NeuroUpdates
Neuroscience Updates, 2024; 2(1): 25-45

Review Article

Beyond Neurons: The Integral Role of Glial Cells in Cognitive Function, Pathology, and Treatment

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Received: December 20, 2023
Accepted: February 15, 2024
Published: April 30, 2024

10.47176/update.2024.25

Checked for Plagiarism: Yes
Peer reviewers approved by:
Dr. Melika Andrew
Editor who approved publication:
Dr. Nasrollah Moradikor
Language Editor:
Dr. Adeel Ahmed Abbasi

ABSTRACT

The brain architecture, once thought to be dominated by neurons, has revealed an equally compelling role played by neuroglia. Initially perceived as merely supportive entities, glial cells have emerged as crucial contributors to brain functionality and integrity. This review highlights the pivotal roles of principal CNS neuroglial cells-astrocytes, microglia, and oligodendrocytes in shaping synaptic plasticity, cognition, and behavior. It then highlights their critical role in the pathology of cognitive and behavioral disorders and sheds light on novel glial cell-targeting interventions for treating such conditions. This review expands our comprehension of brain function and stresses the critical importance of glial cells in future neurological and psychiatric research and treatment strategies. The emphasis on glial cells opens up new pharmacological frontiers, offering hope for more effective remedies for neurological and psychiatric conditions where current treatments have limited success.

KEYWORDS: Neuroglia; Astrocytes; Microglia; Oligodendrocytes; Neurodegenerative disorders; Neurodevelopmental disorders; Neuropsychiatric disorders; Cognition; Behavior

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[DOI: 10.47176/update.2024.25]

1. Introduction

It was in 1846 when Virchow first introduced the term 'neuroglia' or 'nervenkitt,' referring to it as a putty-like substance in the brain for structural support [1]. Subsequently, Golgi suggested that glial cells nourish neurons, owing to their proximity to blood vessels and nerve cells [1]. In 1909, Cajal questioned the function of glia, rejecting both Golgi's nutritive theory and the notion of glia as passive. He speculated that glia might insulate nerve fibers, yet acknowledged his uncertainty about their role [1]. Today, it is well understood that neuroglia are not mere bystanders. Astrocytes, the most abundant brain cells, manage synaptic chemicals, contribute to post-injury gliosis, and supply neurons with substrates for ATP production. They also sustain homeostasis through water uptake and potassium metabolism, and their foot processes are crucial for the integrity and function of the blood-brain barrier (BBB) [2]. Microglia, the resident immune cells of the central nervous system (CNS) [3], are mononuclear phagocytes that have penetrated the neural tube before BBB formation [4,5]. They play a significant role in inflammation and cleanse the CNS of pathogens and cellular debris [6]. Oligodendrocytes produce myelin in the CNS, which supports and insulates axons, enhancing the rapid transmission of impulses. Impulses leap across nodes of Ranvier, rich in sodium ions, in a process known as saltatory conduction [2]. In recent decades, neuroscientific research has unveiled a far more essential role for glial cells than previously imagined. These cells are now recognized as fundamental architects in the cognitive and behavioral function of the brain through shaping neural plasticity, the brain's remarkable ability to develop and reorganize itself in response to experience and learning [7,8]. Disruptions in glia impair neural circuit function and contribute to cognitive decline and neuropsychiatric disorders [9]. This review will highlight the roles of major glial cell types in modulating plasticity mechanisms underlying learning, memory, cognition, and behavior across the lifespan and in disease and then explain novel glia-based therapeutic strategies for such disorders. This review broadens our understanding of brain function and aims to revolutionize the treatment of complex cognitive and psychiatric conditions, as current treatments are often ineffective.

2. Astrocytes in Synaptic Plasticity and Cognition

The cognitive functions of astrocytes stem from their proximity to synapses [10,11], leading to the 'tripartite synapse' concept [12]. This challenges the traditional view of synaptic communication as exclusively neuronal [13], highlighting instead the active role of astrocytes in information transmission at the synaptic level [12,13]. Astrocytes dynamically contribute to the process of synaptogenesis, influencing the development and maturation of both excitatory and inhibitory synapses [14–17]. For example, Hevin, secreted by astrocytes, is essential for glutamatergic synapse formation and maturation [18], as its loss leads to their reduction [17,18]. SPARC, also produced by astrocytes, acts as a competitive inhibitor against Hevin-induced synaptogenesis [14,19]. While Hevin promotes excitatory synaptogenesis, SPARC inhibits this process, showcasing the dynamic regulation by astrocytes [15,19]. Furthermore, Astrocytic Neuronal Cell Adhesion Molecule (NRCAM) has been identified as a critical player in inhibitory synapse assembly and maturation, binding to NRCAM-gephyrin complexes on postsynaptic neurons to induce the formation and function of GABAergic synapses [15,16]. These findings emphasize the active role of astrocytes in shaping the heterogeneity of astroglial cues based on synapse subtypes [14]. In addition, astrocytes influence neuronal plasticity through lactate production. Once considered a metabolic waste product associated with muscle fatigue, lactate has now emerged as an energy substrate in the brain's metabolism and a novel signaling molecule influencing synaptic plasticity, neural circuits, and memory [20,21]. Astrocytic glycogenolysis generates lactate [21], which is then transported to neurons, where it serves as a significant alternative energy source [20,21]. Neurons utilize it as an energy source through oxidative metabolism [22]. This metabolic pathway becomes particularly relevant during periods of heightened neuronal activity when the demand for energy increases [20]. Beyond being an energy substrate, lactate exerts its effect by acting as a signaling molecule [20,22,23]. The presence of lactate can enhance long-term potentiation (LTP), a process linked to reinforcement of synaptic transmission, and promote memory formation [24].

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Furthermore, astrocyte-derived gliotransmitters such as D-serine, glutamate, and ATP/adenosine play key roles in the regulation of plasticity. Although glutamate is traditionally recognized as a neurotransmitter, it also functions as a gliotransmitter [25], with SNARE proteins mediating its Ca2+-dependent release [26]. Similarly, D-serine, synthesized from L-serine by serine racemase [27], is stored in synaptic-like vesicles and released in a Ca2+-dependent fashion [28]. D-serine and glutamate boost N-methyl-D-aspartate receptor (NMDAR)-mediated LTP and memory [29,30], while ATP/adenosine influences plasticity through presynaptic P2X receptors [31]. Besides, short-term biphasic synaptic modulation by gliotransmitters was also studied. It involves first potentiation through glutamate, then depression of neurotransmitter release mediated by ATP/adenosine [32]. Astrocytes regulate synaptic transmission not only through the release of molecules but also by clearing neurotransmitters and ions from the synaptic gap. For example, high-affinity glutamate uptake transporters expressed by astrocytes are essential in reducing excitotoxicity [33], and it has been demonstrated that astrocytic uptake of potassium contributes to short-term plasticity [34]. Moreover, astrocytes regulate water via Aquaporin-4 (AQP-4), a water channel highly concentrated in their membranes [35], which was shown to be implicated in synaptic plasticity, learning and memory [36]. Notably, AQP-4 knockout mice exhibit impaired brain-derived neurotrophic factor (BDNF)-dependent LTP in the hippocampus, highlighting its role in cognitive processes [37].

3. Microglia in Synaptic plasticity and Cognition

Beyond their immune functions, microglia exhibit non-inflammatory physiological roles as key regulators of neural circuit function and refinement [38,39]. In vivo and in vitro studies show that microglial contact directly affects filopodia formation, inducing actin accumulation and transient Ca2+ changes in neuronal dendrites [40,41]. Alternatively, microglial ablation or inhibition reduces spine density, cortical neurons connectivity, and the number of functional excitatory synapses [41,42]. These results confirm that filopodia formation and increased spine turnover are microglial-dependent functions [43]. Recent studies, however, suggest that mice with all microglial cells removed retain intact learning and memory capabilities [44]. Overall, this indicates that microglia are not essential for synaptogenesis to occur but rather have a supportive and modulating role [44]. Microglia may regulate synaptogenesis through the secretion of BDNF and pertinent growth factors [41]. Besides their synaptogenic role, microglia are also involved in synaptic pruning. Studies across different developmental stages and in different areas of the brain provide evidence of the active role of microglia in refining brain functions and neural circuits through tuning the number, connectivity, and arrangement of functional synapses [45]. Synaptic pruning is vigorous during early thymus development [46] and is maintained throughout adulthood in the hippocampus, where microglia continue to ingest and digest pre- and postsynaptic structures [47]. Microglia remodel connections between neurons in an activity-dependent manner where they eliminate synapses in undeveloped neural circuits through the trogocytosis of synaptic structures such as dendritic spines and axon terminals [48,49]. Deficiencies in microglia disrupt the engulfment of synapses, delaying the development of neural circuits [46], and increasing the frequency of excitatory synapses, a characteristic of high synaptic density [50]. Other research suggests that an imbalance of excitatory/inhibitory synaptic transmission emerges from a reduction in microglial synaptic elimination, leading to CNS disorders [51] like memory and sleep difficulties, and various behavioral, mental, and cognitive disorders [52,53]. In another regard, neurogenesis in the adult mammalian brain presents a substantial expression of plasticity [45]. New neurons continuously generate and integrate into pre-existing neural circuits [54]. Out of these newborn cells, only a small portion integrates into the neural circuitry, while the newest cells are eliminated by apoptosis within the first days of their life [45]. These apoptotic newborn cells along with excess new viable cells are cleared out by microglia through phagocytosis [55,56]. Alternatively, microglia support neurogenesis through the release of BDNF and transforming growth factor β (TGF-β) [57,58]. The resulting young neurons exhibit higher excitability than older neurons, which increases their probability of recruitment in memory networks replacing older synapses [59].

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4. Oligodendrocytes in Synaptic Plasticity and Cognition

In humans, developmental myelination continues until the fourth decade of age [60]. A wealth of studies suggest that myelination is a form of plasticity and learning [61]. For instance, a study tracking brain changes in learners of Chinese showed evolving white matter, notably in frontal lobe tracts, suggesting that adult language learning heavily relies on white matter plasticity [62]. Similarly, fractional anisotropy (FA) changes (implying white matter changes) were detected following piano practice [63]. On the other hand, social neglect has been linked to abnormalities in white matter; for example, children experiencing critical socio-emotional negligence in Romanian orphanages showed decreased FA in white matter tracts of the limbic system [64]. In addition, children with developmental language disorder exhibited reduced myelination in brain areas associated with listening, speaking, and learning [65]. This supports the hypothesis that myelin plays a crucial role in behavior, learning, and memory. To explain this role, we first need to define the principle of "Hebbian learning" in neural networks. It says that the efficiency of a given neuron in firing another could increase as that cell is repeatedly involved in the activation of the second: "Neurons that fire together wire together" [66]. In other words, when impulses from converging axons arrive synchronously at a common target, the corresponding synaptic connection is enhanced (LTP). On the flip side, synapses that do not align in timing with the firing of the postsynaptic neuron become weaker (LTD) [67]. Whether spike-time arrival will be synchronized or not, i.e. the timing of action potential arrival, is influenced by factors such as the length of the axon path and the speed at which action potentials travel [67]. Oligodendrocytes play a crucial role in this context, as myelin thickness and internode distance fine-tune conduction velocity across axons [68]. If an axon's conduction velocity cannot achieve synchronous arrival of action potentials, the synapses originating from that axon will weaken and eventually be lost, and vice versa [67].

Table 1: A recap table summarizing the mechanisms by which glial cells contribute to synaptic plasticity and cognitive functions

Glial Cell Type	Mechanism	Contribution to Synaptic Plasticity and Cognitive functions
Astrocytes	Synaptogenesis	Influence development and maturation of excitatory and inhibitory synapses via Hevin, SPARC, and others.
	Lactate Production	Serve as an energy source and signalling molecule, enhancing LTP and memory formation.
	Gliotransmitter Release	Regulate plasticity through D-serine, glutamate, ATP/adenosine affecting NMDAR-mediated LTP and synaptic modulation.
	Neurotransmitter and Ion Clearance	Maintain synaptic environment, reduce excitotoxicity, contribute to short-term plasticity.
	AQP-4 Regulation	Impacts synaptic plasticity, learning, and memory through water transport.
Microglia	Synaptic Pruning	Refine brain functions and neural circuits by tuning synapse numbers and connectivity.
	Supportive Modulation	Regulate synaptogenesis, potentially through BDNF and growth factors.
	Neurogenesis Support	Influence adult neurogenesis via phagocytosis of apoptotic cells and support through BDNF, TGF-β.
Oligodendrocytes	Myelination as Plasticity	Influence learning and memory through changes in white matter, supporting the principle of Hebbian learning.
	Conduction Velocity Adjustment	Myelin thickness and internode distance fine-tune action potential speed, affecting synaptic strength and contributing to LTP and LTD

5. When Glia Go Wrong: Role of Glial Cells in Diseases That Impair Cognition or Behavior

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[DOI: 10.47176/update.2024.25]

While neuroglia plays an important cognitive role in physiological conditions, glial dysfunction is implicated in the pathogenesis of various diseases that disrupt cognition and/or behavior. Key examples are explained below to illustrate.

5.1. Neurodegenerative Diseases

Alzheimer's diease (AD) is the most prevalent neurodegenerative disorder, whose hallmarks include extracellular amyloid-beta (Aβ) plaques and altered intraneuronal neurofibrillary tangles composed of altered tau protein [69]. Microglia play a key role in AD. They initially become activated in response to Aβ accumulation to phagocytose and degrade them, but chronic activation triggers ongoing proinflammatory cytokine and chemokine release [70]. This chronic neuroinflammation leads to synaptic dysfunction and neuronal damage and loss [70,71]. Moreover, microglial toll-like receptors (TLRs), whose signaling pathway is an indispensable component of the innate immune response, are activated by Aβ plaques in AD, and thus contribute to an exacerbated neuroinflammatory milieu [72]. Aβ aggregates act as damage-associated molecular patterns (DAMPs), engaging TLRs on the surface of microglial cells [73,74]. TLR activation initiates a signaling cascade that contributes to chronic neuroinflammation, thus worsening neuronal damage and accelerating AD progression [74]. Astrocytes also become reactive in AD, leading to altered calcium signaling and subsequently to hindered synaptic plasticity and neurotransmission [75]. Another neurodegenerative disease with cognitive implications is Parkinson's disease (PD) [76]. PD is characterized pathologically by the degeneration of dopaminergic neurons in the substantia nigra [77]. This condition is also marked by the presence of Lewy bodies, cytoplasmic inclusions composed of insoluble aggregates of alpha-synuclein (α-syn) [77,78]. Primarily presenting as motor dysfunction, cognitive decline can appear in the later stages of the disease [79]. Besides neurons, glial cells such as astrocytes and microglia also play important roles in the onset and progression of PD [80]. The loss of normal astrocyte functions, particularly their role in maintaining the BBB, is believed to be a factor in the development of PD as disruption of the BBB can lead to the entry of inflammatory substances into the brain and microglial activation, potentially promoting dopaminergic neurodegeneration [81]. Furthermore, A1 subtype reactive astrocytes, found to be abundant in neurodegenerative disorders like PD, is induced by activated microglia secreting certain neuroinflammatory cytokines [82]. A1 astrocytes are unable to promote neuronal growth, survival, synaptogenesis and phagocytosis but instead promote the death of both neurons and oligodendrocytes [82]. As for microglia, they become activated in early PD in response to α-synuclein accumulation and neuronal dysfunction [83]. The extracellular α-syn aggregates signal the activation of the microglial α-synuclein/TLRs/ nuclear factor kappa-B (NF-κB)/ leucine-rich-repeat and pyrin-domain-containing 3 (NLRP3) inflammasome axis, which induces the release of the pro-inflammatory cytokines IL-1β and IL-18, capable of exacerbating cytotoxicity and α-syn build-up [84]. Likewise, mutations in genes like parkin, PTEN-induced kinase 1 (PINK1), leucine-rich repeat kinase 2 (LRRK2), and glucocerebrosidase (GBA) impair both astrocytic and microglial functions like mitochondrial quality control, lysosomal function, and autophagy, leading to a vicious cycle of inflammation [80].

5.2. Neurodevelopmental Diseases

Glial cell dysfunction has been studied in the context of autism spectrum disorder (ASD). A meta-analysis found increased microglial quantity and density along with elevated protein and mRNA expression of glial fibrillary acidic protein (GFAP) in individuals with ASD [85]. Studies have pointed out genes linked to ASD severity in young patients, such as autism susceptibility gene 2 (AUTS2), Fyn binding protein (FYB), forkhead box p2 (FOXP2), and spleen tyrosine kinase (SYK), which influence microglial development and activation [86]. In rodents, genetic alterations affecting microglial activity result in behavioral changes resembling ASD traits. For example, triggering receptors expressed on myeloid cells 2 (Trem2)-deficient mice show characteristic ASD behaviors, such as reduced social interaction and repetitive actions, due to weakened microglia-mediated elimination of synapses [87]. In addition, inadequate myelination of neurons and impaired synaptic function seem to lead to disruptions in brain connectivity within the first

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year of life, leading to autistic social dysfunction during childhood and beyond [88]. Fragile X syndrome (FXS), the most common inherited intellectual disability and a frequent cause of ASD, is caused by a genetic mutation in which over 200 CGG repeats in the FMR1 gene silence it, leading to a loss of the fragile X mental retardation 1 protein (FMRP), which is crucial for normal neurodevelopment [89]. The absence of FMRP disrupts neuron-to-glia signaling, and thus glial cells fail to correctly remodel neural circuits through phagocytosis, contributing to abnormal brain development and function [90]. Rett syndrome (RTT) is initiated by aberrations of the X-linked gene called methyl-CpG-binding protein 2 (MECP2) [91]. Caused by the deletion of the MECP2 gene in astrocytes, abnormal astrocytic calcium homeostasis is a key phenotype in RTT, leading to overactivation of extrasynaptic NMDARs on neighboring neurons, increasing neural network excitability [92]. In Down syndrome, alterations of glial cells accompany the neuronal irregularities, including oligodendrocyte dysfunction, exhibited as delayed myelination of the pathways in the temporal and frontal lobes, as well as increased prominence of microglia [93].

5.3. Neuropsychiatric Disorders

Schizophrenia (SZ) is a psychiatric disorder characterized by delusions and hallucinations (positive symptoms), social withdrawal and motivation (negative symptoms), and cognitive deficits [94]. Although the cognitive dysfunction pathophysiology in SZ is poorly understood, it is hypothesized that impaired maturation of oligodendrocyte precursor cells (OPCs) into oligodendrocytes contributes to poor frontotemporal connectivity and subsequent cognitive dysfunction [95,96]. Studies implementing diffusion-weighted magnetic resonance imaging (dMRI) have assessed the structural connectivity and microarchitecture of white matter, and revealed signs of abnormal myelination, fiber density, or tract coherence in schizophrenic individuals. Remarkably, individuals with cognitive deficits exhibit more prominent white matter microstructural abnormalities [95]. Additionally, the idea of a potential connection between SZ and the immune system was proposed more than a century ago [97], and is backed up by substantial recent research [98,99]. In fact, overactive synaptic pruning during adolescence may underlie SZ etiology. The inherent phagocytic overactivity of microglia in SZ brains has been substantiated, explaining the reduced cortical synaptic density in schizophrenic patients [100].

As for substance use disorders (SUDs), studies have demonstrated that substances of abuse interact with glial cells in the brain, contributing directly to the pharmacodynamic effects behind their abuse potential. Addictive substances also alter brain function by interacting with relevant receptors on glial cells (especially astrocytes and microglia), leading to their associated behavioral changes [101–103]. One important mechanism is glial TLR4 activation. Studies show that various abused substances like certain opioids, psychostimulants, and alcohol activate glial TLR4, leading to the release of proinflammatory signals [104–107]. Disrupting cocaine signaling at microglial TLR4 inhibits cocaine-induced extracellular dopamine in the nucleus accumbens, in addition to cocaine self-administration and conditioned place preference [107]. Moreover, TLR4-mediated immune signaling, specifically through tumor necrosis factor (TNF), drives opioid tolerance so that inhibiting soluble TNF can prevent tolerance, neuroinflammation, and disruptions in glutamate transport, while preserving the effectiveness of morphine for pain relief [108]. Furthermore, upon alcohol consumption, microglia and neurons respond by signaling through TLRs, miRNAs, high-mobility group box 1 (HMGB1), and pro-inflammatory cytokines. Repeated alcohol consumption leads to a gradual, persistent induction of miRNA, HMGB1, and TLR receptors in the brain, which appears to underlie the progressive loss of control of behavior, as well as increased impulsiveness, anxiety, and cravings. In addition, this process intensifies ventral striatal responses, encouraging reward-seeking behavior [109].

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Table 2: A recap table summarizing the role of glial cells in diseases that impair cognition or behavior

Disease Category	Disease	Glial Cell Dysfunction	Impact on Cognition/Behavior
Neurodegenerative Diseases	Alzheimer's Disease (AD)	Microglia and astrocytes contribute to neuroinflammation and synaptic dysfunction through chronic activation and altered signalling.	Leads to neuronal damage and loss, impairing cognition
	Parkinson's Disease (PD)	Disruption in normal astrocyte functions and microglial activation contribute to neurodegeneration. A1 astrocytes promote neuronal and oligodendrocyte death.	Motor dysfunction initially, with cognitive decline in later stages
Neurodevelopmental Diseases	Autism Spectrum Disorder (ASD)	Elevated microglial quantity and density, abnormal gene expression affecting microglial development	Linked to behavioral changes resembling ASD traits such as reduced social interaction
	Fragile X Syndrome (FXS)	Disruption in neuron-to-glia signaling, impairing neural circuit remodeling	Abnormal brain development and function, leading to intellectual disability and ASD traits
	Rett Syndrome (RTT)	Deletion of the MECP2 gene in astrocytes leads to abnormal calcium homeostasis and increased neural network excitability.	Affects neuronal signaling, increasing susceptibility to seizures and learning difficulties
	Down Syndrome	Dysfunctional oligodendrocytes, delayed myelination, increased microglial prominence	Impacts cognitive development and function
Neuropsychiatric Disorders	Schizophrenia (SZ)	Impaired maturation of OPCs into oligodendrocytes, overactive synaptic pruning by microglia	Poor frontotemporal connectivity, cognitive deficits, reduced cortical synaptic density
	Substance Use Disorders (SUDs)	Interaction of substances with glial cells (especially astrocytes and microglia), activation of glial TLR4 leading to neuroinflammation	Alters brain function, contributing to addiction, tolerance, and withdrawal symptoms

6. Glial cell-based Approaches for the Treatment of Cognitive and Behavioral Disorders

6.1. Neurodegenerative disorders: AD and PD

As glial cell dysfunction is intimately related to the pathogenic processes seen in AD and PD, glia has been demonstrated to be an interesting therapeutic target to control neuroinflammation, maintain neuronal survival, and promote tissue repair in these disorders [110,111]. In AD, glial cell-based therapies targeting the TLR signaling pathway aim to intervene in this inflammatory cascade by selectively inhibiting TLRs in microglia [112]. By selectively inhibiting TLRs, the therapy aims to dampen the activation of NF-κB and subsequent transcription of pro-inflammatory cytokines and chemokines, mitigating the chronic neuroinflammation associated with AD [112,113]. Moreover, the manifestation of insulin resistance in the

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brain emerges as a distinctive pathological feature, contributing significantly to synaptic dysfunction and neurodegeneration [114]. The Insulin/Insulin-like Growth Factor-1 (IGF-1) signaling pathway, which is critical for neuronal cellular metabolism and survival, has emerged as a focus for potential therapeutic interventions, with glial cell-based therapies targeting this pathway to alleviate insulin resistance and improve neuronal health in AD patients [115]. Activation of the Insulin/IGF-1 pathway in astrocytes is a critical component of these treatment efforts since it improves nutrition delivery to neurons, which is critical for their energy demands and general function [115,116]. Simultaneously, these therapies include control of the Insulin/IGF-1 pathway in microglia, with the goal of regulating inflammatory responses, while the neuroprotective benefits of this therapy extend synaptic function preservation [117]. Furthermore, the dysregulation of the cyclic AMP (cAMP)/Protein Kinase A (PKA)/ Response Element-Binding Protein (CREB) signaling pathway stands out as a significant contributor to cognitive decline, as this pathway is important for synaptic plasticity and neuronal survival [118]. This pathway, important for synaptic plasticity and neuronal survival, has become a focal point for potential therapeutic interventions aimed at addressing the cognitive impairments in AD [118]. Glial cell-based therapies targeting the cAMP/ PKA /CREB pathway aspire to enhance neurotrophic support, offering a multifaceted approach to counter the cognitive decline associated with the disease [119].

The CAMP/ PKA/ CREB pathway begins with the activation of adenylyl cyclase, leading to the production of cAMP, where the elevated levels of cAMP activate PKA, which in turn phosphorylates the transcription factor CREB [119,120]. Phosphorylated CREB moves to the nucleus, where it controls gene expression related to synaptic plasticity, neurotrophic factor release, and neuronal survival [120]. The purposeful activation of the CAMP/PKA/CREB pathway in astrocytes provides an environment conducive to neurotrophic factor secretion [121]. Furthermore, glial cell-based therapies aim to regulate glial cells by targeting the Hippo pathway, which is well-known for its crucial role in tissue growth regulation [122]. When MST1/2 and LATS1/2 kinases are activated in astrocytes, they cascade down to the downstream effector molecules YAP/TAZ, which increases synaptogenesis [123]. In the context of PD, to address alpha-synuclein aggregation, glial cell-based interventions focus on modifying microglia to increase their phagocytic activity, specifically their ability to ingest and eliminate alpha-synuclein clumps [124]. The focused approach aims to lower the burden of neuroinflammation in the substantia nigra, as excessive inflammatory responses have been linked to the progression of PD [124].

The ultimate goal of these interventions is to protect dopaminergic neurons from the toxic effects of alpha-synuclein [124,125]. Moreover, the Nrf2/Bach1 signaling pathway has an important role in oxidative stress, a crucial factor in the pathogenesis of PD, particularly within the substantia nigra [110]. Again, in glial cell-based interventions designed to counteract this oxidative stress, specific attention is directed towards astrocytes within the substantia nigra [110,126]. These therapies aim to activate the nuclear factor erythroid 2-related factor 2 (Nrf2) in astrocytes [126]. Activation of Nrf2 prompts the expression of antioxidant and detoxifying enzymes, reinforcing the cellular defense mechanisms against oxidative damage [126,127]. Simultaneously, the intervention inhibits Bach1, a transcription factor that negatively regulates the expression of Nrf2 genes, thereby enhancing the antioxidative response [110,126,127]. Additional research advances include modulating other pathways, such as TGF-β signaling in astrocytes and microglia. Moreover, the hippo signaling pathway and Wnt signaling pathways are also modulated. For example, dysregulation of the Wnt pathway is implicated in neurodegenerative disorders [128]. In PD, altered Wnt signaling is associated with impaired synaptic plasticity and dopaminergic neuron degeneration [128,129]. So, glial cell-based therapies aim to target the Wnt pathway, focusing on astrocytes and microglial cells [130].

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Table 3: Recap table summarizing therapeutic approaches targetting malfunctioning pathways in neurodegenerative disorders

	Pathway Name	Role in Disease	Glial Cell Involvement	Therapeutic Strategy
Alzheimer's disease	TLR Signaling Pathway	Contributes to chronic neuroinflammation	Microglial TLR activation by beta-amyloid plaques	Selective inhibition of TLRs in microglia
	Insulin/IGF-1 Signaling Pathway	Implicated in insulin resistance and synaptic dysfunction	Activation in astrocytes enhances nutrition delivery; microglial pathway control regulates inflammation.	Targeting pathway to alleviate insulin resistance and improve neuronal health
	cAMP/PKA/CREB Signaling Pathway	Important for synaptic plasticity, contributes to cognitive decline	Activation in astrocytes promotes neurotrophic factor secretion.	Enhancing neurotrophic support to counter cognitive decline
	Hippo Pathway	Regulates tissue growth and synaptogenesis	Activation of MST1/2 and LATS1/2 in astrocytes enhances synaptogenesis.	Regulating glial cells to increase synaptogenesis
Parkinson's disease	Alpha-Synuclein and Microglial Phagocytosis	Leads to dopaminergic neurodegeneration	Modifying microglia to increase phagocytic activity of alpha-synuclein clumps	Reducing neuroinflammation and protecting dopaminergic neurons
	Nrf2/Bach1 Signaling Pathway	Involves oxidative stress in substantia nigra	Activation of Nrf2 in astrocytes; Inhibition of Bach1	Activating antioxidative responses in astrocytes
	TGF-β, Hippo, and Wnt Signaling Pathways	Linked to impaired synaptic plasticity and neuron degeneration	Modulation in astrocytes and microglia	Targeting pathways to address synaptic plasticity and neuron degeneration

6.2. Neurodevelopmental Disorders

Emerging glial cell-based treatments offer promising approaches for alleviating NDDs. In ASD, IGF can be provided to children within one year postpartum by injection, breastfeeding, as well as through massage therapy to reverse its low levels linked to poor myelination found in ASD [131]. Moreover, the cell-replacement theory of oligodendrocytes and astrocytes can generate extensive myelination that might treat symptoms of ASD [132]. Glial Progenitor Cells (GPCs) might also alleviate the symptoms of this disorder by differentiating into various types of glial cells [132], in addition to other drugs like Minocycline, Luteolin, Celecoxib, and Suramin, which inhibit microglial activation and reduce neuroinflammation, and hence are other possible avenues [133–136]. Microglia-targeting approaches could be significant, considering the microglia's role in synaptic maturation and pruning. This is particularly relevant in FXS, given its relation to abnormal maturation and pruning of synapses [137,138]. Therefore, microglia-dependent reorganization of synaptic connections might serve as a treatment not just for FXS, but potentially for multiple ASDs [136]. In RTT, likewise, irradiation-mediated immune ablation followed by wild-type bone marrow transplantation shows potential by restoring MeCP2-expressing microglia, thus alleviating several aspects of the disorder [139]. Similarly, for Down Syndrome, treatments targeting microglia involve the depletion of those activated cells, which can improve cognitive performance and restore normal dendritic function [140]. Moreover, the use of Acetaminophen affects microglial activation by inhibition of cyclo-oxygenase (COX) enzymes and activation of Trvp1 channels (transient receptor potential cation channel subfamily V member 1 channels), therefore rescuing normal neuronal spine

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phenotype and reversing cognitive deficits [140–142]. Another treatment for Down syndrome involves DNA immunization. Anti-Aβ1–11 vaccination helps produce specific antibodies that remove soluble oligomers and inclusions affecting neuronal function [143]. Such a vaccination promotes a homeostatic expression of microglial phenotype and prevents their overactivation, which might promote inflammation of brain parenchyma and neuron damage [143,144]. Moreover, the vaccine reduces levels of specific astrocytes associated with neurodegeneration, further promoting tissue homeostasis [143,145].

Table 4: A recap table summarizing the key points about emerging glial cell-based treatments for neurodevelopmental disorders

NDD	Treatments	Effects
ASD	IGF injection, breastfeeding, massage therapy in early postnatal period to increase IGF levels	Reverses low IGF levels linked to poor myelination
	Cell replacement with oligodendrocytes and astrocytes to promote myelination	Generates myelination to potentially treat symptoms
	Glial progenitor cell transplantation	Differentiates into glial cells to alleviate symptoms
	Anti-inflammatory drugs (minocycline, luteolin, etc.) inhibiting microglial activation	Reduces neuroinflammation
FXS	Treatments targeting microglial synaptic pruning and maturation	Reorganizes synaptic connections as treatment approach
RTT	Bone marrow transplantation to restore MeCP2-expressing microglia	Alleviates aspects of the disorder
Down Syndrome	Depleting activated microglia	Improves cognitive deficits and dendritic function
	Acetaminophen inhibition of microglial activation	Rescues neuronal spine phenotype and reverses cognitive deficits
	Anti-Aβ vaccination	Removes toxic Aβ species, promotes microglial homeostasis, reduces neuroinflammation

6.3. Neuropsychiatric Disorders

Studies have shown that microglial cells display an increased synaptic engulfment in schizophrenic patients. In this context, it's being proven that in a dose-dependent manner, minocycline inhibits this microglial activity [146]. Kynurenic acid (KYNA) is a metabolite that plays a unique role in brain pathophysiology and gliotransmission [147,148]. An increase in this metabolite's level leads to cognitive impairments (schizophrenia) [149]. Recent therapeutic approaches target an enzyme produced by astrocytes: kynurenine aminotransferase II, responsible for ~75% of the brain KYNA neosynthesis [150], aiming to reduce KYNA cerebral formation levels that might have vast therapeutic benefits. Confident preclinical results involving particular kynurenine aminotransferase II inhibitors have been reported [151]. Antipsychotic medications preserve the white matter in the quest to reduce negative symptoms of schizophrenia [152]. For instance, haloperidol leads to the proliferation of Oligodendrocyte Precursor Cells [153]. Moreover, continuous quetiapine therapy can effectively prevent myelin breakdown, promote re-myelination in the cerebral cortex [154,155], restore spatial working memory, and decrease the activation of astrocytes and microglial cells, therefore reducing the cognitive impairment in schizophrenia [156]. As for SUDs, although we have substantial knowledge on addictive substances actions on neurons, the development of successful treatments remains limited, and efforts targeting dysfunction in the

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mesocorticolimbic system have mostly failed to yield successful results [102]. Exploring treatments that address glial cells and neuroinflammation has shown potential for SUDs [101]. Ibudilast is a phosphodiesterase inhibitor that blocks glial cells' proinflammatory cytokine production and suppresses their activation [157]. A recent study investigated the effects of Ibudilast on the subjective, reinforcing, and analgesic influences of oxycodone in individuals with opioid dependence. The findings suggest that ibudilast reduced drug liking and cravings for opioids, indicating its potential utility in treating opioid use disorders [158]. Moreover, in a study involving individuals with alcohol use disorder, ibudilast was found to reduce functional connectivity between the ventral striatum and reward-processing brain regions when exposed to alcohol-related cues, compared to a placebo. This reduction in connectivity was associated with a decrease in drinks consumed per drinking day, suggesting that ibudilast's effects on drinking outcomes may be linked to its impact on frontostriatal circuits involved in reward processing [159]. Another drug of potential is minocycline, a tetracycline-derived antibiotic that inhibits microglial activation and its release of pro-inflammatory cytokines [160]. A new study examined the impact of its administration on oxycodone's physiological, subjective, and analgesic effects in non-dependent recreational opioid users. The findings indicated that minocycline reduced the positive subjective effects of oxycodone, suggesting its potential to mitigate the abuse properties of mu-opioid-receptor-selective agonists [161].

Table 5: A recap table summarizing key points about emerging glial cell-based treatments for schizophrenia and substance use disorders

Disorder	Treatments	Effects
Schizophrenia	Minocycline inhibiting microglial synaptic engulfment	Dose-dependent inhibition of heightened microglial activity
	Targeting kynurenine aminotransferase II to reduce KYNA formation	Reduces KYNA levels to improve cognition
	Antipsychotics like haloperidol and quetiapine	Promote oligodendrocyte proliferation and myelination, reduce inflammation
SUDs	Ibudilast blocking glial proinflammatory cytokines and activation	Reduced drug cravings, liking, analgesic effects of opioids Decreased connectivity in reward regions and drinking levels
	Minocycline inhibiting microglial activation	Mitigated positive subjective effects of opioids

7. Conclusion

The review illustrates a transformative understanding of neuroglia, evolving from mere structural support to key players in brain function and pathology. Glia are now recognized for their critical roles in synaptic plasticity, cognition, and neural health. This shift in perspective highlights their potential as therapeutic targets for neurodegenerative, neurodevelopmental, and neuropsychiatric disorders. As research advances, glial cell-based therapies promise revolutionary treatments, urging re-evaluation of brain function models and the development of innovative approaches to combat cognitive and behavioral impairments, marking new frontiers in neuroscience and clinical practice.

Acknowledgement:
The authors would like to thank the Medical Learning Skills Academy for submitting this article on their behalf.

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[DOI: 10.47176/update.2024.25]

Authors' Contributions Statement:
Hawraa Tofaili: Conceptualization, Literature Search and Data Collection, Methodology, Writing - Original Draft Preparation, Writing - Review and Editing. **Asmaa Al Masri:** Writing - Original Draft Preparation. **Lama Faour:** Writing - Original Draft Preparation. **Nourhan Kanso:** Writing - Original Draft Preparation. **Maher Jammoul:** Writing - Original Draft Preparation. **Ahmad Al Moughrabi:** Writing - Original Draft Preparation. **Alaa Younes:** Writing - Original Draft Preparation. **Ragheb Al Mokdad:** Writing - Original Draft Preparation. **Rim Karaki:** Writing - Original Draft Preparation. **Aya Zaraket:** Writing - Original Draft Preparation. **Jamil Nasrallah:** Conceptualization, Writing - Original Draft Preparation, Writing - review, Visualization, Supervision, Project Administration.

Funding: Not applicable.

Declarations:

Ethical approval: No ethical approval was required for this study as it was a narrative review.
Consent to participate: No informed consent was required.
Conflict of Interest: The authors declare that they have no conflicts of interest.

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