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A Neuroglial Approach to the Neurodevelopmental and Disruptive Behavior Axis: A Broad Review of Current Literature

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Abstract

Neurodevelopmental and disruptive behavior disorders (NDDs and DBDs) represent a complex and overlapping spectrum of conditions characterized by early-onset cognitive, emotional, and behavioral impairments. Traditionally viewed through a predominantly neuronal lens, recent advances in neuroscience have underscored the critical roles of neuroglial cells—astrocytes, microglia, and oligodendrocytes—in brain development, synaptic modulation, and neuroimmune regulation. This narrative review synthesizes current literature on the involvement of glial dysfunction in the pathophysiology of NDDs and DBDs, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), conduct disorder, and oppositional defiant disorder. We examine evidence from molecular, imaging, and translational studies that highlight neuroinflammation, glial-synaptic interactions, and altered myelination as potential mechanisms linking neuroglial alterations to behavioral phenotypes. Furthermore, we discuss the emerging therapeutic implications of targeting glial cells in early intervention strategies. By adopting a neuroglial perspective, this review aims to offer a more integrated understanding of the biological underpinnings of developmental psychopathology and to pave the way for novel, mechanism-based interventions.

Keywords: neuroglia; neurodevelopmental disorders; disruptive behavior disorders; microglia; astrocytes; neuroinflammation; glial dysfunction; ADHD; ASD

1. Neuroglial Insights into Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, limitations in verbal and nonverbal communication skills, as well as restricted and repetitive behaviors and interests [1]. The etiology of ASD is multifactorial, involving genetic, environmental, immunological, perinatal, biochemical, and neuroanatomical factors [2]. Individuals with autism may have intellectual functioning within the normal range or below expectations. Motor developmental delays and atypical responses to sensory stimuli may also accompany the condition [3]. Epidemiological studies in recent years have shown an increase in the prevalence of ASD. Possible reasons for this rise include increased awareness of autism, changes in diagnostic criteria, the conceptualization of the disorder as a spectrum encompassing a broad range, advancements in research methodologies, and the development of screening tools and diagnostic scales [4]. One epidemiological study reported that the prevalence of autism is 4 to 5 times higher in males than in females, with an average prevalence of 1% across Asia, Europe, and North America . Another more recent study found the global prevalence to be approximately 0.6% [5]. Comorbid

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psychiatric conditions are common in individuals with ASD, with 60–70% of children and adolescents and 70–80% of adults with autism having at least one psychiatric comorbidity. The most frequently co-occurring psychiatric conditions include attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and mood disorders. In addition, intellectual disability is present in approximately 30% of individuals with autism [6].

Structural alterations have been observed in the brains of children with autism. An increase in brain volume is particularly evident during the first year of life, with an average enlargement of approximately 10% observed between the ages of 2 and 4. This increase becomes less pronounced during late childhood and adolescence. The volume increase is more prominent in the left hemisphere compared to the right. Studies have reported a reduction in gray matter and an increase in white matter in the temporal and hippocampal regions. In contrast, cerebellar volume reduction becomes more apparent during adolescence and adulthood [7]. Changes in brain volume are primarily attributed to an increase in the cortical surface area. A decrease in gray matter has been observed in the amygdala and hippocampus. Cortical gyrification increases during childhood but decreases during adolescence [8].

Numerous genetic alterations have been investigated in relation to the development, progression, and outcomes of autism. Some of these genetic changes may lead to autism by disrupting transcription and translation processes in neurons [9]. Another mechanism involves disruptions in synaptogenesis, synaptic pruning, synaptic transmission, neuronal plasticity, and the structural and signaling proteins involved in synaptic function and cell adhesion. Additionally, impairments in epigenetic mechanisms that affect neuronal function or exacerbate dysfunction may also contribute to the onset of autism [10]. Another area of ongoing research involves immune-inflammatory mechanisms triggered by glial cell proliferation and alterations in the intestinal microbiota. All of these factors may interact at various levels, collectively contributing to the pathophysiology, progression, and outcomes of autism [11].

Research on the pathogenesis of autism has primarily focused on neuronal processes. However, the brain contains as many glial cells as neurons, and among these, astrocytes and microglia have been particularly investigated in relation to autism. Both astrocytes and microglia are involved in autism-related processes, either independently or in a coordinated manner [12]. For neural networks to function properly, processes such as synaptogenesis, synaptic maturation, and pruning must remain intact. A balanced ratio between excitatory and inhibitory synapses is crucial. In autism, this balance is disrupted, and the altered excitatory-to-inhibitory synapse ratio is considered one of the underlying mechanisms of the disorder.

Neuroglia can be defined as a heterogeneous group of cells with different embryological origins, structures, and functions, whose primary role is to maintain brain homeostasis, preserve neuronal function, and restore it when disrupted. Neuroglial cells provide essential support to the nervous system. This support operates at various levels:

– **Molecular level**: regulation of ions, protons, reactive oxygen species, neurotransmitters, and metabolites

– **Cellular level**: astrocyte roles in neurogenesis and axon guidance

– **Synaptic network level**: astrocyte and microglial functions in synaptogenesis, synaptic development, and pruning; myelinating functions of oligodendrocytes and Schwann cells

– **Organ level**: astrocyte role in the blood–brain barrier

– **Systemic level**: glial cells acting as central chemoreceptors [13].

Glial cells support neuronal functions and assist in synaptic transmission. Their critical roles include the removal of neurotransmitters from the synaptic cleft, formation and elimination of synapses, ion exchange, regulation of inflammation, protection against excitotoxicity, production of myelin, and clearance of cellular debris [14].

Changes in neuronal and glial cells, which result in impairments in cognitive functions such as social behavior, attention, reward processing, and learning, have been observed in various brain regions, including the prefrontal cortex, hippocampus, cerebellum, and striatum in autism [15].

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Dysfunctions in glial cells can affect neuronal functions and synaptic morphology and function, contributing to the onset or progression of autism. Animal studies using autism models have demonstrated impairments in synaptogenesis, alterations in synapse numbers, disruptions in the excitation/inhibition balance, impaired neuronal plasticity, disorganization of cortical neuronal layers, and changes in the number of parvalbumin- or calbindin-positive neurons in the cortex, striatum, and hippocampus [16]. In brain samples from individuals with autism, changes in glial genes associated with synaptogenesis and glial reactivity have been observed. An increased number of GFAP-positive astrocytes, oligodendrocytes, and microglia has been reported in the striatum. Furthermore, the loss of function in certain genes (e.g., *KANK1*, *PLXNB1*) in glial cells such as astrocytes and oligodendrocytes located in the anterior cingulate cortex, primary visual cortex, dorsolateral prefrontal cortex (DLPFC), and middle temporal gyrus has been proposed to play a role in the pathogenesis of autism [17].

Astrocytes are key cells involved in the maintenance of brain homeostasis. They play a critical role in buffering ions such as K^+, Ca^{2+}, Na^+, and Cl^- in the inter-neuronal environment, thus maintaining the delicate balance required for proper neuronal excitability. Loss of function in water channels such as aquaporins can disrupt potassium flux, affecting neuronal excitability and leading to excessive glutamate release, which may result in excitotoxicity and contribute to the development of neurodevelopmental disorders such as autism [18]. In one study, astrocytes derived from stem cells taken from individuals with autism and transplanted into rodent brains were shown to generate abnormal Ca^{2+} signaling, which was suggested to lead to repetitive behaviors [19]. In Rett syndrome, deletion of the *MECP2* gene specifically from astrocytes impairs glutamate clearance, leading to autistic-like behaviors such as abnormal movements and anxiety; however, re-expression of wild-type *MECP2* in astrocytes has been shown to alleviate these symptoms. In Fragile X syndrome, the loss of function of the *FMR1* gene in astrocytes leads to reduced synaptic support, resulting in decreased glutamatergic synapses [20]. Furthermore, reductions in astrocyte-specific synaptic proteins such as hevin, SPARC, and thrombospondin-1 have been reported to impair synaptogenesis. Similarly, postmortem brain tissue samples from individuals with autism have shown alterations in astrocyte density, morphology, and expression of astrocytic marker proteins such as GFAP, aquaporin-4 (AQP4), S100β, glutaminase, and EAAT2 [21]. Additionally, astrocyte-derived ATP has been shown to regulate autistic behaviors via P2X receptors and GABAergic transmission [22].

ATP released from astrocytes in the medial prefrontal cortex (mPFC) modulates the activation of layer 5 cortical pyramidal neurons through P2X receptors located on GABAergic interneurons. Disrupted ATP transmission from astrocytes in the mPFC is believed to be associated with deficits in social communication and interaction observed in autism. Similarly, impaired astrocytic ATP signaling in the striatum has been linked to stereotypic motor behaviors seen in autism [23]. Postmortem analyses of brain tissue from autistic and typically developing adolescents revealed reduced numbers of astrocytes in the gray and white matter of the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC), accompanied by increased GFAP expression in individuals with autism. Although *NLGN3*—a neuroligin-3 adhesion molecule gene expressed in both neurons and cortical astrocytes and associated with autism—was knocked out in cerebellar astrocytes (Bergmann glia) in mice, this did not affect synapse number, function, or astrocyte morphology in the cerebellum. However, it did result in altered gene expression among other cerebellar cell types [24].

In mouse models with a deficiency in *neuroligin-4* (NLGN4), another cell adhesion molecule, a reduction in microglial cell number and morphological abnormalities have been observed. In male mice specifically, increased purinergic signaling and impaired microglial energy metabolism were reported in the hippocampal CA3 region. Following administration of estradiol to male mice, improvements in microglial function and morphology were noted [25]. Microglia exert inhibitory effects on neuronal and astrocyte function via neuroligin-4 signaling. Given the increased neuroinflammation observed in autism, it is likely that microglia are directly involved in the pathological process. A positive feedback loop involving the reciprocal release of various factors

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between astrocytes and microglia may lead to increased neuronal inflammation. At the same time, these glial cells help maintain the balance between pro-inflammatory and anti-inflammatory responses. Immunological factors of glial origin mediate the inflammatory responses to environmental stress in individuals with autism, in the context of underlying genetic variations [26].

Microglia play a central role in neuroinflammation within the brain, while astrocytes support microglia as part of the brain's immune system. Microglia produce several key molecules involved in neuronal function, such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and interleukins. They also secrete pro-inflammatory and potentially neurotoxic molecules like nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). Another crucial function of microglia is synaptic pruning. Considering that impaired synaptic pruning has been implicated in the pathogenesis of autism, this function is of particular importance [27]. The hypothesis that increased pro-inflammatory cytokines contribute to the development of neurodevelopmental disorders has gained significant attention in recent years. One such cytokine under investigation is interleukin-1 (IL-1), whose signaling pathways are thought to play a role in the development of autism. In a mouse study, blocking the IL-1 receptor in microglia led to increased mTOR signaling activity and impaired synaptic phagocytosis, resulting in an excessive number of synapses and the emergence of autism-like behaviors [28]. Another study demonstrated elevated levels of IL-1β, a pro-inflammatory cytokine released by glial cells, in the brain tissues of individuals with autism [29]. Contactin-associated protein-like 2 (CASPR2) has been identified as a fetal neuronal surface antigen targeted by anti-brain antibodies found in mothers of children with autism. Intrauterine exposure to CASPR2-IgG antibodies has been shown to activate fetal microglia, disrupt glutamatergic synapses in the somatosensory cortex, and contribute to autism development [30]. The impaired synaptic elimination function of these microglia resulted in synaptic overabundance in the cortex and an increased excitation-to-inhibition ratio [31]. Additionally, mutations or dysfunction in genes involved in the negative feedback regulation of protein synthesis—such as *PTEN*, *TSC1*, and *TSC2*, which interact with proteins like eIF4E and mTORC1—have also been linked to autism [32].

In embryos genetically predisposed to autism, exposure to inflammation-triggering environmental stressors (e.g., infections, toxins, medications) or maternal immune responses may lead to increased microglial activation, disrupted synaptogenesis, and ultimately, the emergence of autism [49]. In Rett syndrome, which co-occurs with autism, loss of function in the X-linked *MECP2* gene results in abnormalities in dendritic and synaptic structures. This dysfunction is not limited to neurons; loss of *MECP2* function in microglia has also been implicated in the pathogenesis. Studies have shown that microglia lacking *MECP2* exhibit impaired phagocytic abilities, thereby affecting synaptic pruning processes [33]. In another study, *MECP2*-deficient microglia were found to secrete excessive glutamate, leading to dendritic morphological changes and synapse loss [34]. Increased microglial density, elevated levels of IL-6 and TNF-α, disrupted microglial morphology, and abnormalities in pruning-related receptors have been reported in the brains of individuals with autism [35].

Synaptic dysfunction—including disruptions in the synthesis, localization, and function of synaptic proteins—is considered one of the primary mechanisms underlying autism, and autism spectrum disorder (ASD) is therefore often classified as a "synaptopathy"[36] . During brain development, synapse elimination and maturation are regulated primarily through microglia-mediated pruning and phagocytosis. Impaired function of *autophagy-related gene 7 (ATG7)* prevents microglia from eliminating phagocytosed synapses (synaptosomes), leading to synaptic overabundance and autistic behaviors [37]. In the brains of individuals with autism, particularly during the period of intense synaptic pruning (ages 5–23), reduced numbers of TREM2-positive microglia have been found, especially in the CA1 region of the hippocampus. This results in impaired synapse elimination and decreased connectivity between the prefrontal and hippocampal regions, which may underlie social deficits and repetitive behaviors [38].

Dysfunction in the NOTCH signaling pathway, which regulates neural stem cell proliferation and differentiation during central nervous system development, has also been implicated in autism.

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Aberrant microglial protein synthesis and increased autophagy driven by NOTCH signaling may impair synapse development and exacerbate neuroinflammation by enhancing microglial activation [39]. Disrupted expression of *complement component 3* and *complement receptor 3*genes has been shown to impair microglial synaptic pruning during fetal and postnatal development, leading to abnormal synaptic function potentially associated with autism [40]. A review of 14 studies reported that neuroinflammation contributes to autism pathogenesis, noting increased microglial numbers and density across various brain regions, along with altered morphology and function [41].

Mutations in *PTEN*, a gene associated with autism, have been linked to microglial alterations that affect synaptic pruning. Additionally, in Rett syndrome—which is classified within autism spectrum disorders (ASD)—and in other neurodevelopmental conditions often comorbid with autism, such as tuberous sclerosis complex, Fragile X syndrome, and Down syndrome, changes in microglial phagocytic functions, cytokine responses, transcriptional profiles, morphology, and cell numbers have been reported [42]. Loss of function in *plasticity-related gene 3* (PRG3), which activates the Wnt/β-catenin signaling pathway, has been shown to disrupt microglial activity.

Environmental factors such as viral infections, exposure to heavy metals, and maternal obesity may trigger maternal immune activation, which can lead to glial cell-mediated inflammation in the fetal brain and reduced neurogenesis. These processes may also cause a decrease in the number of Purkinje cells in the cerebellum, contributing to the development of neurodevelopmental disorders like autism [43]. Maternal immune activation during pregnancy is considered a risk factor for autism. During the intrauterine period, when the blood-brain barrier is not yet fully mature, maternal antibodies and cytokines targeting fetal brain antigens can adversely affect fetal synaptic homeostasis and neurogenesis. Animal studies have shown that offspring exposed to maternal immune activation exhibit autistic-like traits, including social deficits, insistence on sameness, and anxiety [44].

From the perspective of ASD pathogenesis, the balance between pro- and anti-inflammatory cytokines released by microglia is critical for the formation, differentiation, and myelination of oligodendrocytes. Maternal immune activation, exposure to toxins, microbiota dysbiosis, and infections can activate microglia and impair oligodendrocyte function. Furthermore, the presence of autism-risk genetic alterations in both microglia and oligodendrocytes may contribute to disease mechanisms. The timing and severity of these processes may influence the degree of cognitive impairment and symptom severity observed in autism [45]. MRI and DTI studies have reported white matter abnormalities and myelin deficits in children and adolescents with autism. During the first two years of life, white matter volume in autistic individuals shows excessive growth, but this is followed by a reduced trajectory compared to typically developing controls in later years. Animal studies using autism mouse models have shown an increased number of oligodendrocytes and premature myelination in the frontal cortex [46]. Oligodendrocyte progenitor cells derived from autism mouse models exhibited increased proliferation and premature maturation in culture. However, many of these excessively proliferated progenitor cells underwent apoptosis and produced abnormal myelin that failed to adequately ensheath axons. In another animal model study, reduced oligodendrocyte and myelin density was observed particularly in brain regions related to social behavior, including the prefrontal cortex, piriform cortex, and basolateral amygdala [47].

One hypothesis regarding mechanisms leading to myelin defects in autism involves autoimmune reactions that damage key myelin proteins such as myelin basic protein (MBP). Pitt-Hopkins syndrome is a neurodevelopmental disorder characterized by language delay, intellectual disability, and autism, caused by a loss of function in the *TCF4* gene located on chromosome 18, which plays a role in oligodendrocyte maturation [48]. Analyses of *TCF4* mutant mice and postmortem patient brains revealed increased numbers of oligodendrocyte progenitor cells in the prefrontal cortex, decreased numbers of mature oligodendrocytes, and reduced myelin levels [49]. Heterozygous deletions in the *ANKS1B* gene cause ANKS1B neurodevelopmental syndrome (ANDS), a rare condition associated with autism spectrum disorder, attention-deficit/hyperactivity disorder, and impairments in speech and motor skills. The *ANKS1B* gene encodes the AIDA-1 protein, which regulates synaptic plasticity [50]. In a mouse model study, *ANKS1B* deficiency led to

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impaired oligodendrocyte maturation and myelination, consistent with white matter abnormalities observed in individuals with ANDS. Furthermore, selective deletion of *ANKS1B* in oligodendrocytes alone resulted in diminished social preference and emotional reactivity. In the same study, the antihistamine clemastine—shown to promote oligodendrocyte maturation and myelination—was able to rescue social deficits in *ANKS1B*-deficient mice [51]. In mice with mutations in the *SHANK3* gene, disruptions were found in glutamate signaling and myelin production within oligodendrocytes, accompanied by white matter abnormalities and motor deficits [52].

The part of this review aimed to present a comprehensive perspective on autism through the lens of neuroglial function, drawing upon recent research. As discussed above, autism spectrum disorders clearly arise from complex interactions between genetic, molecular, immunological, and environmental factors, with neuroglial cells playing crucial roles in pathogenesis. A deeper understanding of the involvement of neuroglial cells in the onset, progression, and manifestation of the disorder holds promise for improving our knowledge and advancing treatment strategies for autism.

2. The Role of Neuroglia in Intellectual Disability

Intellectual disability (ID), previously referred to as mental retardation, is a neurodevelopmental disorder that emerges during the developmental period and is marked by notable impairments in both intellectual functioning and adaptive behaviors [53]. These impairments, which must be evident in childhood or adolescence, represent the core features of the disorder and are critical for diagnosis.

Epidemiological studies suggest that ID affects approximately 1% to 3% of the population, although prevalence rates may vary by geographic and sociodemographic factors [54,55]. The DSM-5 estimates the prevalence of intellectual disability at around 1% in the general population, with severe forms occurring in approximately 6 out of every 1,000 individuals [53].

According to the DSM-5 diagnostic criteria, a diagnosis of intellectual disability requires the presence of all three of the following conditions [53]:

1. Deficits in intellectual functioning – Including limitations in reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience.
2. Impairments in adaptive functioning – Manifesting as significant limitations in personal independence and social responsibility across communication, social participation, and independent living.
3. Onset during the developmental period – Symptoms must be evident before the age of 18.

Clinically, the diagnosis of intellectual disability is based on significantly below-average cognitive and adaptive functioning, as determined through comprehensive clinical evaluation and standardized, individually administered assessment tools. These tools must be norm-referenced and psychometrically validated for the relevant age group, with deficits becoming apparent during the early developmental stages, from infancy to late adolescence. [53,56]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), intellectual disabilities are grouped within the broader category of Neurodevelopmental Disorders. The manual delineates three specific diagnostic entities under this classification: (I) Intellectual Disability, which is further specified as mild, moderate, severe, or profound; (II) Global Developmental Delay (GDD); and (III) Unspecified Intellectual Disability.[53]

The term Unspecified Intellectual Disability is used in DSM-5 for individuals older than five years who are presumed to have intellectual impairment but are unable to complete standardized assessments due to sensory impairments (e.g., blindness, deafness) or the presence of co-occurring psychiatric conditions that interfere with evaluation.

The diagnosis of Global Developmental Delay is applied to children under the age of five who exhibit significant delays in multiple developmental domains and who, due to age-related limitations

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or emerging developmental concerns, cannot be adequately evaluated through standardized testing methods.[53]

Intellectual functioning is typically assessed using standardized intelligence tests, which yield an intelligence quotient (IQ) as a composite score reflecting cognitive ability. These tests are norm-referenced, with a population mean of 100 and a standard deviation of 15. An IQ score of approximately 70 or below—representing performance two standard deviations beneath the mean—is generally indicative of significant cognitive impairment and is one of the key criteria considered in the diagnosis of intellectual disability. [57]

The severity of intellectual disability (ID) has historically been classified based on IQ scores, with approximate distributions as follows:

- Mild ID: IQ between 50–70 (comprising approximately 85% of cases)
- Moderate ID: IQ between 35–50 (about 10%)
- Severe ID: IQ between 20–35 (around 4%)
- Profound ID: IQ below 20 (approximately 1%)

However, contemporary diagnostic criteria no longer rely solely on IQ scores. An individual with an IQ below 70 may not meet the criteria for ID if their adaptive functioning is within an adequate range. Conversely, some individuals with average or even above-average IQs may demonstrate profound impairments in adaptive functioning, qualifying them for an ID diagnosis. Thus, current conceptualizations emphasize adaptive behavior as a core component of diagnosis [58].

Adaptive functioning is typically evaluated using standardized instruments such as the Adaptive Behavior Assessment System [59]. This tool assesses performance across social and practical domains, offering a comprehensive measure of an individual's capacity for communication, social engagement, and independent living. These domains are essential for determining the extent to which an individual can meet the demands of everyday life.[60]

The etiological framework of intellectual disability (ID) encompasses both genetic and environmental factors .Genetically, several well-characterized syndromes contribute to ID. These include Down syndrome (DS), resulting from an extra copy of chromosome 21 [61]; Williams syndrome, associated with a deletion at 7q11.23 on the long arm of chromosome 7[62] Fragile X syndrome (FXS), caused by a mutation and loss of the FMR1 gene product [63]; Rett syndrome (RS), due to mutations in the MECP2 gene on the X chromosome [64]; and tuberous sclerosis (TS), resulting from mutations in TSC1 and TSC2 genes [62].

On the environmental side, malnutrition, traumatic brain injury, maternal perinatal infections, and early childhood central nervous system infections have been implicated in ID development [65].

Traditionally, the pathophysiology of intellectual disability (ID) has been primarily attributed to neuronal dysfunction. However, in recent years, the critical roles of glial cells—particularly astrocytes, microglia, oligodendrocytes, and NG2 glia—in the development of cognitive functions have been increasingly recognized, highlighting that these central nervous system components are as essential as neurons [66]. These cells are not merely passive structural supporters; rather, they actively participate in vital neurobiological processes such as synaptogenesis, synaptic pruning, myelination, neuroinflammation, and metabolic homeostasis [67]

Disruptions in glial function during critical developmental periods leave lasting imprints across the neurodevelopmental trajectory and contribute fundamentally to the neurobiological basis of intellectual disability [68]. Increasingly, scholars argue that intellectual disability should be reconceptualized not merely as a "neuronal deficit" but also as a "glial dysfunction" [69]

This section presents a systematic evaluation of intellectual disability through the lens of glial pathophysiology. The roles of astrocytes, microglia, oligodendrocytes, and other glial cell types in the pathogenesis of intellectual disability will be examined, with particular attention to their involvement across genetically, environmentally, and metabolically mediated subtypes.

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2.1. Astrocytes

Astrocytes maintain cerebral homeostasis through regulation of metabolic processes, neurotransmitter uptake, ion and water balance, and neurovascular coupling[70–72]. In response to pathological stimuli, astrocytes undergo reactive gliosis, marked by altered gene expression, cytoskeletal remodeling, and both neurotoxic and neuroprotective effects [73–75]. These include glutamate clearance, antioxidant defense, BBB maintenance, and neurotrophic support [71,76,77].

Although astrocytes were long considered merely structural support cells, their roles in neurodevelopment have been dramatically re-evaluated in recent years. Astrocytes are now recognized as central regulators of key processes such as synaptic transmission, potassium buffering, glutamate uptake, neurotrophic support, and energy metabolism. These functions are crucial for understanding the micro-level disruptions underlying intellectual disability, positioning astrocytes as key players in its pathophysiology. [67]

The astrocyte–neuron–endothelial cell interaction within the neurovascular unit allows astrocytes to modulate cerebral blood flow and participate in inflammatory regulation[78–80] . Their resilience under metabolic stress and broad functional repertoire make them essential players in CNS development and repair, especially in disorders involving glial dysfunction such as intellectual disability [72,81].Recent studies have also emphasized the potential contribution of astrocytic dysfunction in these disorders, suggesting that astrocytes may play a pathophysiological role in the development of ID.

Recent investigations into the morphology and function of glial cells have highlighted the pivotal role of astrocytic abnormalities in the pathogenesis of intellectual disability (ID) [82]. Initially, Rett syndrome (RS) was attributed to MeCP2 deletions in neurons [83,84]; however, subsequent studies demonstrated that MeCP2 loss in astrocytes also impairs their ability to support neuronal development [85]. Similarly, co-culture experiments revealed that astrocytes derived from Fragile X Syndrome (FXS) models hinder dendritic and synaptic growth in neurons [86,87]. Emerging evidence suggests that the neuronal abnormalities observed in genetic disorders such as DS and FXS play a central role in their clinical presentation [88].

Moreover, astrocytes from Down syndrome (DS) models have shown toxic effects on neurons both in vitro and in vivo, further supporting the notion that astroglial dysfunction contributes to ID-related neuropathology [89]. While these findings underscore a strong link between astrocyte pathology and neuronal development in ID, further research is warranted to clarify the mechanisms involved.

For instance, in Down syndrome models, overexpression of the astrocyte-derived protein S100B has been shown to increase oxidative stress and negatively impact neuronal survival [90]. In Fragile X syndrome, impaired inter-astrocytic communication directly affects synaptic plasticity and contributes to learning difficulties [91]. The presence of FMRP expression not only in neurons but also in astrocytes further supports the notion that the pathophysiology of such disorders extends beyond neurons alone [92].

Reactive astrocytes contribute to synaptic instability and promote neuronal apoptosis, primarily through the secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [93].

Beyond their contribution to neuroinflammation, astrocytes critically regulate neuronal ion homeostasis—a process essential for maintaining proper electrophysiological function. Disruptions in this regulation are frequently observed in intellectual disability (ID) and related neurodevelopmental disorders, often leading to neuronal hyperexcitability and cell death [94].

In Down syndrome (DS), astrocytes display spontaneous calcium oscillations, which are associated with reduced excitability in cocultured neurons [95]. Additionally, decreased zinc levels in DS astrocytes impair synaptic transmission and neuronal communication [96].

Tuberous sclerosis (TS) models have demonstrated a downregulation of potassium channels on astrocyte membranes, compromising their potassium-buffering capacity. The breakdown of inter-astrocytic gap junctions further disrupts potassium redistribution, ultimately leading to abnormal

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neuronal excitation and seizures characteristic of TS[97,98]. Other astrocyte-specific ion channels, such as TREK-1 and Bestrophin-1 (BEST1), mediate both fast and slow glutamate release, affecting neighboring neurons [99]. Connexin hemichannels also modulate extracellular ATP and glutamate levels, further influencing synaptic signaling and CNS activity [100].

Collectively, these alterations in astrocytic ion channels—including K^+ channels, BEST1, and connexins—contribute significantly to the pathogenesis of ID, although the underlying molecular mechanisms remain to be fully elucidated [101]. Metabotropic glutamate receptor 3 (mGluR3), involved in calcium signaling, is also downregulated in Rett syndrome (RS) astrocytes, which may further destabilize synaptic environments [102].

Moreover, dysregulation of astrocytic glutamate transport has been implicated in the loss of excitatory–inhibitory balance, particularly in forms of intellectual disability such as Fragile X and Rett syndromes [69]. This imbalance predisposes individuals to epileptiform activity and contributes to impairments in attention and learning processes.

Astrocytic dysfunction in glutamate handling represents another crucial mechanism in ID. In fragile X syndrome (FXS), impaired mGluR5 signaling reduces GLT-1 expression, thereby limiting glutamate uptake and disturbing glutamate–GABA balance—ultimately causing neurotoxicity and dendritic atrophy [103,104]. Similarly, in TS models, expression of the glutamate transporters GLT-1 and GLAST is diminished, resulting in elevated extracellular glutamate, excitotoxicity, and compromised synaptic plasticity [105,106].

However, reactive astrocytes do not exclusively exert pathological effects. In certain contexts, they may confer neuroprotection. For instance, in both RS and DS models, upregulated mGluR5 expression in astrocytes enhances glutamate clearance, thereby preventing excitotoxic neuronal injury and supporting synaptic integrity [107,108].

Astrocytes are further implicated in glutamate metabolism, a process essential for maintaining excitatory-inhibitory balance in the CNS. In FXS models, downregulation of GLT-1 and a disrupted glutamate/GABA ratio are associated with shortened dendritic length and impaired synaptic architecture [109].

Astrocytes also play a critical role in guiding synaptic pruning during development. When pruning does not occur with proper timing, it can result in synaptic excess and inefficiency at the network level [68].These findings suggest that intellectual disability may not only stem from synaptic deficits, but also from errors in developmental timing and the absence of precise glial surveillance.

In conclusion, astrocytes play an active and determinant role in the pathophysiology of intellectual disability, rather than being passive bystanders. Therefore, therapeutic strategies targeting glial cells must comprehensively address the metabolic, neurotrophic, and synaptic functions of astrocytes. This emerging focus represents a promising avenue for future interventions in intellectual disability [110]

2.2. Microglias

Microglia originate from yolk sac-derived mesodermal precursors and infiltrate the developing brain during early embryogenesis [111,112]. They play essential roles in neurodevelopment, including neurogenesis, synaptogenesis, apoptosis, axon guidance, and regulation of vascular architecture [113,114]. A specific subset of CD11c+ microglia has been shown to promote oligodendrocyte maturation and myelination via IGF-1 secretion, suggesting a direct role in white matter integrity [115,116]. Microglia are dynamic and plastic cells that can adopt either pro-inflammatory (M1-like) or anti-inflammatory (M2-like) phenotypes in response to stimuli [80,117]. Through these states, they influence cytokine signaling, blood-brain barrier permeability, and glial activation, positioning them as central mediators of both immune defense and potential contributors to neurodevelopmental disorders such as intellectual disability [111,118].

Although microglia have long been identified as the resident immune cells of the central nervous system, growing evidence highlights their active participation in neurodevelopmental processes, including synaptic pruning, plasticity modulation, and the refinement of neuronal circuits. In the

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context of intellectual disability, several studies have demonstrated that microglial dysfunction may impair early synaptogenesis and disrupt the maturation of neural networks, potentially contributing to long-term cognitive deficits [67,119–121]

Synaptic pruning carried out by microglia during early childhood is crucial for the refinement of cortical circuits. Both excessive and insufficient pruning may underlie the neuroanatomical and functional basis of intellectual disability. [122].

In X-linked intellectual disability syndromes such as Rett syndrome, dysregulated glutamate release mediated by microglia may directly damage neuronal dendrites [123]. Similarly, impaired expression of the MeCP2 gene at the microglial level leads to insufficient support for neuronal function In these models, genetic correction of microglia alone has been sufficient to reduce neuronal damage, highlighting the therapeutic potential of targeting microglial function. [124].

Moreover, microglia act as both initiators and sustainers of the neuroinflammatory processes often accompanying intellectual disability. Their chronic activation disrupts cytokine homeostasis, thereby contributing to a neurotoxic microenvironment detrimental to neuronal function [125].

Increased levels of pro-inflammatory markers documented in genetic forms of intellectual disability—particularly Fragile X and Down syndrome—reinforce the hypothesis that widespread microglial dysfunction contributes to the systemic pathophysiology of these conditions [126,127].

Microglia have also been shown to contribute indirectly to intellectual disability through their interactions with oligodendrocytes during the process of myelination. This relationship is particularly critical during developmental periods and plays a key role in maintaining synaptic integrity [128,129].

Collectively, these findings demonstrate that microglia are implicated in intellectual disability not only through inflammatory pathways, but also via synaptic, metabolic, and genetic mechanisms.

Targeting microglial function during early developmental stages may represent a strategic intervention point for promoting neurodevelopment and preventing the progressive components of intellectual disability.

2.3. Oligodendrocytes

Oligodendrocytes are glial cells responsible for the formation of the myelin sheath around axons in the central nervous system. A single oligodendrocyte may myelinate up to 30 axonal segments, a process essential not only for rapid action potential conduction but also for the maturation and maintenance of cognitive functions [130]. The communication between oligodendrocytes and axons is mediated through ligand- and voltage-gated ion channels, enabling bidirectional interactions, particularly during early development [131–133]. This ensures the preservation of oligodendrocyte integrity and protects them from neurotoxic environments caused by excessive neurotransmitter release or ion channel activity [132,134].

In pathological states, oligodendrocyte dysfunction often results in demyelination, which is a prominent feature in aging, neurodegenerative diseases, and psychiatric conditions such as schizophrenia, bipolar disorder, and Alzheimer's disease [135–137]. Myelin loss in these contexts may underlie deficits in neural connectivity and cognitive processing, contributing to the pathogenesis of intellectual disability [137].

In various genetic syndromes associated with intellectual disability—such as Down syndrome, Prader-Willi syndrome, and Tuberous Sclerosis—disruptions have been observed in oligodendrocyte differentiation, proliferation, or myelination processes. [138]. Myelin abnormalities occurring particularly during developmental periods may lead to persistent dysfunctions in cortico-subcortical networks, often resulting in impairments that are difficult to reverse.

In mouse models carrying the DYRK1A mutation, a delay in early stages of oligodendrocyte development and a reduction in the expression of myelin-associated proteins have been observed. These alterations have been linked to delayed motor coordination and impaired cognitive performance. [139].

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Environmental factors also influence oligodendrocyte function. In particular, early perinatal hypoxia, heavy metal toxicity, and alcohol exposure have been shown to suppress the differentiation of oligodendrocyte progenitor cells, leading to permanent white matter damage. [140]. Many of these mechanisms are particularly relevant in explaining the underlying pathophysiology of non-genetic cases of intellectual disability.

Moreover, the communication network established between oligodendrocytes, microglia, and astrocytes is critical for maintaining myelin integrity. Recent studies have shown that microglia-derived cytokines can suppress oligodendrocyte maturation, suggesting that a pro-inflammatory microenvironment may exert detrimental effects on the myelination process. [128].

Enriched environmental stimuli during childhood—such as play, language interaction, and physical activity—have been shown to enhance oligodendrocyte activity and promote myelination, which in turn positively influence cognitive outcomes. [141].

These findings underscore the significance of not only cellular but also environmental intervention strategies. Although the role of oligodendrocytes in intellectual disability has often been overlooked, their contribution to myelination and cognitive development—through both genetic and environmental mechanisms—is undeniable. Therefore, it becomes increasingly clear that white matter, and the glial systems that shape it, occupy a central position in the pathophysiology of intellectual disability

2.4. Glial Coordination: The Microenvironmental Basis of Intellectual Disability

The developing brain is not composed solely of neurons; fundamental processes such as synaptogenesis, myelination, maintenance of metabolic homeostasis, and modulation of inflammatory responses are orchestrated by the coordinated actions of glial cells. Disruption of this intricate network of interactions represents one of the most complex yet critical mechanisms underlying intellectual disability [142].

A constant bidirectional signaling exchange exists between astrocytes and microglia. Astrocyte-released molecules such as ATP and glutamate modulate microglial activity, whereas cytokines secreted by microglia—particularly IL-1β and TNF-α—can influence astrocytic calcium waves and gliotransmitter release. The microenvironment shaped by the interaction of these two cell types plays a pivotal role in determining synaptic plasticity [69].

In early childhood, excessive microglial activation leads to the release of pro-inflammatory agents that suppress the maturation of oligodendrocyte progenitor cells, delay myelination, and contribute to the development of intellectual disability [128]. These findings suggest that intellectual disability may result not only from intracellular dysfunctions but also from disruptions in intercellular communication.

2.5. Clinical Implications and Therapeutic Targets of Glial Dysfunction

Over the past decade, growing evidence has challenged the long-held view of glial cells as passive supporters, instead establishing them as active regulators of neurodevelopment [67]. In neurodevelopmental disorders with multifactorial etiologies—such as intellectual disability (ID)—both individual and interactive dysfunctions of glial cells contribute to a complex microenvironmental pathology that shapes the clinical phenotype.

Contemporary literature increasingly shows that treatments focusing solely on neuronal targets often yield limited efficacy. For instance, in animal models of Rett syndrome, restoration of microglial function alone has led to significant behavioral improvements and a reduction in neuronal degeneration [124].This finding offers a compelling example of how glial cells may serve as direct therapeutic targets.

Similarly, in genetic forms of ID such as Fragile X and Down syndrome, disruptions in glial glutamate regulation contribute to an imbalance between excitatory and inhibitory signaling. This disturbance has been linked to co-occurring symptoms including epilepsy, attention deficits, and learning difficulties [91].

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Table 1. Clinical Relevance of Glial Types and Their Biomakers.

Biomarker	Glial Origin	Associated ID Subtypes	Clinical Relevance
GFAP	Astrocytes	Down syndrome	Neuroinflammation marker
S100B	Astrocytes	Fragile X, DS	Oxidative stress, neurotoxicity
IL-1β	Microglia	Rett syndrome	Pro-inflammatory signature
CX3CL1	Neuron–Microglia axis	Various	Synaptic modulation, immune crosstalk

With the increasing detectability of glial biomarkers—such as GFAP, S100B, IL-1β, and CX3CL1—in serum and cerebrospinal fluid, it has been proposed that glial signatures may aid in subclassifying intellectual disability [90]. The clinical application of these biomarkers is expected to gain importance in the coming years, particularly for early diagnosis, risk stratification, and monitoring of treatment response. Glia-targeted pharmacological interventions remain in the experimental stage. However, certain agents such as L-serine, minocycline, and N-acetylcysteine have shown potential in stabilizing glial functions and are currently being tested in models of neurodevelopmental disorders. In parallel, non-pharmacological approaches—including environmental enrichment, physical activity, and play-based therapies—have also been demonstrated to exert beneficial effects on glial plasticity [143].

In conclusion, intellectual disability (ID), as a multidimensional neurodevelopmental disorder, cannot be fully explained by neuronal degeneration alone. This review has highlighted the central roles of glial cells—particularly astrocytes, microglia, and oligodendrocytes—in the pathophysiology of ID. In both genetically and environmentally driven forms of ID, glial dysfunctions directly affect cognitive performance by disrupting synaptic organization, myelination, and neuroinflammatory processes. Disruptions in inter-glial communication further compound these effects, contributing to the heterogeneity observed in clinical presentations. Therefore, a comprehensive assessment of the glial system is essential in the diagnosis, monitoring, and treatment of ID.

3. Attention Deficit/Hyperactivity Disorder and Neuroglia

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and adolescents, characterized by inattention, hyperactivity, and impulsivity [144]. The DSM-5 describes three clinical presentations of ADHD: predominantly inattentive, predominantly hyperactive/impulsive, and combined type. Generally, the most frequently observed types among patients are the inattentive and combined types; however, in children aged 3–5 years, the hyperactive/impulsive type is more prominent [145,146].

The prevalence of ADHD in children and adolescents ranges between 1.0% and 7.0% [147]. In this age group, ADHD is more common in boys than girls, with male-to-female ratios ranging from 3:1 to 10:1; however, this distribution becomes more balanced in adulthood [148,149].

The etiology of ADHD is considered multifactorial and polygenic. Nevertheless, environmental factors such as exposure to polychlorinated biphenyls and lead, prenatal exposure to organophosphates, low birth weight, prenatal nicotine exposure, stress, and alcohol consumption are also associated with increased ADHD prevalence [150]. Genetic contribution to ADHD is among the highest of all psychiatric disorders [151]. The heritability of ADHD is estimated to be between 70% and 80%[152,153] . These estimates are consistent across childhood and adolescence [154] and appear to be similar for both boys and girls [155].

The pathophysiology of ADHD is also associated with oxidative stress and neuroinflammation, stemming from the imbalance between oxidants and antioxidants, catecholaminergic dysregulation, medications used in treatment, and genetic and environmental factors. All of these can exacerbate oxidative stress and neuroinflammation, triggering a vicious cycle that may worsen symptoms [156]. Studies have shown a relationship between cytokines and ADHD symptoms in children and adolescents. Elevated levels of IL-16 (associated with hyperactive-impulsive symptoms) and IL-13 (associated with inattention) have been found [157]. Serum IL-6 levels are also significantly higher in

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children with ADHD compared to controls [158]. Inflammatory cytokines caused by stress or allergic inflammation are hypothesized to affect the maturation of the prefrontal cortex and alter neurotransmitters involved in ADHD [159].

Another possible pathophysiological mechanism associated with ADHD involves dysregulation in monoaminergic neurotransmission systems, particularly dopaminergic and noradrenergic pathways. Both excessive activity (e.g., during stress) and insufficient activity (e.g., drowsiness) disrupt the functioning of these systems [160]. Studies also implicate serotonergic [161], glutamatergic [162] and GABAergic [163] systems in ADHD, suggesting that altered levels of these neurotransmitters are linked to the disorder. Experimental models have shown that methylphenidate can restore impaired glutamatergic transmission in the prefrontal cortex and alleviate behavioral symptoms of ADHD, possibly through AMPA glutamatergic receptors [164]. The mechanisms of action of drugs used in ADHD treatment also emphasize the role of these neurotransmitter systems, as these medications typically target related biological pathways (e.g., methylphenidate acts via DAT and NET)[165].

A potential association between specific antibodies and immune system dysregulation in ADHD has been investigated, with significant positive immunoreactivity against Purkinje cells observed in the cerebellum of children with ADHD [166]. Additionally, increased levels of antibodies against Purkinje cells and elevated serum levels of interleukins IL-6 and IL-10 have been found in ADHD patients [167]. Moreover, high levels of autoantibodies against dopamine transporters [168] and basal ganglia have been identified in these individuals [169].

More than 60% of individuals with ADHD frequently present with at least one comorbid psychiatric disorder, most commonly depression, anxiety, and disruptive behavior disorders [170–172]. Autism spectrum disorder (ASD) is also frequently comorbid with ADHD [173]. Furthermore, patients with ADHD show higher rates of obesity, sleep disorders, asthma, autoimmune and inflammatory diseases, as well as other somatic and metabolic problems [174].

Treatment options may include non-pharmacological, pharmacological, or combined approaches. Non-pharmacological treatments involve stimulating specific neuropsychological domains related to ADHD through psychosocial, cognitive, and behavioral therapies. These are particularly recommended as first-line or adjunct treatments for children aged 6 and under and for those with less severe symptoms [175–177]. However, most studies indicate that these psychotherapeutic interventions are less effective and less definitive in reducing the core symptomatology of ADHD compared to pharmacological treatments [175].

Clinical guidelines generally recommend stimulant medications (lisdexamfetamine and methylphenidate) as the first-line pharmacological treatment for patients aged 6 years or older with moderate to severe symptoms. For patients who cannot tolerate or do not respond to these medications, non-stimulants such as atomoxetine are considered second-line treatments due to their different side effect profiles and varying efficacy. These are followed by adrenergic agents (e.g., clonidine and guanfacine) or alternative non-stimulant medications such as tricyclics and bupropion [176,178–180].

Neuroglial cells are primarily divided into three types: astrocytes, oligodendrocytes, and microglia [181]. These are further classified based on origin into two groups: macroglia and microglia. Macroglia—which include astrocytes and oligodendrocytes—are derived from the neuroectoderm, while microglia originate from the mesoderm [182,183]. Microglia are the resident immune cells of the central nervous system (CNS) and serve as the principal mediators of neuroinflammation [184]. Astrocytes also play similar roles in immune functions [185].

In their resting state, glial cells are known to secrete anti-inflammatory cytokines (such as IL-4 and IL-10), neuronal growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-4/5 [186,187]. Moreover, microglia fulfill neuroprotective roles by contributing to neurogenesis and the maintenance of synaptic homeostasis [188].

Upon activation, glial cells undergo morphological changes and respond to various pathological conditions. Activated glial cells release pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-

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α. These cytokines—especially when released by microglia—can exert cytotoxic effects on neurons and other glial cells, particularly oligodendrocytes [189]. Excessive glial activation can trigger systemic inflammation in the brain, leading to synaptic elimination and dysfunctional synaptic plasticity [190]. Pro-inflammatory cytokines can induce excitotoxicity through increased glutamate release, changes in ion channel expression, and immune activation of the blood-brain barrier. It has been suggested that elevated levels of cytokines in the bloodstream during the neonatal period may lead to neurodevelopmental disorders in children due to immune activation [191].

3.1. Astrocytes and ADHD

Astrocytes play a central role in maintaining physiological homeostasis in the brain [192]. Their major functions include regulating metabolic processes in brain tissue (such as glucose metabolism, ion concentration, water content, and pH balance), providing structural support (formation of functional barriers), facilitating brain development (proliferation, gliogenesis, neuroplasticity), intercellular communication (gliotransmission, regulation of synaptic transmission and plasticity), neuroprotection, and cerebral defense (e.g., regulation of cerebral blood flow, protection against glutamate-induced excitotoxicity, and inflammatory responses) [181].

Astrocytes have a crucial role during early postnatal periods—critical developmental windows characterized by high plasticity in the brain. During these stages, neural circuits are highly sensitive to environmental and experiential stimuli, affecting cognitive and behavioral outcomes. The formation, differentiation, and maturation of astrocytes occur in these critical periods [193]. Numerous reviews [194], have comprehensively examined the role of astrocytes in processes such as synaptic pruning, maintaining the excitation/inhibition balance, and responding to environmental stimuli. Disruptions during these critical periods have been suggested to contribute to the development of neurodevelopmental and neuropsychiatric disorders [193].

Astrocytes are essential in modulating synaptic transmission, mediating tonic inhibition via GABA, glutamate metabolism, and supplying nutrients to neurons [195,196]. Impairments in the astrocytic modulation of neuronal energy metabolism have been proposed as a potential mechanism in the etiology of ADHD [197].

A recent study demonstrated that astrocyte-specific disruption of SynCAM led to ADHD-like behavioral symptoms in mice [198]. This finding suggests that impaired communication between astrocytes and neurons may contribute to ADHD-related symptoms.

G-protein-coupled receptor kinase-interacting protein-1 (GIT1) is a multifunctional signal adaptor [199] associated with ADHD [200]. Git1−/− mice exhibit ADHD-like phenotypes, such as abnormal theta rhythms in EEG, hyperactivity, and impaired recognition memory—all of which are reversed with amphetamine treatment [200]. A study showed that Git1−/− mice had significant astrogliosis in brain regions associated with the basal ganglia circuitry, along with changes in GABA and parvalbumin expression. These structural and functional alterations may represent a neural correlate of the ADHD-like behavioral symptoms reported in these mice. This is consistent with the previously proposed dopamine hypothesis, as dopamine is closely linked to basal ganglia function [201].

In a mouse model study titled "Gi GPCR-Mediated Bidirectional MSN-Astrocyte Interactions," medium spiny neurons (MSNs) were observed to release GABA when depolarized to upstate levels. This GABA activated Gi protein-coupled GABA-B receptors (GPCRs) on striatal astrocytes, leading to increases in intracellular calcium (Ca^{2+}) signaling. Using DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technology and clozapine-N-oxide (CNO), selective stimulation of the Gi pathway in astrocytes triggered Ca^{2+} signaling, increased expression of the astrocyte-derived synaptogenic molecule thrombospondin-1 (TSP1), and strengthened excitatory synapse formation and transmission. This cycle resulted in phenotypes of hyperactivity and attention deficit in mice [202].

Growing evidence suggests that certain genes may play a role in ADHD pathophysiology [203]. One such gene is NDRG2 (N-myc downstream-regulated gene 2), which is involved in cell

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proliferation and differentiation and is considered a tumor suppressor gene [204]. An abnormal haplotype on chromosome region 14q11.2 has been associated with ADHD through NDRG2 [205]. This gene is predominantly expressed in astrocytes within the central nervous system (CNS). NDRG2 affects astrocyte morphology—its silencing leads to shortened astrocytic processes [206]. It also plays a critical role in facilitating astroglial glutamate uptake [207]. NDRG2 is expressed in several brain regions associated with memory, including the cerebral cortex, hippocampus, and olfactory bulb [208]. In NDRG2 knockout (NDRG2−/−) mouse models, behavioral symptoms such as hyperactivity, impulsivity, and inattention have been observed. These disturbances were found to be linked to insufficient glutamate clearance and were alleviated by NDRG2 protein therapy—but not by methylphenidate [209]. The administration of NDRG2 peptide has been shown to ameliorate hyperactivity observed in Ndrg2−/− mice, offering a potential alternative treatment for ADHD patients who do not respond to methylphenidate therapy [210]. A specific single nucleotide polymorphism (SNP) in the NDRG2 gene, rs1998848, has been associated with ADHD susceptibility and reduced NDRG2 expression. Children who are heterozygous for this SNP show a significantly higher risk of ADHD compared to those with the homozygous genotype, and their peripheral blood cells exhibit lower levels of NDRG2 mRNA [209].

Currently, the first-line treatment for ADHD consists of psychostimulants (e.g., methylphenidate and amphetamines) that target dopaminergic and noradrenergic pathways [211]. However, considering the potential contribution of glial dysfunction, future research should explore pharmacological strategies that enhance astrocyte function or mitigate excessive inflammatory responses, thereby offering a complementary approach to the management of ADHD [212].

3.2. Oligodendrocytes and ADHD

The primary function of oligodendrocytes is the production of the myelin sheath. A single oligodendrocyte can myelinate up to 30 axons, although this number can vary significantly [213]. The close relationship between oligodendrocytes and myelinated axonal segments allows for interaction via ligand- and voltage-gated ion channels and receptors. This interaction is critical for communication between oligodendrocytes and neurons [214–216]. The direct structural relationship influences both the process of myelination and the conduction of action potentials along axons. The contact between oligodendrocytes and neuronal axons maintains the physiological activity of oligodendrocytes and protects cells from damage caused by excessive neurotransmitter accumulation or overactivation of ion channels [214,215].

Ribasés et al. demonstrated an association between CNTFR and ADHD in both children and adults [217]. CNTF is a multifunctional neuropeptide that provides survival and regulatory signals to neurons, astrocytes, and oligodendrocytes, and appears to reduce damage during inflammatory responses. CNTF also plays a fundamental role during nervous system development [218]. In the context of ADHD, which can be conceptualized as a neurodevelopmental disorder, direct involvement of CNTF signaling pathways in pathogenesis appears plausible. Moreover, polymorphisms in cytokine genes may be associated with risk factors for ADHD, such as premature birth and perinatal infection. These changes may alter neuroinflammatory responses, ultimately leading to disruptions in neural circuit development [219].

One neurobiological hypothesis for the developmental origins of ADHD involves a myelination disorder characterized by insufficient production of myelin sheaths by oligodendrocytes [220]. Supporting this, a large-scale genome-wide association (GWA) meta-analysis including over 20,000 ADHD cases identified a significant variant (rs1142027) in the ST3GAL3 gene [221]. This gene is involved in the sialylation process and affects the structure of glycoproteins in neuronal membranes. In mouse models, St3gal3 deficiency has been linked to impaired motor function, cognitive deficits, reduced myelin thickness, and decreased myelin protein levels [222]. These deficits also significantly impact hippocampal neuronal development, synaptic connectivity, and neuronal plasticity. In conclusion, these molecular pathways involving genes such as ST3GAL3 play a critical role in

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understanding the neurodevelopmental impact of oligodendrocyte-related myelination disorders in ADHD.

The emergence of delayed and/or impaired myelination as a prominent pathophysiological mechanism in ADHD also presents a promising target for therapeutic interventions [220].

3.3. Microglias and ADHD

During prenatal and early postnatal stages, microglia play an active role in brain development; they support neurogenesis, gliogenesis (including oligodendrocyte formation), and cerebral vascular development. Microglia also regulate synapse formation and function, neuronal apoptosis and survival, and the process of myelination [223,224]. For these reasons, microglia are thought to play either a causal or contributory role in nearly all brain disorders, ranging from neurodevelopmental conditions to neurodegeneration. In both humans and mice, microglia constitute approximately 10% of the cells in the central nervous system (CNS); however, their density varies across different CNS regions [225,226]

Pyroptosis is a lytic type of cell death triggered by inflammasomes—cytosolic sensors of pathogenic and harmful stimuli [227]. Activated inflammasomes cause the dimerization of pro-CASP1 and its conversion into active CASP1, which subsequently cleaves pro-interleukin-1β (IL-1β) and pro-IL-18 into their mature forms. CASP1 also activates Gasdermin D (GSDMD), inducing pyroptosis, IL-1β release, and inflammation [228,229]. To examine whether CASP1 deficiency could disrupt normal brain function by impairing microglial pyroptosis, behavioral tests were performed on Casp1^-/- mice [230]. These mice did not exhibit autism spectrum disorder-like behaviors (e.g., impaired social interaction, repetitive behavior, or deficits in learning and memory), but instead demonstrated hyperactivity (via open field test), inattention (via 5-choice serial reaction time test), and impulsivity. Notably, during the three-chamber interaction test, the test mice displayed increased climbing behaviors on cylinders containing stranger mice and showed escape tendencies. These inappropriate behaviors were associated with human ADHD.[231]. The researchers then evaluated whether restoring Casp1 expression exclusively in microglia would be sufficient. iCasp1 (Cre-inducible Casp1 expression) mice were crossed with Cx3cr1-Cre mice [232–234]. The resulting Casp1^-/-; iCasp1; Cx3cr1-Cre mice displayed normalized behaviors, indicating that loss of Casp1 leads to ADHD-like behavioral changes, and that restoring Casp1 in Cx3cr1+ cells—including microglia—can reverse these effects.[235]. Similar hyperactivity and impulsivity were observed in mice deficient in pyroptosis-related components such as GSDMD and IL-1 receptor (Il-1r). These findings align with previous studies reporting ADHD-like behaviors in the absence of IL-1 signaling [236–238].

Dopamine (DA) is crucial for motivation and inhibitory control—both impaired in ADHD [212]. Microglia and astrocytes in the striatum and prefrontal cortex regulate dopamine release and reuptake [239]. Inflammatory changes in these glial cells may disrupt dopaminergic metabolism and contribute to ADHD symptoms [240].

Polymorphisms in genes involved in immune signaling and myelination may also increase susceptibility to glial dysfunction in ADHD. For example, variations in inflammatory genes can enhance microglial responses to infections or toxins, worsening attentional deficits [241]. Prenatal alcohol or tobacco exposure may also initiate inflammatory responses that impair glial development, raising ADHD risk [242].

In rats treated with methylphenidate (MP), increased microglial activity was observed in the insular cortex, hippocampus, and thalamus [243]. Chronic MP treatment, through DAT and NET blockade, elevates monoamine levels in the synaptic cleft and alters both dopamine neuron counts in the substantia nigra and the extent of microgliosis [244].

High levels proinflammatory cytokines may affect synaptic plasticity and neurogenesis [245], and impair cognitive processes like working memory and reaction time, which are often affected in ADHD [246]. These cytokines can also perpetuate a cycle of microglial activation, sustaining neuroinflammation and potentially contributing to ADHD pathophysiology [247]. To date, no study

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has directly examined microglial activation in ADHD. This remains a vital area for future research to clarify whether inflammation plays a direct pathogenic role in ADHD [219].

4. Tic Disorders And Neuroglia

Tic disorders are common neuropsychiatric conditions of childhood and adolescence characterized by sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations, which can be voluntarily suppressed to a varying extent for brief periods [248,249]. Tics are often preceded by a premonitory urge, and the phenomenology of tic disorders includes fluctuations over time, suggestibility, and reductions in tic frequency with distraction Motor and vocal tics can be categorized as either simple or complex . Simple motor tics involve only a single muscle group or body part (e.g., face, neck, shoulders, or hands) and are typically short, abrupt, repetitive, and apparently purposeless [250]. Motor tics are most frequently observed in the eyes and mouth regions, followed by the neck and extremities, while involvement of the feet and midline axial structures is least common [251]. Examples of motor tics include eye blinking, eye rolling, wide mouth opening, head tilting, shoulder shrugging, or hand flapping. Phenomenologically, simple motor tics are subdivided into three types: clonic, dystonic, and tonic tics [252]. Clonic tics refer to rapid, brief, shock-like movements such as eye blinking or facial grimacing. Dystonic tics are characterized by slower, sustained abnormal postures, including prolonged upward deviation of the eyes, eye closure, jaw clenching, or torticollis-like head turning. Tonic tics consist of sustained isometric contractions, such as abdominal or limb stiffening [252–254]. Blocking tics are those that transiently interrupt ongoing motor activity or speech without loss of consciousness [255].

Complex motor tics involve coordinated sequences of movements affecting multiple muscle groups and may resemble purposeful actions. Examples include touching, hitting, shaking, kicking, jumping, echopraxia (mimicking others' movements), and copropraxia (performing obscene or socially inappropriate gestures). Simple vocal tics are defined as meaningless sounds generated by the passage of air through the nose, mouth, or throat. Examples include coughing, throat clearing, grunting, animal-like noises, and tongue clicking. Complex vocal tics, by contrast, involve multiple muscle groups and are characterized by the utterance of words, phrases, or even complete sentences. Shouting, echolalia (repeating another person's speech), and coprolalia (uttering socially inappropriate or obscene expressions) are typical examples. Vocal tics are also referred to as "phonic tics" in some literature [254,255].

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), tic disorders are classified into five categories: Provisional Tic Disorder, Persistent (Chronic) Motor or Vocal Tic Disorder, Tourette's Disorder (Tourette Syndrome, TS), Other Specified Tic Disorder, and Unspecified Tic Disorder [256]. For a diagnosis of any of the first three disorders, symptom onset must occur before the age of 18 and the symptoms must not be attributable to another medical condition (e.g., Huntington's disease), substance use, or medication side effects.

Provisional Tic Disorder is diagnosed when motor and/or vocal tics have been present for less than one year since onset. In contrast, both TS and Persistent Motor or Vocal Tic Disorder require that tics have persisted for more than one year, although tic-free intervals may occur during this time. Persistent Tic Disorder is diagnosed when either motor or vocal tics are present during the course of illness. TS is diagnosed when both motor and vocal tics occur at some point during the illness, though not necessarily simultaneously. Compared to individuals with Persistent Motor Tic Disorder, patients with TS tend to exhibit greater tic severity, a higher prevalence of complex motor tics, and more frequent psychiatric comorbidities [257].

DSM-5 also includes Other Specified Tic Disorder (used when the reason for not meeting full criteria is specified) and Unspecified Tic Disorder (used when insufficient information prevents more specific diagnosis) for cases that do not meet the full criteria for the primary tic disorders but still cause clinical concern. Importantly, the severity of tics is not specified within the diagnostic criteria. In contrast to DSM-IV, which required a minimum tic duration of four weeks for Provisional Tic Disorder and no tic-free period longer than three months for TS and Persistent Tic Disorder, these

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duration-related conditions have been removed in DSM-5 [258]. The term "Transient," previously used in DSM-IV, has been replaced with "Provisional" in DSM-5 to reduce conceptual confusion [259]. Additionally, the word "stereotyped" has been removed from the definitions of tic disorders to avoid diagnostic confusion with Stereotypic Movement Disorder. The requirement for tics to cause clinically significant impairment or distress, previously found in DSM-IV-TR, has also been removed, acknowledging that symptoms may not always cause distress. In fact, many children with tics report that comorbid neuropsychiatric conditions are more impairing than the tics [260]

4.1. Epidemiology

Accurately determining the true prevalence of tic disorders (TDs) remains challenging due to factors such as underrecognition of symptoms, low rates of medical consultation, underdiagnosis in mild cases, and the waxing and waning nature of tics over time [261]. Tic disorders are more frequently observed in children than in adults and are significantly more prevalent in males than in females, with a male-to-female ratio of approximately 2.4:1 [256,262].

A meta-analysis reported that Provisional Tic Disorder is the most common form of TD in children, with a prevalence of 2.99% (95% CI: 1.60–5.61%). Tourette Syndrome (TS) was found to have a prevalence of 0.77% (95% CI: 0.39–1.51%), with rates in males (1.06%) being nearly four times higher than in females (0.25%). Among adults, TS has a lower estimated prevalence of 0.05% (95% CI: 0.03–0.08%) [262]. Another study evaluating community-based samples reported that among school-aged children, Provisional TD affects approximately 11–20%, TS affects 0.26–3.8%, Chronic TD affects 0.5–3%, and Chronic Vocal TD may be present in up to 0.9% of children [263]. Additionally, the prevalence of TS appears to be higher in children with autism spectrum disorder (ASD). In this population, 22% were found to have chronic motor tics, and 11% met the diagnostic criteria for TS [264].

4.2. Etiology

Dysregulation within the Cortico-Striato-Pallido-Thalamo-Cortical (CSPTC) network is widely regarded as the most plausible pathophysiological mechanism underlying tic disorders (TDs) [265]. Neuroimaging studies have revealed reduced volumes of the striatum and globus pallidus in individuals with Tourette Syndrome (TS)[266]. Recent investigations have also examined alterations in brain anatomy and functional connectivity among patients with TS [267]. One such study demonstrated a correlation between hippocampal volume and tic severity [268]. Furthermore, another study reported altered connectivity between the cerebellum and frontal, cingulate, and sensorimotor cortices, suggesting dysfunction within cortico-basal ganglia-cerebellar circuits in TS [269]. Alterations in white matter structural connectivity have been reported in individuals with Tic Disorders (TD), including reduced connectivity between the caudate nucleus and the anterior-dorsolateral prefrontal cortex [270]. Moreover, inverse correlations have been observed between tic severity and connectivity between the supplementary motor area (SMA) and basal ganglia (BG), whereas positive correlations have been reported between tic severity and connectivity between the motor cortex and the striatum/thalamus [271,272]. Another study found increased basal ganglia-cortical and thalamocortical connectivity, but decreased connectivity within cortico-cerebellar circuits and among certain cortical regions [273].

Genetic alterations in the SLITRK1 gene have also been identified in TD patients [274,275]. SLITRK1 (Slit and Trk-like family member 1) encodes a single-pass transmembrane protein implicated in neuronal development, particularly in neurite outgrowth and synaptogenesis. Dysregulated expression of SLITRK1 may disrupt the maturation of cortico-striatal-thalamo-cortical circuits, thereby contributing to imbalances in dopaminergic and glutamatergic neurotransmission that underlie the motor symptoms observed in TD, although the precise mechanisms remain incompletely understood (28).

The Cortico-Striato-Pallido-Thalamo-Cortical (CSPTC) network, which underlies Tourette Syndrome, can be functionally divided into two subsystems: expression networks and control

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networks (29). Expression networks are involved in the manifestation of tics, associated psychiatric symptoms, and broader brain state changes. These circuits mediate both naturally occurring and experimentally evoked behaviors [276]. Regions such as the sensorimotor cortex, putamen, globus pallidus, substantia nigra, subthalamic nucleus, thalamus, and ventral tegmental area are closely linked to the emergence and severity of involuntary tics [277,278]. Several studies have demonstrated increased premotor and primary motor cortex activity, as well as activation in limbic and sensory areas prior to tic onset. During tics, abnormally elevated motor activity has been observed in motor regions both within and beyond the CSPTC circuit [279–283].

Premonitory urges, which are sensory phenomena typically preceding the manifestation of tics, remain neurobiologically unclear. Neuroimaging studies, including functional MRI (fMRI) and positron emission tomography (PET), have highlighted the involvement of sensory and limbic brain regions in the generation of these urges [283–285]. For instance, in an fMRI study conducted by Neuner et al. [283], activation was observed prior to tic expression in the premotor and primary motor cortices, somatosensory regions (such as the parietal operculum), the putamen, as well as in limbic and paralimbic structures including the anterior cingulate cortex, insula, and amygdala.

Comorbid conditions such as Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD) have also been linked to dysregulation within the Cortico-Striato-Pallido-Thalamo-Cortical (CSPTC) circuitry [276]. While localized disinhibition in the central associative-limbic striatum and the nucleus accumbens has been associated with ADHD, alterations in the central and ventral portions of the anterior striatum appear to be related to OCD [286–288].

Control networks are thought to regulate voluntary tic suppression and modulate behavioral states such as stress and arousal that influence symptom expression [276]. The frontal cortex has been implicated in modulating basal ganglia activity, thereby facilitating tic suppression [289]. Supporting this, one fMRI study demonstrated that increased frontal cortical activity was associated with enhanced activation in the caudate nucleus and a corresponding reduction in activity in the globus pallidus, putamen, and thalamus [289]. Furthermore, magnetic resonance spectroscopy (MRS) studies suggest that voluntary tic suppression may result from local tonic inhibition mediated by extracellular gamma-aminobutyric acid (GABA) in the supplementary motor area (SMA) [290].Although the specific environmental contributors to tic disorders remain unclear, numerous studies have investigated prenatal and perinatal epigenetic influences [291].

Table 2. Tic Disorders and Considered Risk Factors.

Risk Factor	Associated Findings / Studies
Exposure to maternal stress during pregnancy	Interview-based study [291]
Nausea and vomiting during the first trimester of pregnancy	Interview-based study [291]
Absence of prenatal care in the first trimester	Retrospective review study [292]
Higher number of prenatal visits	Retrospective review study [292]
Low Apgar score at 5 minutes	Retrospective review study [292]
Low birth weight	Systematic review [293,294]
Maternal smoking during pregnancy	Systematic review [293,294]
Maternal alcohol consumption during pregnancy	Prospective prenatal cohort study [295]
Maternal cannabis use during pregnancy	Prospective prenatal cohort study [295]
Parity (number of previous births by the mother)	Prospective prenatal cohort study [295]
Inadequate weight gain during pregnancy	Prospective prenatal cohort study [295]
History of psychiatric disorder in either parent	Case-control study [296]
Poor parental relationship within the nuclear family	Survey-based study [297]

Tic disorders, including Tourette Syndrome (TS), are currently considered polygenic disorders, involving the interaction of multiple susceptibility genes. A population-based cohort study utilizing the Genome-wide Complex Trait Analysis (GCTA) program estimated the heritability of TS to range

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between 0.58 and 0.77. The same study demonstrated a significantly higher risk of tic disorder among first-degree relatives compared to second- and third-degree relatives, suggesting a strong familial aggregation [298]. Notably, siblings of individuals with tic disorders had a significantly higher risk of developing the disorder than maternal half-siblings, despite similar environmental exposures, pointing to a relatively limited role of shared environment in its etiology [298].

Although several candidate susceptibility genes for TS have been proposed, replication remains limited due to small sample sizes and the genetic and phenotypic heterogeneity of the disorder [299]. In one TS-affected family, a chromosomal insertion or translocation involving CNTNAP2 at 7q35-q36 was found, possibly disrupting the distribution of potassium channels in the nervous system [300]. Another case study identified a deletion in exons 4, 5, and 6 of the NLGN4 gene at Xp22.32–p22.31 in a TS-affected family, which has also been associated with autism spectrum disorder, ADHD, learning disabilities, anxiety, and depression [301]. A mutation in the HDC gene at 15q21.2, known to affect histaminergic neurotransmission, has also been linked to TS pathogenesis [302]. In addition, IMMP2L, located at 7q31.1 and encoding a mitochondrial inner membrane peptidase subunit, has been associated with TS [303,304]. In animal models, mutations in Immp2l were shown to increase mitochondrial superoxide production and cellular oxidative stress [305]. However, a more recent study using skin fibroblasts from TS patients with IMMP2L deletions found no significant evidence of mitochondrial dysfunction [306].

A genome-wide scan using single nucleotide polymorphism (SNP) genotyping microarrays revealed rare copy number variants (CNVs) affecting exons of genes such as NRXN1, AADAC, CTNNA3, FSCB, and KCHE1–KCHE2–RCAN1 in TS patients [307]. Further CNV analysis of individuals of European ancestry with TS confirmed a significant association between NRXN1 deletions, CNTN6 duplications, and increased TS risk [308]. Whole-exome sequencing studies have also identified high-risk genes for TS, including CELSR3 on chromosome 3p21.31 [309] and ASH1L on chromosome 1q22 [310]. Another study highlighted potentially deleterious variants of the OPRK1 gene, which encodes the kappa opioid receptor, on chromosome 8q11.23 [311]. Genome-wide association studies (GWAS) conducted by the Brainstorm Consortium suggested an association between TS and the COL27A1 gene on chromosome 9q32–33 [312,313]. Taken together, these findings indicate that tic disorders are not monogenic, but rather result from complex interactions between genetic predisposition and environmental factors. In addition to genetic contributions, abnormal immune responses have been proposed as a key etiological mechanism in TS. Various lines of evidence—from postmortem studies, animal models, and laboratory investigations—suggest the involvement of immune dysregulation. These include elevated levels of pro-inflammatory cytokines such as interleukin-12 and tumor necrosis factor [314], deficiencies in T-cell regulation [315]; increased titers of adhesion molecules indicative of systemic inflammation [316]; altered immunoglobulin profiles [317]; presence of oligoclonal bands in cerebrospinal fluid [318–320]; microglial activation, and exaggerated systemic immune responses coupled with dysfunctional neuroimmune communication [321]

4.3. Glial Cells

The central nervous system (CNS) contains various types of glial cells, including astrocytes, oligodendrocytes, and microglia [322]. Astrocytes are the most abundant glial cells and play a multitude of roles in brain function. Oligodendrocytes are glial cells responsible for forming the myelin sheath around neuronal axons, which is essential for proper signal transmission. Microglia, although classified as glial cells, are considered the monocytes of the CNS and are specialized for the phagocytosis of pathogens and cellular debris [323].

Despite their different embryonic origins—astrocytes deriving from ectodermal lineage and microglia originating from the yolk sac [324,325] these cells are anatomically proximate within the CNS. Microglia are distributed homogeneously throughout the brain and fulfill conserved functions across various species [326,327]; enabling them to monitor their microenvironment actively and efficiently. In contrast, astrocytes display regional heterogeneity within the brain [328,329]; are in

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close contact with synapses and microglia [330], and act as integrative hubs for the collective functionality of neural networks.

Microglia and astrocytes do not merely serve as supportive cells for neurons; they have been shown to play bidirectional roles in neurodevelopment and regeneration [331]. Under normal physiological conditions, these cells remain in a resting state. However, upon bodily stress or disease, both astrocytes and microglia become reactive, a transition that can result in both beneficial and detrimental outcomes. The interactions between microglia and astrocytes are crucial not only in neurodevelopment but also in the progression of neurological diseases. These interactions guide neuronal production and maturation, facilitate the clearance of cellular waste, and help maintain homeostasis within the CNS during development. In pathological states, they become activated and exhibit both overlapping and distinct functions, mutually regulating and supporting one another. Consequently, the interplay between astrocytes and microglia has become a growing focus of scientific interest [332,333].

Throughout neural development, microglia–astrocyte interactions provide key insights into neural stem and progenitor cell behavior and contribute to homeostatic balance through morphological changes and molecular crosstalk. When transitioning from physiological to pathological states, disruptions in this balance trigger a shift from resting to reactive modes, which play a decisive role in the regulation of inflammation and regeneration. Due to the variability and complexity of these interactions, it is essential to comprehensively evaluate the roles of these cells at different developmental stages and across various neurological disorders [323].

4.4. Microglia and Neurogenesis

Microglia interact directly with neurons through surface molecules and regulate developmental neuronal apoptosis [329,330]. Microglia-mediated neuronal death creates favorable conditions for the subsequent phase of astrogliogenesis, facilitating proper astrocyte maturation and spatial distribution. Moreover, the interaction between microglia and astrocytes exerts a significant influence on neural maturation. Notably, the phagocytic capabilities of both microglia and astrocytes strongly impact synaptic pruning. During the removal of neuronal corpses, small apoptotic dendritic fragments are engulfed by astrocytes, while somata and apical dendrites are phagocytosed by migrating microglia [331]. In addition, IL-33 secreted by developing astrocytes enhances the phagocytic capacity of microglia, whereas insulin-like growth factor 1 (IGF-1) produced by microglia increases the phagocytic activity of astrocytes. These reciprocal interactions further accelerate neuronal maturation [332,333]. Beyond synaptic pruning, microglia–astrocyte interactions contribute to the regulation of synaptic density and help preserve structural and functional balance within synapses [323].

4.5. Neuroinflammation and Tourette Syndrome

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple involuntary motor and vocal tics that begin in childhood and persist for more than one year [334]. It affects approximately 0.3–1% of the population [335]. TS commonly co-occurs with attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and other psychological conditions [336,337]. The disorder can significantly impair daily functioning, adversely impacting both physical and mental health, diminishing academic performance, and even leading to social dysfunction.

In recent years, accumulating evidence has suggested that infections or allergic reactions may contribute to the pathogenesis of TS and other neuropsychiatric disorders via neuroinflammatory mechanisms [338,339]. Studies have shown that, in a subset of individuals with TS, tic symptoms may be triggered or exacerbated following pathogenic infections or allergic episodes [340,341]. However, the exact mechanisms by which these factors initiate or aggravate TS symptoms remain unclear.

4.6. Inflammatory Factors

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Pathogens may contribute to the onset of TS by activating T cells to produce pro-inflammatory factors or by stimulating B cells to generate anti-neuronal antibodies that damage neurons. A deficiency in regulatory T cells (Tregs) has been identified in individuals with TS, which may lead to reduced immune regulation and increased pathogen clearance. Such infectious triggers can cause peripheral immune hyperactivation and the excessive release of inflammatory mediators, disrupting neuroimmune interactions. This disruption may result in imbalances in neurotransmitter systems, particularly dopamine (DA) and glutamate (Glu), thereby contributing to tic generation. Moreover, anti-neuronal antibodies may bind to neuronal surface antigens, activate microglia, and cause dopaminergic neuronal injury, ultimately leading to TS symptomatology [342].

4.7. Production of Inflammatory Mediators via Peripheral Immune System Activation

The loss of immune tolerance to autoantigens observed in TS may be associated with Treg cell deficiency [343], potentially reducing the capacity to suppress autoreactive T lymphocytes. Upon pathogenic infection, the overactivation of autoimmune responses leads to a massive release of pro-inflammatory factors. These peripheral inflammatory cytokines may increase the permeability of the blood-brain barrier (BBB), allowing them to influence microglia and astrocyte activity. Such immune-mediated alterations can disrupt neurotransmitter homeostasis and contribute to the development of TS [342].

4.8. Peripheral Immune System Overactivation

Peripheral immune system hyperactivation has also been observed in individuals with Tourette syndrome (TS). Researchers have identified elevated numbers of natural killer (NK) cells and CD8+ T cells, along with a reduction in CD4+ T cells and a decreased CD4+/CD8+ ratio in these patients [344,345]. One study reported elevated plasma IL-12 levels in individuals with TS [346,347]. IL-12 plays a critical role in the differentiation of CD4+ T cells into helper T (Th) cells and the activation of NK cells, indicating excessive peripheral immune activation in TS patients [348]. Another study demonstrated an increased presence of CD95+ Th cells in TS, suggesting a hyper-reactive immune profile [349]. CD95 (Fas), upon activation, induces apoptosis in peripheral T cells via interaction with Fas ligand, which further implies an upregulated peripheral immune response [350]. In both TS patients and individuals with bacterial infections, elevated levels of soluble CD14 (sCD14) have been observed in serum [351]. sCD14 promotes the production of pro-inflammatory cytokines that enhance bacterial resistance [352]. These pro-inflammatory cytokines may cross the blood-brain barrier (BBB), influence microglia and astrocyte activity, and trigger neurotransmitter abnormalities that contribute to TS pathogenesis.

4.9. Microglial Activation Mediated by Inflammatory Factors

It has been demonstrated that cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) can penetrate the BBB and enter cerebral vasculature or brain parenchyma [353]. TNF-α can indirectly promote the production of neurotoxic metabolites, thereby disrupting brain development through alterations in neurotransmitter metabolism [354]. Microglia in the brain can be activated by circulating pro-inflammatory cytokines, leading to increased neuronal excitability and further release of inflammatory mediators [353]. Recent studies suggest that microglia play a central role in neuroinflammation associated with tic disorders.

Microglial activation in the brain appears to be driven by elevated blood levels of chemokine ligand 5 (CCL5), upregulation of immune-related genes, and histamine (HA) deficiency. These mechanisms are detailed below [342]:

1. **Elevated Blood CCL5 Levels**: Pathogenic infections can lead to overactivation of T lymphocytes and increased CCL5 secretion by immune cells. CCL5 can cross the BBB via its receptors CCR1 and CCR5 to enter the central nervous system. Elevated serum CCL5 levels in TS patients suggest a possible role of this chemokine in neuroinflammation [351,352]. The CCL5-CCR1

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interaction may promote microglial activation via the CCR1/TPR1/ERK1/2 pathway, while CCL5-CCR5 signaling may induce neuronal pyroptosis through the CCR5/PKA/CREB/NLRP1 axis, contributing to neural dysfunction and tic expression [353,354].

2. **Upregulated Immune-Related Genes**: Several hub genes, such as ICAM1, CCL2, HMOX1, MYC, and SOCS3, have been found to be upregulated in TS. These genes are involved in immune and inflammatory processes, particularly those related to interleukin and interferon signaling pathways [355]. Gene expression analyses in the caudate nucleus and putamen reveal that the majority of upregulated genes in these regions are immune-related and may enhance microglial activation and inflammatory responses [356].
3. **Histamine Deficiency**: Histamine deficiency increases the secretion of pro-inflammatory mediators such as IL-1β, sensitizing microglia to inflammatory stimuli and promoting their polarization toward the M1 phenotype [357]. Histamine normally acts through H4 receptors to suppress microglial inflammatory responses and regulate their function [357,358]. A deficiency of the Hdc gene, known to be associated with TS, results in a reduction of IGF-1-positive protective microglia, increasing susceptibility to neuronal damage [358,359]. Enhanced M1 polarization, especially in the striatum, may lead to dopaminergic neuroinflammation and dysfunction, potentially triggering the development of tics [360–362]. These findings indicate a potential interaction between immune responses and dopaminergic dysregulation in TS pathophysiology.

4.10. Other Mechanisms of Immune-Neural Crosstalk Disruption Mediated by Inflammatory Factors

Inflammatory factors may contribute to the pathophysiology of TS via multiple mechanisms. These include disruption of astrocyte-neuron metabolic interactions that impair synaptic regulation, gut-brain axis dysfunctions linked to microbiota alterations, and disturbances in the kynurenine pathway, leading to neurotransmitter imbalances. Impaired function of astrocytic glutamate transporter 1 (GLT-1), for instance, may disrupt corticostriatal circuitry and promote repetitive behaviors. Alterations in gut microbiota—such as increased *Prevotella* or decreased *Bifidobacterium*—may influence inflammatory responses, GABA levels, and dopaminergic activity, thereby exacerbating TS symptoms. Furthermore, infections that shift tryptophan metabolism toward the kynurenine pathway may induce glutamatergic hypofunction via NMDA receptor antagonism and nicotinic receptor blockade, contributing to tic behaviors [362–365].

4.11. Anti-Neuronal Antibodies

In patients with Tourette Syndrome (TS), the presence of anti-neuronal and antinuclear antibodies in the serum suggests that autoimmune mechanisms may play a role in the etiopathogenesis of this disorder. It has been proposed that immune responses following pathogenic infections—particularly those caused by *Streptococcus pyogenes* (GAS)—may lead to the production of autoantibodies targeting neurological structures. In this context, antibodies produced against streptococci have been reported to cross-react with neuronal surface antigens such as lysoganglioside-GM1 and neuronal glycolytic enzymes (e.g., pyruvate kinase) in the basal ganglia, due to molecular mimicry [366].

IgG antibodies detected in the sera of TS patients have shown immunological cross-reactivity with brain tissues, particularly in the hippocampus (CA3 subregion), basal ganglia, cerebellum, and dentate gyrus (DG). These antibodies have been found to bind various neuronal surface proteins including dopamine-1 receptor (D1R), dopamine-2 receptor (D2R), N-methyl-D-aspartate receptor (NMDAR), GABA receptors, AMPA receptor, HCN4, and contactin-associated protein-like 2. This binding is believed to disrupt neurosynaptic transmission and contribute to the manifestation of motor and vocal tics [366,367]. However, the precise neuronal antigens targeted by these autoantibodies in TS patients remain unclear. Therefore, identifying novel autoantibodies and their specific antigenic targets in TS and related neuropsychiatric syndromes is of great significance for understanding disease pathogenesis [368].

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4.12. Signaling Pathways Involved in Neuroimmune Interaction

Previous studies have shown that several signaling pathways are involved in TS-related neuroinflammation. Among these, the Ca(2+)/calmodulin-dependent protein kinase II (CaMKII) pathway, the JAK-STAT pathway, and the NF-κB pathway are known to play significant roles in inflammation processes initiated by microglial activation [369].

4.13. CaMKII Signaling Pathway

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activation may be triggered via anti-neuronal antibodies or NMDAR activity, and has been associated with antibody reactivity to neuronal surface antigens in the caudate-putamen region. Activation of NMDAR increases intracellular Ca^{2+} levels, thereby activating CaMKII. CaMKII modulates inflammatory responses through ERK/p65/STAT3 and Drp1/ROS/NF-κB signaling pathways, promotes M1 microglial polarization, and upregulates tyrosine hydroxylase expression—an enzyme crucial for dopamine biosynthesis. Additionally, CaMKII can regulate NMDAR sensitivity through glutamatergic transmission. Thus, antibody-mediated CaMKII activation may trigger TS symptoms by promoting both neuroinflammation and dopaminergic dysregulation [342,370–372].

4.14. JAK2/STAT3 Pathway

The JAK2/STAT3 pathway is a key signaling route regulating inflammation-related gene expression, activated by cytokines such as IL-1β, TNF-α, and IL-6 during immune responses to pathogens. Upon stimulation with immune activators like LPS, STAT3 becomes phosphorylated and translocates to the nucleus, where it initiates transcription of inflammatory genes. STAT3 also interacts with other transcription factors, such as NF-κB p65, to amplify the inflammatory response. Microglial activation via this pathway may influence both cytokine production and neurotransmitter release, contributing to the onset of TS [342,373].

4.15. NF-κB Pathway

Microglia can be activated through the NF-κB signaling pathway via lipopolysaccharide (LPS), initiating neuroinflammation. This pathway is regulated by several other signaling cascades, including PI3K/Akt, TLR/NLRP3, TLR/MyD88, BDNF/TrkB/MyD88, EGF/EGFR, and Nrf-2/HO-1. In the PI3K/Akt pathway, Akt phosphorylation facilitates NF-κB activation; TLR/NLRP3 and TLR/MyD88 pathways have been shown to play pro-inflammatory roles in experimental models of TS. BDNF-TrkB interaction also enhances pro-inflammatory responses through the MyD88/NF-κB axis, contributing to TS development. Moreover, inhibition of the Nrf-2/HO-1 and EGF/EGFR pathways can enhance NF-κB activation, thereby promoting inflammatory processes [342,374].

4.16. Other TS-Related Pathways

Glutamate (Glu) signaling via NMDAR and the subsequent activation of the MAPK/CREB pathway play significant roles in both the neuroinflammatory and neurotransmitter-based mechanisms of TS. MAPK family kinases such as JNK, ERK, and p38 regulate the expression of inflammatory genes and cytokine release. Likewise, the PI3K/AKT/mTOR pathway is essential for dopamine release and neuronal development, and disruptions in this pathway may lead to dopaminergic imbalances. Increased expression of the *FLT3* gene and the association of certain *FLT3* SNPs with PI3K/AKT/mTOR activation in TS patients further support the genetic involvement of this pathway in TS pathophysiology [342,375].

4.17. Postmortem and Imaging Findings

Lennington et al. (2016) conducted transcriptomic analyses of postmortem brain samples from nine adult patients diagnosed with TS. They reported increased expression of CD45+ microglia and

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upregulation of immune response-related genes in the striatum, particularly within the basal ganglia. These findings suggest that microglial activation becomes more prominent in severe and treatment-resistant forms of TS [376]. These postmortem observations are supported by findings from positron emission tomography (PET) studies. Kumar et al. (2015) used the radioligand (11) C-[R]-PK11195 (PK) to assess microglial activity and found bilaterally increased PK binding in the caudate nuclei of children diagnosed with TS and PANDAS. This indicates localized inflammatory microglial activation in the striatum [377].

5. Neuroglial Dysfunction in Disruptive Mood Dysregulation Disorder and Irritability

Disruptive Mood Dysregulation Disorder (DMDD) and irritability are important neuropsychiatric concepts in child and adolescent psychiatry. Irritability is a developmentally critical affective response characterised by increased sensitivity to negative emotions such as anger, restlessness, or impatience (likely mediated by amygdala hyperreactivity and prefrontal cortex dysfunction). It usually manifests as intense and uncontrolled responses to stimuli such as disappointment, frustration, or perceived environmental threats [378]. DMDD is characterised by persistent irritability and frequent tantrums that begin in childhood. These symptoms seriously impair the child's daily functioning and usually begin before the age of 10[379]. Irritability is a distinguishing feature of DMDD and leads to chronic affective dysregulation. It is a symptom that can be seen in many psychiatric disorders, such as Major Depressive Disorder, Bipolar Disorder, Oppositional Defiant Disorder, Attention-deficit/Hyperactivity Disorder, and Autism Spectrum Disorder. DMDD and irritability are associated with functional differences in brain regions such as the amygdala and prefrontal cortex. In DMDD, irritability is particularly associated with amygdala activity during facial expression recognition, indicating a neural pattern distinct from Bipolar Disorder [380]. High levels of irritability are associated with impairments in executive functions such as emotional control and cognitive flexibility. Children with DMDD experience difficulties particularly in the areas of emotional regulation and flexibility [381]. In children and adolescents, irritability is often associated with deficiencies in the perception and processing of rewards and threats, and it has been shown that the amygdala and certain subregions of the frontal cortex play a special role in this process. Although differences in activity are also observed in these brain regions in adulthood, it is understood that the resulting functional patterns vary depending on age [382]. When evaluated at the neurochemical level, irritability in children and adolescents is associated with tonically low dopamine levels and weak phasic responses of dopamine in subcortical structures. In contrast, increased transmission in serotonergic and dopaminergic systems is thought to play a role in adults. These findings suggest that irritability is a phenomenon that evolves with age and has variable developmental neurobiological foundations [382,383].

Neuroglial dysregulation, particularly disorders involving microglia, which are the resident immune cells of the brain, are increasingly being linked to irritability and related neuropsychiatric symptoms in both human and animal studies. Animal models show that systemic inflammation activates microglia, which leads to increased expression of proinflammatory cytokines and changes in brain function, thereby contributing to behavioural symptoms such as irritability [384]. In humans, microglial gene expression is highly sensitive to environmental stimuli, and the dysregulation of these cells has been linked to changes in brain regions and neural pathways related to mood and behaviour [385,386]. Neuroglia, particularly microglia and astrocytes, play central roles in mood regulation. Microglia, as immune cells of the central nervous system, regulate inflammation, synaptic plasticity, and inter-neuronal communication. Microglia activated in response to stress and inflammation can negatively affect neuronal networks and synaptic plasticity by secreting pro-inflammatory cytokines; these processes can lead to disruptions in mood regulation [387–389]. In addition, gene-environment interactions such as histamine signalling can modulate microglial function and increase susceptibility to neuroimmune dysregulation and irritability [390]. Increased microglial activity, particularly in areas such as the prefrontal cortex and amygdala, can lead to

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disturbances in mood regulation and behavioural changes such as irritability [391,392]. In addition, exosomes and microRNAs secreted by microglia and astrocytes play a decisive role in mood by affecting critical pathways such as synaptic function, neurotrophic factor production, and immune response [387,388]. In particular, excessive or insufficient activation of microglia can lead to neuronal death, decreased neurogenesis, and loss of synaptic connections, which are associated with mood dysregulation [393–395].

In mouse models, LPS (lipopolysaccharide) administration has been found to cause significant glial activation and irritability in the central nervous system. LPS activates microglia and astrocytes, leading to increased proinflammatory cytokines (e.g., IL-1β, TNF-α) and oxidative stress; these processes are associated with neuronal damage and behavioural changes (e.g., depressive-like behaviour, cognitive impairment, irritability)[396–398]. LPS-induced glial activation occurs via TLR4/NF-κB signalling pathways, resulting in neuroinflammation, decreased synaptic proteins and synaptic dysfunction [399–401]. Microglial activation has been shown to be associated with depressive and irritability-like behaviours, particularly through molecular regulators such as NLRC5 and NLRP3 inflammasomes [398,402]. Furthermore, in models created with LPS, glial activation has been reported to be significant in both acute and chronic applications [403].

Astrocytes regulate neurotransmitter balance, glutamate balance, and synaptic transmission, and disruptions in these functions contribute to mood instability [404,405]. Astrocytes synthesise and recycle brain-derived neurotrophic factor (BDNF), which plays an important role in regulating brain function and managing emotional processes, thereby contributing to synaptic plasticity [406]. Astrocytes play an important role in regulating behaviour through dynamic calcium (Ca2+) signalling. These calcium fluctuations vary considerably across different brain regions and time scales, enabling astrocytes to influence neuronal activity, synaptic transmission and ultimately behavioural outputs such as cognition, emotion and homeostasis [407–410]. Advances in imaging and genetic tools have revealed that the most behaviourally significant calcium events typically occur in fine astrocytic processes that were previously difficult to study. These micro-regional Ca2+ events can respond rapidly to local neuronal activity, suggesting that astrocytes play a direct and subtle role in modulating neural circuits. Additionally, disruptions in astrocyte calcium signalling are associated with neuropsychiatric and neuroinflammatory disorders such as depression, where specific calcium channels like Orai1 regulate both astrocyte reactivity and behaviour changes caused by inflammation [408,411,412].

Oligodendrocytes play a critical role in maintaining white matter integrity and accelerating nerve transmission in the brain. Research has shown that chronic social stress reduces oligodendrocyte gene expression in areas such as the prefrontal cortex and amygdala, and that this can affect both white and grey matter. In particular, a significant decrease in oligodendrocyte genes associated with myelin and myelin-axon integrity has been observed in mice exposed to chronic social stress. Additionally, it has been suggested that impaired oligodendrocyte function, along with increased microglia activity in the amygdala region, may affect emotional regulation and irritability [413]. Oligodendrocytes and other glial cells also play a role in mood regulation through myelination and metabolic support [404,405]. Glial cell dysfunction causes disturbances in synaptic pruning, myelination, and blood-brain barrier integrity, paving the way for fluctuations in behaviour and mood [387,404].

In recent years, glial-targeted anti-inflammatory treatments and approaches aimed at stabilising glial function have shown promise in the treatment of mood disorders and irritability [404,414]. For example, folic acid treatment can improve anxiety and depression-like behaviours in adulthood by reducing glial activation and increasing the expression of anti-inflammatory cytokines (IL-10, IL-13) through epigenetic mechanisms [415]. Glutamate modulators such as Riluzole can reverse glial dysfunction caused by chronic stress and the behavioural disorders associated with it [416]. Antidepressants have also been shown to have a direct effect on astrocytes, contributing to the reorganisation of neural networks by regulating glial physiology and trophic factor release [417,418].

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As a result, treatments targeting glial functions are emerging as a promising approach to managing irritability and mood disorders. However, inter-individual differences and the lack of glial biomarkers pose significant challenges in the treatment development process [404,419]. Furthermore, current research on the neuroglial basis of DMDD and irritability is limited. To advance this field, systematic postmortem analysis of microglial and astrocytic changes in human brain tissue is required. Longitudinal neuroimaging studies tracking changes in glial activity throughout developmental processes may also be useful in elucidating the behavioural consequences of age-related glial functional changes. These efforts may contribute to the development of more targeted and personalised treatment strategies for irritability-related psychopathologies.

6. Specific Learning Disorder in Terms of Neuroglia

Specific learning disorder, specifically dyslexia, is a neurodevelopmental disorder characterized by unexpected difficulties in the acquisition of reading skills [420,421]. Dyslexia is characterized by chronic and pronounced reading difficulties that cannot be explained by deficits in non-reading factors such as intelligence level, motivation, sensory abilities or educational opportunities [422]. According to a widely accepted definition, dyslexia is a specific learning disability of neurobiological origin, manifested by difficulties in accurate and/or fluent word recognition, spelling and decoding skills. This definition emphasizes that dyslexia is caused by a dysfunction specifically in the phonological component of language and is independent of general intelligence. Dyslectic individuals typically have poor phonological processing skills. These individuals have difficulty learning the sound equivalents of letters and reading words aloud, but do not have any underlying visual, auditory or intellectual disability [423].

Although the neurobiology of dyslexia is mostly addressed at the neuronal circuits and cognitive level, in recent years it has been understood that glia cells also play critical roles in learning and memory processes [424]. Although glia have long been considered only as cells that support nerve cells, recent research suggests that interactions between glia and neurons may be important in neurodevelopmental disorders.

6.1. Microglial Activity and Synaptic Regulation

Microglia, which optimize neuronal connections through synaptic pruning during the developmental process, play a critical role in neural circuit formation as immune cells of the central nervous system [425]. This pruning process leads to the loss of functional synapses when it is excessive and the preservation of weak connections when it is insufficient; in both cases, cognitive efficiency is affected [426]. It has been suggested that increased slow wave EEG activity in children with learning disabilities may be associated with inadequate microglial pruning indicating synapse redundancy [427]. Models of dyslexia associate the poor synaptic integrity observed in language networks with microglial dysfunctions. Especially the connection weaknesses found in the left temporal region may be considered as a result of excessive or insufficient synaptic pruning that occurs during the developmental period [428].

Microglial synaptic pruning is triggered by complement components such as C1q and C3 targeting synapses so that microglia select these structures for phagocytosis [425]. Overactivation can lead to the loss of critical connections in language circuits in dyslexia. In addition, TREM2 and CX3CR1 receptors on the microglia membrane detect signals from neurons and decide which synapses to protect [426]. Dysfunction of these receptors may predispose to over- or under-pruning and disruption of information integrity during reading.

Research shows that not only the amount but also the timing of microglial synaptic pruning is decisive for the healthy development of neural networks. Early or delayed microglial activity during critical developmental periods may lead to excessive synaptic elimination or insufficient pruning in reading circuits, disrupting the maturation process of functional connections. This temporal irregularity may alter the organization of neural networks associated with reading, especially in

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temporal-parietal regions, and may contribute to the cognitive differences observed in dyslexia [429,430]

The interaction between microglia and neurons is not only limited to structural support, but also involves functional feedback mechanisms. In a study by Badimon et al. (2020) in mouse models, microglia were shown to recognize hyperactive neurons and suppress their activity through ATP and glutamate signaling [427]. Disruption of this negative feedback mechanism may lead to functional disruptions in reading tasks that require timing precision by weakening neural synchronization. Microglia also promote synaptic maturation and neuron survival by secreting cytokines such as IL-1β and trophic factors such as IGF-1; disruption of these molecular mechanisms may contribute to reduced processing speed and language fluency problems [427].

6.2. Astrocytes and Dyslexia

Astrocytes are glial cells in the central nervous system defined by their star-shaped branching morphology and in direct contact with neurons. Although they have traditionally been described as support cells, it is now known that these cells assume central functions in roles such as regulating active synaptic functions, maintaining ion and neurotransmitter homeostasis, and contributing to synaptic plasticity. These cells regulate the chemical environment around the synapse, determining the duration and intensity of signals. Astrocytes are particularly involved in vital functions such as reuptake of glutamate, maintenance of ion homeostasis and regulation of neurovascular interaction [431,432].

Astrocytes not only provide clearance of neurotransmitters, but also contribute to the maintenance of cellular energy balance by providing metabolic support to neurons. In particular, they are active in the glutamate-glutamine cycle: they take up glutamate from the synaptic cleft, convert it into glutamine via the enzyme glutamine synthetase, and then deliver it back to the neurons. This cycle both maintains neurotransmitter balance and sustains synaptic function [431,433]. In addition, astrocytes deliver lactate from glucose to neurons as an energy substrate. This energy transfer system, called the "astrocyte-neuron lactate shuttle", is activated during times of increased cognitive load (e.g., during reading, learning, and attention-demanding tasks), helping to meet the metabolic needs of neurons [432,434]. In dyslexic individuals, disruption of this astrocyte-derived energy flow can limit the capacity of neurons to process excitatory signals and lead to symptoms such as mental fatigue or processing inefficiency during reading.

In brain regions associated with dyslexia, particularly in the left temporo-parietal cortex, the ratio of N-acetylaspartate (NAA), an indicator of energy metabolism, and choline (Cho) metabolites (NAA/Cho), reflecting cell membrane structure and turnover, is altered (NAA/Cho), a sign of astrocyte dysfunction and metabolic imbalance [434–436]. This can result in over- or under-stimulation of neurons, leading to impairment in the reading process.

The neuroinflammatory and synaptic plasticity functions of astrocytes are becoming increasingly important in the neurobiology of dyslexia. Astrocytes are capable of rapid and dynamic responses to environmental inputs through intracellular calcium signaling, which plays a critical role in regulating information transmission at the synaptic level [437]. In dyslectic individuals, abnormalities in calcium fluctuations observed in astrocytes can disrupt the delicate balance in synaptic transmission, leading to disruptions in neuronal communication. In addition, inflammatory cytokines secreted by astrocytes, especially molecules such as interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α) and chemokines, are effective in remodeling synaptic structure and regulating synaptic plasticity [438–440]. In neurodevelopmental disorders such as dyslexia, excessive or insufficient inflammatory responses may negatively affect the stability of synaptic connections, leading to decreased learning and cognitive functions.

The involvement of astrocytes in neuroinflammatory processes has a direct impact on the number and functionality of synaptic connections and can lead to disruption of synaptic plasticity mechanisms such as long-term potentiation (LTP) and depression (LTD). This may undermine the integrity of neural circuits, leading to a decline in skills such as phonological processing and reading

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fluency in dyslectic individuals [438,440]. Moreover, chronic inflammatory processes are associated with oxidative stress and glial dysfunction in the brain microenvironment, which reduces the overall efficiency of synaptic metabolism and predisposes to cognitive fatigue and attention problems [439]. In light of these mechanisms, neuroinflammatory responses of astrocytes are emerging as a critical component of the pathophysiology of dyslexia and offer a potential biomarker and therapeutic target for targeted anti-inflammatory and glial modulatory therapies.

6.3. Oligodendrocytes and the Relationship of Myelinization with Dyslexia

Oligodendrocytes are glial cells in the central nervous system that surround axons with a myelin sheath. Myelin ensures the fast and efficient transmission of neuronal action potentials through the saltatory conduction mechanism. This fast signal transmission enables synchronized information transfer between different brain regions and plays a critical role in the efficient execution of complex cognitive functions, especially multistep processes such as reading [441,442]. The capacity of oligodendrocytes to synthesize and maintain the myelin sheath is essential for the healthy progression of neurodevelopmental processes.

Neuroimaging studies in individuals with dyslexia show that there is a decrease in myelin density and disorganization in the white matter tracts of language processing circuits, especially in the left temporo-parietal and arcuate fasciculus. These abnormalities lead to reduced conduction velocity of action potentials and impaired network synchronization due to underdevelopment or disruption of the structural integrity of the myelin sheath. Longitudinal studies have shown that in typically developing children, myelination increases in parallel with the acquisition of reading skills, whereas in dyslectic children, myelination is delayed or irregular. For example, myelin signal in the left anterior arcuate fasciculus was significantly lower in 5-year-old children at risk for reading difficulties, In adult dyslectics, compensatory hyper-myelination has been reported to develop in this region [443,444] Compensatory hyper-myelination is thought to be a plasticity mechanism applied by the brain in response to conduction deficits experienced during development. This mechanism attempts to optimize signal transduction by increasing myelin production in other brain regions [443,445]. Experimental animal studies show that environmental stimuli stimulate the proliferation and differentiation of oligodendrocyte precursor cells, resulting in increased myelin synthesis. These findings suggest that not only genetic factors but also experiential and environmental factors are determinant on white matter development in dyslexia [444,445].

The functions of oligodendrocytes are not limited to myelin production but also include the capacity to regulate myelin integrity and quality in accordance with neuronal activity. Defects in the structural and functional integrity of myelin lead to delays and asynchronies in signal transmission, especially in language circuits, resulting in decreased phonological processing, reading fluency, and overall cognitive performance [442–444]. Therefore, it has been suggested that increasing early experiential stimulation and pharmacological and neuromodulation-based approaches focusing on myelin plasticity may have promising potential in the treatment of dyslexia [445].

6.4. The Role of Neuron-Glia Interaction Disorders in Dyslexia

Although the dominant role of neuronal activity in learning and cognitive processes has traditionally been emphasized, in recent years it has become clear that interactions between glial cells and neurons are crucial for synaptic plasticity, network synchronization and the holistic regulation of learning processes. These cellular interactions take place in structures defined as “tripartite synapses”, where astrocytes, together with presynaptic and postsynaptic neurons, are an active component regulating synaptic transmission. Microglia, on the other hand, ensure network stability by providing feedback to synaptic pruning and neuronal activity. Thus, neuron-glia interactions have not only supportive but also functionally directive roles [426,439].

Glial cells form a complex signaling network in the central nervous system, which enables synaptic plasticity, metabolic support and myelination processes to function in harmony. The reciprocal cellular interactions between microglia, astrocytes and oligodendrocytes play a vital role

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in the sustainability of neuronal functions and the proper development of neural circuits. In dyslexia, disruption of signaling pathways and molecular interactions between these glial cells leads to functional irregularities in synaptic and neuronal networks. These disorders predispose to cognitive deficits, especially in language and reading centers [425,431,443].

Inflammatory and trophic factors secreted by microglia regulate the metabolic functions of astrocytes, while maintaining the energy and neurotransmitter balance provided by astrocytes supports myelin production by oligodendrocytes. In dyslexia, imbalance of microglial activity leads to increased inflammatory responses, weakening of astrocytic support mechanisms and impaired oligodendrocytic myelin synthesis [425,431,433]. Thus, this disruption in glia-glia communication negatively affects neuronal signal transduction and synaptic integrity, reducing the efficiency of reading circuits [443,445].

The myelin abnormalities observed especially in the left temporo-parietal regions and arcuate fasciculus reflect disruptions in the myelination process regulated by oligodendrocytes with microglia and astrocytes. Asynchrony in these regions leads to decreased phonological processing and cognitive speed, while disruption of synaptic regulation and metabolic support functions of microglia and astrocytes leads to weakened synaptic connections and impaired network stability [425,431,444]. Thus, any disruption in the communication between glial cells prevents the optimal functioning of neuronal networks and emerges as an important mechanism in the emergence of dyslexia symptoms [443].

This holistic perspective emphasizes that the treatment of dyslexia should focus not only on neurons but also on glial cells and their interactions. Regulating the dynamic interactions of glial cells and correcting defects may improve the functional capacity of reading circuits by improving synaptic plasticity, energy metabolism and myelination. Further research in this area at the molecular and cellular level will contribute to the development of new dyslexia-specific therapeutic targets and optimize early intervention strategies [425,431,443,445,446].

Table 3. Relation of Glial Cell Disorders to Learning and Reading Functions.

Glial Cell Type	Possible Dysfunction	Impact on Learning Function
Microglia	Excessive or insufficient synaptic regulation	Lack or excess of connectivity in optimal reading network formation
Astrocyte	Slowness in glutamate reuptake, inadequate metabolic support	Prolongation of synaptic signals, neuronal over/underexcitation, mental fatigue and processing inefficiency during reading
Oligodendrocyte	Delayed/deficient myelination	Decreased neural conduction velocity, impaired synchrony between brain regions, decreased reading speed and fluency

7. Cognitive and Neuropsychological Impacts

Dyslexia is accompanied by impairments in auditory timing, attention and executive function, and it has been suggested that these impairments are caused not only by language processing errors but also by disruptions in neuroglial mechanisms that regulate the millisecond synchronization of neural networks. Considering the myelin spirals of oligodendrocytes that optimize conduction velocity, the circuit thinning of microglia through synaptic pruning, and the regulatory role of astrocytes on glutamate balance, the poor rhythm perception, difficulty in working memory loading, and attentional drift found in dyslectic individuals may be attributed to white matter and glial dysfunctions underlying the reading cycle that requires “fine time resolution” [447].

MRI studies of white matter integrity have revealed that inadequate myelination particularly affects the temporo-parietal and occipito-temporal pathways and is directly related to reading fluency [448]. Myelin water imaging data showing reduced myelin ratios in individuals with low reading performance suggest that these structural deficits may be related to reading ability. In

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particular, oligodendrocyte-mediated myelin plasticity has been shown to regulate action potential conduction time on the microsecond scale. Such conduction differences may disrupt cognitive synchronization in processes that require high time sensitivity, such as letter-sound integration [449,450]. These microscopic deviations in conduction velocity may limit phonological decoding and reading comprehension capacity by narrowing the sensitive temporal window required during letter-sound matching.

Another cellular basis for the neurocognitive deficits that accompany dyslexia may be dysregulation of the synaptic pruning function of microglia. These cells eliminate dysfunctional synapses during the developmental process, particularly refining auditory and fronto-parietal connections [451]. Recent GWAS findings focusing on glia-specific gene expression suggest that dyslexia risk loci statistically overexpress astrocyte- and oligodendrocyte-rich transcripts [452]. Thus, the heterogeneous cognitive profiles observed in dyslexia may be explained by different dominant patterns of impairment across glia types: myelin delays may favor timing-based symptoms, whereas microglial/astrocytic dysfunction may favor executive function and attention components.

Clinically, rhythm-based interventions, neuromodulation protocols targeting myelin plasticity, or pharmacological strategies supporting glial metabolism could be integrated into cognitive rehabilitation programs to provide more holistic outcomes.

Intervention Approaches and Therapeutic Strategies

In the treatment of dyslexia, interest in neurobiological intervention strategies focusing on the regulatory roles of glial cells in the nervous system in learning and reading processes has increased significantly in recent years.

In particular, it is suggested that functional disorders of microglia, astrocytes and oligodendrocytes may contribute to dyslexia by negatively affecting synaptic plasticity, network integrity and information transmission rate. In this context, glial-targeted interventions go beyond traditional educational therapies and offer new neurodevelopmental-based approaches [453,454].

Transcranial direct current stimulation (tDCS) is one of the most widely studied noninvasive neuromodulation methods in dyslectic children. Anodal tDCS applied to the left temporo-parietal regions has been shown to significantly improve phonological processing and word recognition skills [455,456]. This effect is thought to be mediated not only through cortical excitability but also through modulation of microglia-mediated synaptic pruning and oligodendrocyte-mediated myelin plasticity [453]. imilarly, high-frequency transcranial random noise stimulation (hf-tRNS) has also attracted attention and has been reported to improve reading performance by synchronizing neuronal activity over a wider frequency range [457].

Neurofeedback applications are one of the new intervention areas related to glial dynamics. These EEG-based methods aim to normalize increased theta and decreased beta activity. At this point, the metabolic support and gliotransmission functions of astrocytes, which provide the synaptic balance associated with these waves, gain importance. As a matter of fact, some studies have shown that training aimed at theta/beta ratio can increase reading fluency and attention continuity [456].

In the pharmacological field, there is no approved treatment specific to dyslexia, but research on glia-targeted agents continues. In particular, oligodendrocyte-targeted molecules to increase myelin production and agents that can regulate the glutamate reuptake system of astrocytes are considered as potential therapeutic candidates [454].

In conclusion, understanding the neuroglial impairments associated with dyslexia paves the way for holistic approaches that aim to intervene not only in the behavioral but also in the neuronal microenvironment. Neuromodulation and glia-centered therapies may form the basis of more effective and individualized intervention protocols in the future.

8. Conclusions

Emerging evidence increasingly supports the pivotal role of neuroglial cells—particularly astrocytes, microglia, and oligodendrocytes—in shaping neurodevelopmental trajectories and

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modulating behavioral regulation. This review highlights how neuroglial dysfunction may serve as a shared biological substrate underlying a range of neurodevelopmental disorders (NDDs) and disruptive behavior disorders (DBDs), suggesting a shift from a neuron-centric to a more integrated neuroimmune perspective. Findings from both preclinical and clinical studies indicate that glial-mediated processes, such as synaptic pruning, neuroinflammation, and myelination, may contribute to the onset and persistence of behavioral dysregulation in vulnerable individuals.

Despite significant advances, several critical gaps remain. Future research should aim to clarify causal pathways, explore glia-specific biomarkers, and evaluate the therapeutic potential of targeting glial function in early developmental stages. Integrating neuroglial mechanisms into existing diagnostic and treatment frameworks may not only deepen our understanding of the pathophysiology of NDDs and DBDs but also facilitate more precise and biologically informed interventions. Overall, a neuroglial approach offers a promising frontier in the effort to unravel the complex interplay between brain development and behavior.

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