extracellular Vehicles; miRNA, micro-RNA; Syt1, Synaptotagmin1; Nlg1, Neuroligin1; LPS, Lipopolysaccharide; NL, Neuroligins; NMDA, N-methyl-D-aspartate; PBMC, A peripheral blood mononuclear cell; TTX, Tetrodotoxin; OLD, Oligodendrocytes; DC, Dendritic cells; MYD88, Myeloid Differentiation Primary Response 88; DD, Death-Domain; INT, Intermediate; TIR, Toll-interleukin-1 receptor domain; IRAK4, IL-1R-associated kinase; TIRAP, Toll/IL-1 receptor domain-containing adapter protein; Mal, MyD88 adapter-like; TRAF6, TNF receptor-associated factor 6; TAK1, Transforming growth factor-β-activated kinase 1; IKK, IκB kinase; NEMO, NF-κB essential modulator; IκBα, Inhibitor of nuclear factor-kappa Bα; IRF7, Interferon regulatory factor 7; IFN, Interferon; MAP3K, Mitogen-activated protein kinase kinase; SARM, Sterile α and armadillo-motif containing protein; IL6R, IL-6 specific receptor; LCN2, Lipocalin-2; NGAL, Neutrophil Gelatinase-Associated Lipocalin; Aβ, Amyloid-Beta; APP, Amyloid Precursor Protein; CNTNAP2, Contactin Associated Protein-like 2; TSC, Tuberous sclerosis complex; BAF, Brg1-associated factors; TLE, Temporal Lobe Epilepsy; NKCC1, Na-K-2Cl transporter; KCC2, K-Cl co-transporter; MRS, Magnetic resonance spectroscopy; NO, Nitric Oxide; BDNF, Brain-Derived Neurotrophic Factor; NSAID, Non-steroidal anti-inflammatory drugs; BBB, Blood-brain barrier; LTP, Long-Term Potentiate; SLE, Systemic Lupus Erythematosus; Th 1, T helper 1; Th 17, T helper 17; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; INF-γ, interferon-γ; Treg, T regulatory.

Author Contributions

SRA and MZ designed the research study; performed the research, AMA, AD, HA, AM, AAGA, UR, MM, SA, ERH analysed & interpreted the data, SRA, UR, MM, SA, ERH wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have significantly contributed to this work and agreed to be accountable for all its aspects.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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