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Review

Environmental Enrichment as a Possible Adjunct Therapy in Autism Spectrum Disorder: Insights from Animal and Human Studies on the Implications of Glial Cells

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Abstract: Background/Objectives: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by genetic, environmental, and epigenetic factors, leading to cognitive, emotional, and social impairments. Due to the heterogeneity of ASD, conventional therapies often have limited effectiveness, highlighting the need for complementary interventions. Enriched environments (EEs), characterized by enhanced sensory, cognitive, and motor stimulation, have shown promise in alleviating ASD symptoms. This review examines the role of glial cells in mediating the effects of EE. Methods: A literature review was conducted, analyzing studies on EE interventions in animal models and humans, with a focus on glial involvement in neuroplasticity and synaptic remodeling. Results: Evidence from animal models suggests that EE induces significant glial modifications, including increased synaptogenesis and enhanced neuronal connectivity. Studies in rodent models of ASD have demonstrated that EE reduces stereotypical behaviors, improves social interactions, and enhances cognitive function, effects that are closely associated with astrocyte and microglia activity. Similarly, human studies indicate that EE interventions lead to reduced autism symptom severity and improved cognitive outcomes, further supporting the hypothesis that glial cells play a central role in mediating the beneficial effects of EE. Conclusions: This review highlights the potential of EE as a modulator of the brain's microenvironment, emphasizing the critical role of glial processes in ASD intervention. These findings suggest that future therapeutic strategies for ASD should integrate approaches that specifically target a glial function to optimize intervention outcomes. However, further research is needed to optimize EE protocols and address ASD heterogeneity.

Keywords: enriched environments; autism spectrum disorder; neuroplasticity; glial cells; intervention

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1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social behavior, deficits in verbal and non-verbal communication, restricted interests, and aberrant repetitive behavior [1,2]. The etiology of ASD involves a multifaceted interplay of genetic factors—including idiopathic–syndromic continuum—along with environmental and epigenetic influences, collectively disrupting

typical brain development and function [3,4]. This disruption manifests as deficits across multiple domains, including social behavior, cognitive processes, emotional regulation, and sensory integration [5]. Despite advances in both pharmacological and behavioral therapeutic interventions, the heterogeneity of ASD presents significant challenges in identifying universally effective treatments.

In this context, enriched environments (EEs) have emerged as a promising complementary approach for ASD treatment. Originally studied in animal models, EEs are characterized by modifications in the environment and lifestyle that promote sensory, cognitive, and motor stimulation, which have been shown to enhance neuroplasticity and lead to behavioral improvements, including enhancements in sexual behavior, learning, and memory [6,7]. Extending this concept to human studies, evidence suggests that enriched environments can result in significant improvements in autism symptomatology and cognitive abilities [8–10].

Recent research highlights the role of glial cells as potential mediators of the neuroplastic changes associated with enriched environments. Traditionally regarded as mere support for neurons, glial cells are now recognized as active participants in synaptic plasticity and brain repair [11]. This article explores the potential of EE to modulate glial processes, proposing that these changes may underlie the observed behavioral and cognitive improvements in children with ASD. A deeper understanding of these mechanisms may pave the way for innovative therapeutic strategies tailored to the unique neurobiological needs of individuals with ASD.

2. Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by repetitive stereotyped behaviors, cognitive inflexibility, socio-affective impairments, deficits in verbal and non-verbal communication, and difficulties in social interactions across various contexts, as well as sensory processing challenges. Individuals with ASD exhibit neurodevelopmental alterations that emerge early in life (within the first three years) and often persist throughout the lifespan to varying degrees [1,12]. According to the DSM-V, the severity of ASD is determined by impairments in social communication, restricted interests, and repetitive behavioral patterns, including attachment to specific objects, stereotyped speech, simple motor stereotypes, restricted interests, and hyper- or hypo-reactivity to sensory stimuli. While there is currently no cure for ASD, appropriate treatment can foster relatively typical development and help reduce maladaptive behaviors. Additionally, ASD is frequently accompanied by impairments in adaptive functioning, sensory processing disorders, aggression, or self-injury [1].

2.1. Epidemiology and Prevalence

ASD is a prevalent condition, affecting approximately 1% of the global population. It occurs more frequently in males than in females, with a male-to-female ratio of approximately 4:1. However, research suggests that autistic females tend to exhibit higher cognitive abilities than autistic males, indicating that the condition may have a greater impact on males than on females with ASD [13–16].

Studies indicate that 50 to 70% of individuals with ASD experience cognitive and behavioral challenges, including aggressive behaviors, resistance to instructions or demands, difficulties adhering to social norms, and heightened negative emotionality, among others [17]. Additionally, approximately 30% of individuals with ASD have an intellectual disability. Among children with ASD, 82% require reasonable adjustments or curricular adaptations to meet their specific educational needs [18].

Several comorbidities have been associated with ASD. For instance, abnormalities in electroencephalographic activity and seizure disorders have been observed in 20% to 25% of individuals with ASD [13]. One of the most common comorbidities is sleep disturbances, affecting approximately 40 to 80% of children with ASD. These disturbances include irregular sleep–wake patterns, decreased sleep efficiency, reduced total sleep duration, delayed sleep onset, increased nighttime awakenings, bedtime resistance, and excessive daytime sleepiness [19–21].

Additionally, comorbidities frequently observed in individuals with ASD, such as mood disorders and gastrointestinal dysfunction, should be acknowledged. The gut–brain axis has also been identified as a key pathway linking gastrointestinal disturbances with ASD symptomatology. Dysbiosis in gut microbiota composition has been associated with disruptions in microbial metabolite production, which may influence neurodevelopment, neurotransmitter signaling, and social behavior. Emerging evidence suggests that microbiota-targeted interventions, including probiotics and fecal microbiota transplantation, may modulate brain function and mitigate both behavioral and physiological symptoms in ASD [22].

2.2. Etiology

There is no consensus on the etiology of ASD, as most cases are idiopathic, and no single factor fully explains the pathology and prevalence of ASD [4]. However, based on the potential causes of ASD, it can be classified into two main types: primary autism, which has a genetic basis, and secondary autism, which arises because of various environmental, metabolic, and immunological factors. Secondary autism has been associated with immune system dysfunctions, malnutrition, vitamin deficiencies, food allergies, gluten intolerance, gastrointestinal issues, thyroid dysfunction, prenatal complications, maternal infections during pregnancy, advanced parental age, exposure to antiepileptic drugs such as valproic acid, lead or mercury poisoning, substance abuse during pregnancy, and environmental radiation, among others [23].

In clinical research, three main risk factors have been linked to the development of ASD: genetic predisposition [24,25], prenatal exposure to teratogens [12], and epigenetic mechanisms [26].

2.2.1. Genetic Predisposition

One of the first studies that suggested a genetic component in ASD was conducted by Folstein and Rutter [27]. Their research revealed that autism is more likely to occur in both monozygotic twins, whereas this concordance is significantly lower in dizygotic twins. This assertion was later confirmed by subsequent studies [25,28], which found that the concordance rate for monozygotic twins is approximately 70%, compared to nearly 0% for dizygotic twins [25].

Primary autism has a genetic basis, in which polygenic inheritance, where multiple genes across different chromosomal loci contribute to the disorder. Various studies have identified genetic alterations associated with ASD, including mutations in genes involved in cell signaling proteins, which are crucial for neuronal differentiation, development, growth, and synaptogenesis [25,29]. Additionally, autoantibodies targeting specific brain tissues and proteins—such as myelin basic protein, neurofilament proteins, and vascular endothelium—have been detected in individuals with ASD [23,25,30].

2.2.2. Prenatal Exposure to Teratogens

Exposure to at least one of three teratogens during the prenatal period is considered a risk factor for the development of autistic traits: thalidomide [31], valproic acid (VPA) [32], and ethanol [33].

Thalidomide is a potent sedative that was widely used in the 1950s to treat pregnancy-induced nausea. However, its teratogenic effects became evident due to the occurrence of rare congenital malformations, such as amelia (absence of one or more limbs), phocomelia (underdevelopment of limb bones), and finger hypoplasia or absence [34]. Strömland et al. [31] reported that about 5% of Swedish children exposed to thalidomide during gestation met the criteria for ASD according to the DSM-III-R. The sensitive period for the teratogenic effects of thalidomide is 20 to 36 days after conception (35 to 51 days from the first day of the last menstrual period), a critical window for neural tube closure and the development of the first neurons, which form the motor nuclei of the cranial nerves [35]. Notably, autistic individuals exhibit cranial nerve nucleus abnormalities, which have been linked to early developmental deficits associated with ASD [36].

Valproic acid (VPA) is a widely used antiepileptic drug; however, when administered during the first trimester of pregnancy, it has been linked to an increased risk of myelomeningocele [32,37]. Additionally, it is a well-documented teratogen responsible for fetal valproate syndrome [32,38]. Williams et al. [32] reported six cases of children with fetal valproate syndrome who also met the diagnostic criteria for autism according to the DSM-IV, suggesting a potential relationship between VPA exposure and autistic behaviors.

One of the most extensively used animal models for ASD research involves prenatal injection of VPA on day 12.5 of gestation in rats. Offspring of female rats exposed to VPA at this stage exhibit brain abnormalities similar to those observed in autistic individuals, including: (a) shortening of the region caudal to the facial nucleus and lengthening of the region rostral to it; (b) reduced cerebellar nucleus interpositus (analogous to the globose and emboliform nuclei in humans); (c) decreased number of motor neurons in the oculomotor, trigeminal, abducens, and hypoglossal nuclei of cranial nerves; and (d) smaller cerebella with a reduction in Purkinje cells, more pronounced in the posterior lobe than in the anterior lobe [36,39].

Schneider and Przewłocki [12] investigated the behavior of rats exposed to VPA on gestational day 12.5. Their findings demonstrated that VPA-exposed rats displayed the following:

1. Lower pain sensitivity but higher sensitivity to non-painful stimuli;
2. Diminished acoustic prepulse inhibition;
3. Locomotor and repetitive/stereotypic-like hyperactivity, coupled with reduced exploratory behavior;
4. Decreased frequency of social behaviors and increased latency to initiate social interactions.

These behavioral abnormalities closely resemble autistic traits. In a subsequent study, Schneider et al. [7] explored the effects of EE in VPA-exposed rats. They found that EE reduced stereotypical behaviors while enhancing social interactions and exploratory activity. Additionally, VPA-exposed rats raised in an enriched environment exhibited greater pain sensitivity and lower anxiety compared to those housed in a standard environment.

Although autistic behavior has not been traditionally linked to prenatal alcohol exposure, Nanson [33] reported six case studies of children who met the diagnostic criteria for autism, all of whom had a history of fetal alcohol syndrome. Later studies confirmed this finding, revealing a clear correlation between the severity of ASD and the degree of prenatal alcohol exposure. Moreover, research has reported comorbidities between fetal alcohol syndrome and Asperger syndrome, as well as autistic-like behaviors, such as impaired social skills [40]. However, further research is required to establish a more definitive conclusion regarding this association.

2.2.3. Epigenetic Mechanisms

Epigenetics focuses on heritable changes in gene expression, with DNA methylation being one of its primary regulatory mechanisms. This process involves the addition of methyl groups to cytosines within the DNA sequence, typically leading to gene silencing. In individuals with ASD, specific epigenetic modifications, such as hypermethylation or hypomethylation of genes associated with synaptic plasticity and neuronal communication, have been identified. These alterations can disrupt critical biological pathways essential for proper brain development [26].

Furthermore, environmental factors—including drugs and/or alcohol consumption and maternal stress during pregnancy—can influence epigenetic marks, thereby increasing the risk of ASD. These epigenetic modifications affect regulatory regions of the genome, impacting key neurodevelopmental processes such as synapse formation and the regulation of executive functions [26].

Abnormal DNA methylation patterns have been observed in several neurodevelopmental and neurodegenerative disorders, including ASD, where they may disrupt transcriptional regulation, chromosomal stability, and tissue-specific gene expression [41]. Notably, the 15q11–q13 chromosomal region is frequently implicated in ASD, with candidate genes such as GABRB3, GABRA5, GABRG3, UBE3A, and others showing epigenetic dysregulation in both syndromic and nonsyndromic cases [42]. Experimental models have further underscored the impact of environmental exposures on epigenetic modulation in genetically predisposed subjects. For example, the imprinting defects seen in Angelman syndrome, a condition that shares phenotypic overlap with ASD, provide evidence that epigenetic dysregulation—via altered DNA methylation of key regulatory genes like UBE3A—may contribute to the manifestation of ASD [41].

2.3. Behavioral Features of ASD

ASD is primarily characterized by its behavioral manifestations. This behavioral dominance has facilitated the identification and classification of a range of behavioral alterations used to diagnose ASD [5]. These distinct behavioral changes are often described as a triad: deficits in verbal and/or non-verbal communication, deficits in social skills, and the presence of repetitive behaviors and restricted interests. However, it is important to note that ASD is a spectrum, meaning that clinical manifestations, both in terms of type and severity, can vary significantly across individuals. Additionally, these features, and their intensity, can severely impact learning, development, and, consequently, the quality of life individuals may attain.

Communication impairments in ASD can manifest both verbally and non-verbally, varying according to the individual's intellectual and behavioral development. At the verbal level, impairments may involve the absence of verbal communication or a severe delay in language acquisition. In other cases, there may be an initial period of speech development that later stagnates or even regresses, leading to a loss of communicative functions. Moreover, when verbal language is present, it tends to be rigid, restricted, lacking semantic and pragmatic content, and characterized by a tendency toward literal interpretation and reversal of personal pronouns [43].

Additionally, echolalia, verbal auditory agnosia, phonological–syntactic syndrome, selective mutism, and prosody disorders may arise [44,45]. Non-verbal language is affected by the limited eye contact and attentional engagement typically observed in individuals with ASD, making it difficult for them to establish social relationships as they may appear impolite or disinterested. Similarly, deficits in performing and understanding social gestures hinder the integration of non-verbal communication within a social context [46]. These communication impairments—both verbal and non-verbal—restrict the development

of linguistic skills, reducing the individual's autonomy, hindering the formation of social relationships [47], and compromising or even preventing academic progress.

Some studies have identified early signs of social behavior deficits, which can be observed as early as the first months of life. These include poor eye contact, lack of visual tracking and orientation, failure to respond to their name, and infrequent social smiles [48,49]. However, these signs often go unnoticed by parents.

During the early years of a child's life, deficits in social skills become more evident. These may include difficulties in initiating and/or maintaining relationships with peers, family members, or adults; a preference for spending time alone while avoiding physical contact; unconventional use of toys (e.g., stacking toy cars); difficulty understanding and expressing emotions; and a lack of interest in interacting with others. These challenges often lead to the perception that individuals with ASD may spend their entire lives in isolation [50].

Regarding repetitive behavior patterns and restricted interests, the DSM-V [1] describes them as consistent motor and/or verbal behaviors (e.g., vocalizations such as words, sounds, or hand flapping). Additionally, ritualized behaviors and inflexibility toward changes in routine are common (e.g., repeatedly watching or listening to the same movie or song). Individuals with ASD may also exhibit overly specific and restricted interests, often diverging from what is socially accepted [51].

Other behaviors identified within the spectrum, though not part of the disorder's core behavioral triad, include self-injurious behaviors, problematic behaviors (e.g., aggression, negativism, property destruction, etc.), and difficulties in emotional regulation (e.g., extreme irritability or anger, excessive joy, etc.) [5]. Furthermore, the presence of hyper- or hyposensitivity can influence their behavior and may even pose health risks by altering their perception of physical sensations, such as hunger, fatigue, or pain [51].

2.4. Neurobiology of ASD

Although the diagnosis of ASD is primarily based on its behavioral phenotype, various studies have sought to investigate the brain characteristics that may be associated with the disorder. This interest, coupled with technological advancements in non-invasive techniques, has enabled research into biological markers in individuals with ASD from early childhood through adulthood. These studies focus on both cortical and subcortical regions, as well as their connectivity, providing evidence to support theories about the neuronal processes underlying ASD. Postmortem and structural magnetic resonance imaging (MRI) studies have highlighted the frontal lobes, amygdala, basal ganglia, and cerebellum as being pathological in autism. Amaral et al. [52] suggest that the heterogeneity of both the core and comorbid features predicts a heterogeneous pattern of neuropathology in ASD.

2.4.1. Neural Alterations

One proposed theory suggests that ASD involves brain overgrowth during the early years of life, followed by a subsequent deceleration. This growth pattern begins with a reduced head size at birth, followed by a sudden and excessive increase [53,54]. This theory is supported by neuroimaging studies, which have identified overgrowth in regions of the frontal lobe, cerebellum, and limbic structures during early childhood [53–56].

Another hypothesis suggests alterations in brain structures involved in the reward system, which may explain why individuals with ASD show a stronger preference for non-social rewards over social ones [57]. Several studies have employed different techniques to identify structural or morphological abnormalities in the brains of individuals with ASD. Among the most extensively studied brain regions is the amygdala.

The amygdala is one of the most studied areas in ASD due to its role in emotional processing. Some studies report an increase in the size of the ASD's amygdala by up to 15% during childhood, compared to control groups. In contrast, other studies conducted in adolescents and adults found no differences, and some even observed a smaller amygdala volume relative to the control groups. These findings support the hypothesis proposed by Courchesne [53]. Additionally, this amygdalar overgrowth has been linked to greater social and communicative impairments in ASD [58].

Other studies using functional magnetic resonance imaging (fMRI) have found that individuals with ASD exhibit reduced activation of the right amygdala and the fusiform gyrus in response to a social stimulus (such as gaze perception), compared to individuals without ASD [59]. Regarding the fusiform gyrus, its activation has been linked to eye gaze fixation, and in ASD, hypoactivation of this area has been observed [60].

Similarly, MRI revealed that brain volume undergoes accelerated growth during the early years of life, approximately between the ages of 2 and 4, continuing until before adolescence [56]. This increase in brain volume has been attributed to an increase in both gray and white matter. Specifically, an increase in white matter has been found in the brain lobes, with a greater effect observed in the frontal lobes [61].

Another reported anomaly concerns cortical minicolumns, which have been found to increase in number, become narrower, and contain smaller neuronal cell bodies and nucleoli, as well as a reduced neuropil space. This anomaly has led to the hypothesis of a probable deficit in cortical inhibition, which may explain the sensory deficits, information processing difficulties, and the high prevalence of seizures observed in ASD [62].

Moreover, irregularities in brain activation and connectivity have been found through fMRI studies assessing various cognitive tasks. The most notable findings from these studies suggest that both individuals with ASD and neurotypical individuals use the same brain structures to perform tasks. However, the activation patterns and connectivity differ. Specifically, reduced activation, connectivity, and correlation have been observed in cortical regions involved in higher-order tasks, such as working memory, language, and problem-solving [63,64]. These anomalies have been linked to alterations in the corpus callosum, although the results remain inconclusive [65].

The cerebellum has gained increasing attention in recent years due to its extensive connectivity with regions such as the thalamus and frontal lobes, which are crucial for cognitive, emotional, and sensorimotor integration. Emerging evidence suggests that cerebellar dysfunction may play a significant role in the pathophysiology of ASD, contributing to deficits in motor coordination, executive function, and social cognition. In individuals with ASD, a reduction in Purkinje cells has been observed in both the cerebellar hemispheres and the vermis, potentially disrupting cerebellar modulation of higher-order cortical processes [66]. However, further research is needed to deepen our understanding of the alterations in these brain structures in relation to ASD.

2.4.2. Glial Alterations

Despite the substantial impact of neuroglial cells on neurodevelopment processes such as synaptic stripping, brain immune function, the epigenetic interface for environmental stimuli, stem cell development, and synaptic transmission, research on ASD has largely overlooked these cells, since ASD studies have primarily focused on neurons and brain regions' functionality. Recent findings have demonstrated that dysfunctions in macroglia, such as astrocytes and oligodendrocytes, as well as in microglia, also play a critical role in the pathogenesis of ASD. Unfortunately, the results of these studies are often complex and heterogeneous, reflecting the intricate molecular and cellular mechanisms underlying ASD. Nevertheless, some studies have demonstrated that VPA-exposed rats exhibited

neuroglial pathological phenotypes. This new perspective opens a relatively unexplored field of research, placing neuroglial disorders at the forefront [39,67].

For instance, Bronzuoli et al. [68] examined the role of neuroglial cells—astrocytes, oligodendrocytes, and microglia—in VPA-prenatally exposed rats. The researchers assessed the autistic-like behavior of the rats at different developmental stages: infancy (postnatal day 13), adolescence (postnatal day 35), and adulthood (postnatal day 90). Behavioral evaluations included isolation-induced ultrasonic vocalizations, the three-chamber sociability test, and the hole board test to assess stereotypical behaviors. Results indicated that VPA-exposed offspring emitted fewer ultrasonic vocalizations when isolated, suggesting impaired early social communication. During adolescence and adulthood, these rats exhibited reduced sociability and increased stereotypic behaviors, aligning with key features of ASD.

Astrocytes form non-overlapping domains and establish contact with thousands of synapses, actively regulating their formation and maturation through molecules such as thrombospondins, glypican 4, and neuroligins. They also modulate neuronal excitability by maintaining extracellular K^+ homeostasis and clearing glutamate via EAAT1 and EAAT2, thereby preventing excitotoxicity. Through metabotropic neurotransmitter receptors, astrocytes activate intracellular signaling cascades, including the PLC-IP_3 pathway, which increases cytosolic Ca^{2+}, particularly within synaptic processes [69].

Astroglial–neuronal communication is bidirectional, with astrocytes releasing gliotransmitters such as D-serine, ATP, and, under specific conditions, glutamate, thereby influencing synaptic plasticity. Additionally, they regulate neurotransmission through ion and neurotransmitter uptake, transcriptional modulation, and the secretion of synapse-regulating proteins. These multifaceted functions position astrocytes as key regulators of neuronal homeostasis and synaptic plasticity, underscoring their critical role in the functional dynamics of the central nervous system [69].

Pathological alterations in astroglia are complex and are categorized into different forms. (i) reactive astrogliosis; (ii) astroglial atrophy with loss of function; and (iii) pathological remodeling of astrocytes. This pathological phenotype has been associated with alterations in neurogenesis, synaptogenesis, reduced homeostatic capacity, lack of neuronal trophic support, and reactive gliosis. In addition to preserving brain stability, microglia act as the brain's defense system. Glial cells rapidly respond to brain injuries by undergoing significant morphological, biochemical, and functional changes [67].

Respecting the astrogliosis, it has been reported that VPA-exposed rats exhibit this process. For instance, Traetta et al. [70] investigate the role of microglia–astrocyte communication in neuroinflammation and synaptic alterations in an autism model induced by prenatal VPA exposure. In VPA-exposed Wistar rats, microglia and astrocytes exhibited a reactive phenotype with microgliosis and astrogliosis by postnatal day 35. In vitro experiments confirmed these alterations, demonstrating that microglia from VPA-exposed rats exhibited chronic inflammation, impaired phagocytic response, and disrupted communication with both neurons and astrocytes. Dysfunctional microglia–astrocyte crosstalk may be a key contributor to neuroinflammation in autism, highlighting a potential therapeutic target for future interventions.

Similarly, Russo et al. [71] examined the role of astrocytes in neuronal dysfunction in non-syndromic ASD using iPSC-derived neural cultures. Synaptogenesis and neuronal activity were assessed via a multi-electrode array (MEA) platform, alongside investigations into astrocyte-mediated neuronal maintenance. Findings revealed that ASD-derived neurons exhibited reduced synaptic gene expression, lower synaptic protein levels, diminished glutamate release, and decreased spontaneous firing rates. ASD astrocytes impaired neuronal development, whereas control-derived astrocytes rescued neuronal morphology and

synaptogenesis deficits. IL-6 secretion was identified as a key factor underlying neuronal dysfunction, and its blockade successfully enhanced synaptogenesis.

On the other hand, oligodendrocytes are considered to be myelinating cells of the brain and constitute approximately 75% of all glial cells in the adult central nervous system (CNS). Notably, in the peripheral nervous system, their functional counterparts are Schwann cells. Beyond axonal myelination, oligodendrocytes regulate extracellular potassium homeostasis, provide metabolic and trophic support to myelin, secrete glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), and modulate axonal growth. These functions underscore their critical role in CNS physiology, and they have been implicated in the pathogenesis of both neurodevelopmental and neurodegenerative disorders [41].

In animal models of ASD, reduced proliferation of oligodendroglial cells and decreased levels of myelin basic protein (MBP) suggest impaired myelination processes. Disruptions in oligodendrocyte maturation, evidenced by abnormal white matter development in ASD patients and altered protein expression in animal models, appear to be linked to chromosomal abnormalities, particularly in the 15q11–q13 region, and may contribute to impaired neuronal connectivity and behavioral deficits [72]. In this context, Graciarena et al. [73] investigated whether alterations in oligodendrocyte-lineage cells and myelination occur in a murine model of ASD induced by prenatal VPA exposure. The researchers found that adult VPA-exposed mice exhibited hypomyelination in the basolateral amygdala and piriform cortex, regions implicated in social behavior. This hypomyelination was accompanied by a reduction in the number of oligodendrocyte-lineage cells and mature oligodendrocytes in the piriform cortex and a decrease in mature oligodendrocytes in the medial prefrontal cortex, despite no overall alterations in prefrontal myelination. Interestingly, the number of oligodendrocyte progenitor cells remained unchanged, and there were no differences in histone deacetylase activation in oligodendrocyte-lineage cells in adulthood.

At the molecular level, alterations in gene and protein expression were identified in neuroglial cells across key brain regions, including the hippocampus, prefrontal cortex, and cerebellum. These changes were most pronounced during infancy and adolescence, primarily manifesting as transcriptional modifications, and appeared to diminish by adulthood. Despite these molecular and behavioral alterations, there was no evidence of significant widespread or chronic neuroinflammation in the glial cells [68].

Both animal model studies and clinical observations reveal glial abnormalities in ASD. Genes associated with ASD susceptibility play crucial roles in brain development and are highly expressed in glial cells. Notably, mutations in genes encoding neuroligins (NLs), which are critical for the formation and function of synaptic structures, have been linked to ASD. These mutations have also been associated with other neurodevelopmental disorders, including autism. Research on transgenic mice carrying these mutations shows impaired social behavior and heightened stereotypical behaviors, suggesting a conserved role of NLs in ASD across species. NLs are specifically expressed in astrocytes and oligodendrocytes, with growing evidence indicating their role in regulating synaptogenesis and synaptic transmission—both of which are disrupted in ASD [67].

In broad terms, the etiological processes underlying ASD are summarized in Figure 1, which illustrates how disruptions in the intrauterine environment—whether due to teratogens or other environmental factors—can trigger microglial activation and, consequently, alter gene expression. In individuals with a genetic predisposition, these perturbations may lead to dysfunctions in both macroglial cells and neurons. Macroglial impairments, in turn, can affect neuronal physiology and development, ultimately contributing to the neurobiological alterations characteristic of ASD.

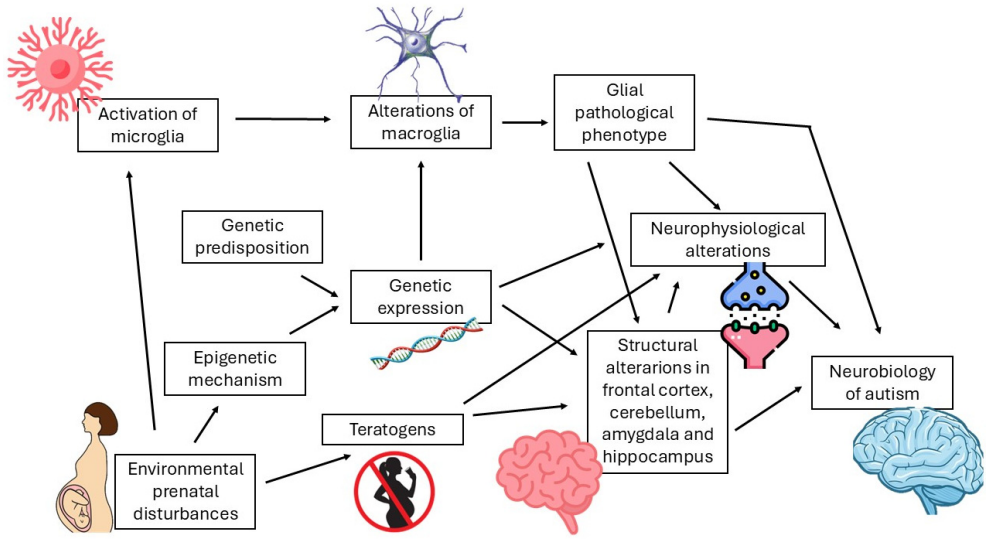


Figure 1. Schematic representation of the possible interaction among the etiological mechanisms and the main neurobiological impairments reported for individuals with ASD.

2.5. Treatments for ASD

Currently, a variety of treatments and therapies are available for managing ASD; one of the most common is pharmacological treatment. However, there is currently no medication with sufficient scientific evidence to support its efficacy for addressing the core symptoms of ASD [74]. Nevertheless, pharmacological treatments have proven helpful in addressing comorbidities associated with ASD, such as irritability, inattention, sleep disturbance, and others [5]. The following is a non-exhaustive list of pharmacological treatments that have been used to address certain symptoms in individuals with ASD.

Specifically, antipsychotics, such as aripiprazole and risperidone, are considered effective for managing irritability and aggression [75,76]. Medications such as melatonin and trazodone are commonly used to address sleep disorders in individuals with ASD. Moreover, medications typically prescribed for Attention-Deficit/Hyperactivity Disorder (ADHD), including methylphenidate, clonidine, and guanfacine, have shown efficacy in alleviating certain ASD symptoms [5,76]. More recent research has explored the potential of N-acetylcysteine, balovaptan, ketamine, riluzole, memantine, and cannabinoids in reducing ASD-related symptoms such as aggression [76]. However, to date, risperidone and aripiprazole remain the only medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of ASD.

Despite their use, pharmacological treatments for ASD face several challenges. One major barrier is the heterogeneity of the disorder, which limits the ability to generalize and replicate results across the entire ASD population. Additionally, concerns regarding both the short- and long-term effects of medication, along with the prevalence of polypharmacy, complicate the use of pharmacological interventions in treating ASD [5]. As a result, non-pharmacological treatments, such as behavioral therapies, have also been explored as alternatives. Behavioral therapy, particularly Applied Behavior Analysis (ABA), is one of the most widely used interventions for individuals with ASD [77].

ABA is an intervention grounded in the principles of behaviorism, aimed at increasing, decreasing, maintaining, or generalizing specific behaviors by focusing on the observable relationship between behavior and environment [78]. It employs systematic processes to shape behavior, promoting desired behaviors while discouraging undesirable ones, to enhance the individual's skills and abilities. In the context of ASD, ABA primarily targets improvements in verbal, intellectual, and social functioning [79].

Several methodologies have been developed within the framework of ABA to address the needs of individuals with ASD, including Discrete Trial Training, Early Intensive Behavioral Intervention, Pivotal Response Training, Verbal Behavior Intervention, the UCLA Model, and the Lovaas Method, among others. Despite ABA's broad recognition and the extensive scientific evidence supporting its effectiveness in treating ASD, several criticisms have been raised regarding its approach. Key concerns include its insufficient consideration of the neurological characteristics of individuals with ASD, the rigor of the research supporting its use, its scope, ethical implications, and the economic costs of its application [77,79].

Comprehensive treatment models, which consist of long-term interventions designed to produce broad developmental impacts, also play a significant role in ASD treatment. One such model, the Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH), emphasizes structured teaching, the use of schedules and agendas, modifications to physical space, and adaptations in the type of information presented to individuals with ASD. Evidence suggests that this approach has led to improvements in communication skills, social interaction, motor skills, and imitation, as well as a reduction in maladaptive behaviors. However, additional research is needed to generalize these findings to the broader ASD population [80].

Cognitive–behavioral therapy (CBT) is another widely used intervention, particularly for high-functioning individuals with ASD. This approach assumes that cognition influences behavior and vice versa, with the goal of monitoring and modifying cognitive and behavioral patterns to generate positive changes. CBT has been found effective in treating anxiety, improving social skills and adaptive behaviors, and reducing disruptive behaviors, although scientific evidence supporting its effectiveness in reducing disruptive behaviors remains limited. This therapy has shown promise in addressing emotional aspects, such as helping individuals with ASD recognize and express their feelings. However, further research is needed to solidify the scientific evidence supporting CBT's application for ASD [81].

From an occupational therapy perspective, the Ayres Sensory Integration model is another proposed intervention for ASD. This model explains the relationship between sensory processing deficiencies and the environment, highlighting neuroplasticity as a key component of intervention. Despite limited evidence supporting its widespread application, studies indicate that this model has led to improvements in sensorimotor skills, social skills, attention, self-regulation, and even academic skills, such as reading and writing. However, further research is needed to confirm its efficacy [82,83].

Family-based interventions also play a critical role in the treatment of ASD. Programs such as the Hanen More Than Words Program provide early intervention for parents of children with ASD, equipping them with tools and strategies to enhance their child's communication development. These interventions involve combined sessions aimed at helping families transform everyday activities into learning opportunities for their child. Such programs have proven effective not only in reducing disruptive behaviors but also in alleviating the stress experienced by parents [84].

Given the broad range of methods and interventions available for treating ASD, it is clear that the disorder's heterogeneity poses a significant challenge to the generalization of results across the population. Evidence suggests that no single treatment approach is universally effective for all individuals with ASD. Furthermore, some interventions may be more effective when used as adjuncts, such as in combination with pharmacological treatments. Lifestyle changes, such as environmental enrichment, may also offer potential benefits when integrated with behavioral interventions, as discussed in the following section.

3. Environmental Enrichment

To date, environmental enrichment (EE) lacks a universally accepted definition. However, the core concept suggests that it is essential to provide an environment abundant in diverse and salient stimuli for the individuals who inhabit it [85–89]. One of the pioneers in establishing the EE in animals was Robert Yerkes, who, at Quinta Palatino in Havana, Cuba, provided captive primates with spacious enclosures, favorable climates, food, water, and stimulating objects to compensate for the environmental limitations they faced in captivity [90]. Thus, enriched environments can be understood as settings originally designed to offer animals motor, sensory, social, and cognitive stimuli, enabling behaviors that are otherwise constrained in environments such as laboratories or zoos [88].

Specifically in research contexts, the design of an EE varies, as the size and type of stimuli depend on the species to be housed. However, it must meet certain essential criteria that distinguish it: in addition to providing stimuli, these must be adjusted throughout the subjects' stay. The space itself should also be larger compared to typical laboratory accommodations [85,87]. In this regard, enriched environments have been broadly applied to describe a diverse range of interventions aimed at enhancing cognitive, emotional, social, and motor functions. However, the lack of a clear and systematic classification makes it challenging to compare studies and pinpoint the specific mechanisms underlying each type of intervention. To address this gap, we propose a structured framework that categorizes EE interventions based on their primary focus, encompassing at least four key domains: cognitive stimulation, social interaction, physical activity and health, and sensory stimulation.

Interventions centered on cognitive stimulation are designed to enhance learning, memory, and executive function through exposure to novel and cognitively demanding stimuli. These typically include objects that promote exploration and problem-solving, spatial navigation tasks, and periodic reconfiguration of the environment to foster adaptability and cognitive flexibility. Such approaches have been shown to promote synaptic plasticity, particularly in the hippocampus and prefrontal cortex, which are critical for higher-order cognitive processes [91].

In contrast, social interaction within an EE plays a crucial role in shaping affiliative behaviors and social cognition, aspects that are particularly relevant in therapy of ASD. Strategies such as group-based social skill interventions, immersive socialization interventions, and/or referential communication training programs have been demonstrated to modulate the social skills and prosocial behaviors [92].

Physical activity represents another fundamental dimension of EE, given that exercise has a profound impact on neurogenesis, synaptic plasticity, and stress resilience. Animal model interventions in this category include access to running wheels, climbing structures, and task-directed motor training, all of which have been associated with increased hippocampal neurogenesis, enhanced mitochondrial function, and improved regulation of the hypothalamic–pituitary–adrenal axis. These factors are particularly relevant for mitigating the heightened stress reactivity often observed in ASD models [93].

Another crucial component of EE is sensory and experiential diversity, which aims to enhance sensory processing and perceptual integration—functions frequently disrupted in ASD. This category includes exposure to varied tactile stimuli through different textures and materials, complex auditory inputs such as species-specific vocalizations, controlled lighting conditions, and olfactory enrichment. These interventions have been linked to cortical plasticity changes and may help restore the balance between excitatory and inhibitory neuronal activity, a fundamental mechanism underlying the neurobiology of ASD [94].

In this context, following Donald Hebb's principles, it is argued that the environment can influence both psychological and biological processes, leading to changes in neural

functionality and morphology that may persist over the long term [95]. In his book, Hebb stated that "When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased [96]". Thus, researchers have proposed that EE can impact various levels, including biochemical [97], which led to the emergence of new scientific investigations that continue to explore the effects and applications of this environment, particularly due to its potential use in the treatment of neurodegenerative diseases.

EE has proven to be neuroprotective in various instances of neural insult or injury, such as seizures [98], and in models of neurodegenerative disorders like Parkinson's disease [99] and intellectual disability such as Down syndrome [100]. The beneficial effects of EE on neural outcomes following injury are often attributed to increased neurogenesis and enhanced neuronal survival. However, glial cells, including microglia and astrocytes, play a crucial role as the primary immunocompetent cells of the brain. Their functions are pivotal in both injury response and tissue repair. Increasingly, it is recognized that glial activity during the repair process may serve as a fundamental mechanism underlying the neural improvements and rehabilitation observed after exposure to EE [12].

3.1. Neurobiological Effects of EE

The neurobiological effects observed in animal models exposed to EE depend on various factors, including age, gender, duration of exposure, and the specific life stage during which the exposure occurred, among others. Nevertheless, the primary effects reported can be summarized as follows: improved synaptic efficacy, increased cortical thickness, and glial changes [101–103].

3.1.1. Synaptic Efficacy

Studies have demonstrated that rodents exposed to EE exhibit functional changes in the synaptic and cellular properties of neurons in various brain regions. For example, in the dentate gyrus of the hippocampus, increases in synaptic transmission and cell excitability become evident after short-term exposure to EE [102].

This enhancement of synaptic efficacy has been confirmed in animal models of certain syndromes. For instance, Begenisic et al. [100] showed that genetically modified mice, used as a model for Down syndrome, exhibited a reduction in GABAergic inhibition and improved synaptic plasticity in the hippocampus following exposure to EE during the adult period (>60 postnatal days). These animals also demonstrated enhanced visuospatial memory in the Morris Water Maze. Thus, it is evident that EE could serve as an adjunctive therapy for neurodevelopmental disorders.

3.1.2. Cortical Thickness

A series of experiments conducted by Diamond and colleagues revealed that rats housed in an enriched environment exhibited greater cortical thickness compared to those in standard and impoverished environments. This increase in cortical thickness was associated with greater dendritic density, dendritic spines, and synapses, indicating enhanced neuronal connectivity. Conversely, rats housed in impoverished environments showed cortical thinning, suggesting reduced neuronal stimulation and activity [101].

The influence of the duration of exposure to the enriched environment was also examined. Interestingly, a 30-day exposure was found to be more effective in inducing changes in cortical thickness than longer exposures, such as 80 days. This finding could be explained by the possibility that prolonged exposure to an unchanging enriched environment may become monotonous and lose its ability to effectively stimulate the brain [101].

Additionally, the combination of social interaction and varying objects was found to be essential to maximize the effects of enrichment. For example, rats housed alone in an enriched environment did not exhibit significant changes in cortical structure, suggesting that social interaction is a crucial component of enrichment [101].

3.1.3. Glial Plasticity

Glial plasticity can occur following exposure to EE due to several factors, including increased gliogenesis [104] and improvements in glial morphology [105]. In this regard, Ehninger and Kempermann [104] reported that there was no generalized cell proliferation or genesis across all cortical regions following EE exposure in adult mice, which included mice housed in bigger cages and a running wheel that allowed them an increase in physical activity. However, they observed a regional increase in glial cells. Specifically, they found that 40 days of exposure to EE led to a significant increase in the number of new astrocytes in layer 1 of the motor cortex. This result was interpreted as a plastic reaction to environmental enrichment.

Viola et al. [105] conducted a study evaluating astrocyte changes induced by EE in the hippocampus as a potential regulator of synaptic plasticity in mice. The enrichment housing apparatus contained two running wheels and a variety of objects, including toys, tunnels, hiding places, and nesting material. While no changes in the number of astrocytes were observed, their morphology exhibited a significant increase in the branching, number, and length of primary astrocytic processes, which extended in parallel orientation to CA1 nerve fibers. This transformation led to astrocytes adopting a more stellated morphology, which may be linked to the increase in hippocampal synaptic density observed in previous studies. These findings support the idea that structural modifications in astrocytic networks are fundamental to the plasticity processes occurring in the brain.

These glial changes have also been associated with improvements in cognitive functions, such as visuospatial memory. For example, Soffié et al. [106] analyzed the effects of EE on short-term memory for event durations and astrocyte characteristics (e.g., cell density, cell area, and GFAP immunoreactivity percentage) in the hippocampus, frontal cortex, and corpus callosum. This study included old rats (23 months) housed either under standard conditions or in an EE, as well as young adult rats (5 months) housed under standard conditions. The results confirmed memory and acquisition deficits associated with aging. However, EE reversed these deficits, improving acquisition speed, and enhanced the retention of short signal durations ("choose short effect").

Morphological analyses revealed that old rats housed under standard conditions exhibited numerous hypertrophied astrocytes with elongated processes in the hippocampus and corpus callosum. In contrast, old rats housed in EE conditions showed decreased astrocyte number and size. The combination of enriched housing and behavioral testing had additive effects, resulting in a significant reduction in astrocyte number, size, and GFAP immunoreactivity in old rats. These findings suggest that EE and behavioral testing may mitigate aging-induced gliosis, particularly in the hippocampus, highlighting their potential to counteract both the neurobiological and cognitive effects of aging [100].

On the other hand, oligodendrocyte transcription factor 2 (Olig2) is a key regulator of oligodendrocyte development, playing an essential role in differentiation and regeneration throughout adulthood. It modulates the functional specificity and activity of a Smarca4/Brg1-dependent chromatin-remodeling complex, a crucial mechanism for initiating the transcriptional programs that drive oligodendrocyte maturation and myelination in the CNS. Consistent with this, EE has been shown to enhance the number of bromod-

eoxyuridine (BrdU)-positive newborn cells in the mouse amygdala, with nearly all of these cells expressing the oligodendrocyte precursor marker Olig2 following just one week of enrichment [107].

In this context, in the study of Forbes et al. [108], mice were randomly assigned to either a hypoxic or normoxic rearing condition. At postnatal day 3 (P3), pups were exposed to an oxygen concentration of 10–11% within a sealed acrylic chamber for eight consecutive days (P3–P11), a developmental window analogous to 23–40 weeks of gestation in humans with respect to white matter oligodendrocyte development. To ensure proper nutrition during hypoxia, transgenic pups were housed with two foster mothers. Following hypoxic exposure, mice were allocated to either an enriched or a standard environment. The enriched environment consisted of larger Plexiglas cages outfitted with diverse tactile and cognitive stimuli—including suspended metal chains, wooden blocks, running wheels, and various plastic objects rearranged every three days—and accommodated groups of 8–12 mice, while standard cages contained only nesting materials and housed smaller groups. Hypoxic damage in this model led to white matter injury characterized by glial cell loss and disrupted myelination, which were linked to cognitive and behavioral deficits, evaluated by the inclined beam-walking task. Remarkably, early and continuous environmental enrichment promoted endogenous repair of the developing white matter by enhancing oligodendroglial maturation and myelination, as evidenced by RNA-sequencing data revealing oligodendroglial-specific responses to hypoxic injury, as well as a better performance in the inclined beam-walking task.

Environmental enrichment (EE) has been shown to mitigate cognitive impairments and reduce anxiety- and depression-like behaviors by modulating microglial activity and function in the brain [109]. For instance, Sah et al. [110] demonstrated that EE effectively reduces elevated trait anxiety, even when introduced during adulthood. EE cages consisted of a bigger cage, extra bedding material, and various toys, including a transparent tunnel, transparent T-shaped tunnel, rope ladder, wood bridge, wood suspension bridge, and ping pong ball. The anxiolytic effects of EE were associated with a decrease in microglial density in both the dentate gyrus (DG) and medial prefrontal cortex. Additionally, EE reduced the density of microglia in the anterior DG, suggesting a role in the normalization of neuroinflammatory imbalances.

Additionally, EE suppresses the production of the pro-inflammatory cytokine IL-18 and promotes the expression of the anti-inflammatory cytokine IL-10. Across various animal models, EE has been demonstrated to influence inflammatory pathways, exerting anti-inflammatory effects and modulating microglial activation. Some studies suggest that EE can attenuate neuroinflammation and oxidative stress [109].

Considering the studies discussed, it is evident that environmental enrichment (EE) influences both neural and glial processes. These enriched environments promote neuroplasticity and modulate glial cell activity, leading to more efficient synaptic connectivity and enhanced neuronal survival (Table 1). Consequently, EE is associated with improvements in cognitive function, supporting its potential as a complementary therapeutic strategy for neurodevelopmental disorders. Moreover, because EE does not involve adverse side effects, it may serve to potentiate other therapeutic interventions administered to individuals with ASD.

Table 1. Impact of environmental enrichment (EE) on synaptic, glial, and cognitive plasticity across different brain regions.

Author	Main Findings	Brain Structure
Begenisic et al. [100]	Genetically modified mice showed improved synaptic plasticity and visuospatial memory after EE exposure.	Hippocampus
Diamond et al. [101]	Rats in EE showed greater cortical thickness compared to standard and impoverished environments.	Cortex
Diamond et al. [101]	Thirty-day exposure to EE induced more cortical thickness changes than eighty-day exposure.	Cortex
Diamond et al. [101]	Social interaction was essential for maximizing EE effects.	Cortex
Ehninger and Kempermann [104]	Forty days of EE exposure led to a significant increase in astrocyte numbers in the motor cortex layer 1.	Motor cortex
Viola et al. [105]	EE exposure led to increased branching, number, and length of astrocytic processes in the hippocampus.	Hippocampus
Soffié et al. [106]	EE reversed aging-related memory deficits, improved acquisition speed, and reduced astrocyte hypertrophy in aged rats.	Hippocampus and corpus callosum
Forbes et al. [108]	EE promotes endogenous repair of hypoxia-induced white matter injury by enhancing oligodendroglial maturation and myelination.	White matter
Sah et al. [110]	EE promotes a normalization of neuroinflammatory imbalances due to anxiety.	Dentate gyrus and medial prefrontal cortex

3.2. Effects of EE on Autistic-like Behaviors in Animal Models

Studies investigating the effects of EE on autism have primarily been conducted using animal models. For example, Schneider et al. [9] evaluated the impact of EE on rats exposed to VPA, an animal model of ASD. They compared rats raised in standard conditions with those exposed to EE, which included spacious environments, novel objects, exercise wheels, and increased sensory and social stimulation. The results indicated that EE reversed most of the behavioral alterations induced by VPA. The enriched rats exhibited higher sensitivity to pain, better sensory processing, less repetitive activity, lower anxiety, and increased exploration. Additionally, they showed an increase in social interactions, with significant differences observed in adolescence and adulthood compared to the standard control groups. Furthermore, EE also benefited rats not exposed to VPA, reducing anxiety and enhancing sociability, suggesting general effects on brain plasticity. These findings support EE as a potential therapeutic strategy for ASD, promoting improvements in sensory modulation, emotional regulation, and social interaction. Given that previous studies in humans have reported similar benefits, it is suggested that EE could serve as an effective complementary intervention to alleviate ASD symptoms and improve quality of life.

Dorantes-Barrios et al. [6] conducted a study suggesting that enriched environments can mitigate cognitive and behavioral deficits in a rat model of ASD. Using a model based on prenatal exposure to VPA, the researchers explored how EE influences memory and sexual behavior in adulthood. The results showed that EE improved cognitive performance in the Morris water maze task, reducing the time it took for rats to find a hidden platform, suggesting improvements in spatial learning and memory. Furthermore, while VPA-exposed rats exhibited deficits in the object recognition task, EE enhanced their performance in this task, indicating a positive impact on memory and exploration. Regarding sexual behavior, EE reduced mounting and intromission latency and increased ejaculatory frequency in VPA-treated rats, suggesting recovery in the affected reproductive processes. These findings reinforce the importance of EE as an effective strategy to counteract ASD-related alterations, demonstrating its potential to improve cognition, social behavior, and reproductive processes in animal models.

Mansouri et al. [111] conducted a study exploring the effects of EE on male rats exhibiting autistic-like behaviors induced by maternal separation prior to weaning. The maternal separation model is commonly used to simulate early-life stressors, which are

thought to contribute to the development of neurodevelopmental disorders, including ASD. In this study, rats were subjected to maternal separation between postnatal days 1 and 14, a period known to be critical for the establishment of neurobiological systems involved in social, emotional, and cognitive functions. After weaning, these animals were placed in either enriched or standard housing conditions.

The results revealed that EE had a positive effect on reducing repetitive behaviors, such as marble burying and self-grooming, which are commonly associated with ASD in animal models. These behaviors are often considered core symptoms of autism and reflect abnormalities in sensory processing and self-regulation. Environmental enrichment, which included enhanced sensory, cognitive, and social stimulation, is known to facilitate neural plasticity and may help mitigate some of the deficits observed in neurodevelopmental disorders. This improvement in repetitive behaviors suggests that EE can potentially modulate the underlying neural circuits involved in these behaviors, such as those related to the striatum and prefrontal cortex.

However, this study also highlighted a significant caveat: while EE ameliorated certain aspects of behavior, it exacerbated anxiety-like symptoms in the same cohort of rats. This is a noteworthy observation, as the transition to an enriched environment was found to increase anxiety levels, potentially due to heightened sensory stimulation and social interaction demands, which can overwhelm animals with a predisposition to anxiety. The rats' behavioral responses in anxiety paradigms, such as the elevated plus maze, indicated that while the enrichment reduced repetitive behaviors, it concurrently induced heightened stress responses, a phenomenon that has been documented in later research [112].

One possible explanation for this dichotomous effect lies in the complex and often unpredictable interactions between the stress response systems and the neuroplastic changes induced by EE. Environmental enrichment can lead to the activation of neurotrophic factors, such as BDNF, which have been implicated in both the beneficial and adverse effects of environmental manipulations. The increased levels of BDNF observed in previous studies may enhance synaptic plasticity but also exacerbate vulnerability to stress by altering the regulation of stress-responsive systems, such as the hypothalamic–pituitary–adrenal axis. These changes could contribute to the observed anxiety behaviors in the animals.

In other animal models of autism, Yamaguchi et al. [113] reported significant improvements in social behaviors and reductions in cognitive decline in mice prenatally exposed to VPA when subjected to EE. In their study, the authors focused on examining the potential therapeutic effects of EE, a strategy known for its ability to promote neuroplasticity and improve behavioral outcomes in various neurodevelopmental and psychiatric disorders. EE consisted of the introduction of novel stimuli, social interactions, and physical exercise.

In this context, EE led to improvements in social behaviors, such as sniffing, which is a typical social interaction in rodents. This suggests that EE may promote the restoration of social processing circuits that are often impaired in ASD models. Furthermore, this study also found a reduction in cognitive decline in VPA-exposed mice. Given that cognitive deficits are core features of ASD, the improvements observed in memory and learning tasks after EE intervention are particularly noteworthy. These findings suggest that EE may counteract the cognitive impairments associated with prenatal VPA exposure, potentially by facilitating synaptic plasticity, enhancing hippocampal function, and improving neurotrophic signaling.

3.3. Effects of EE on Autistic Humans

Considering the significant advantages of EE in animal models of autism, Reynolds et al. [114] emphasized that the core components of EE include exposure to a variety of novel sensorimotor, cognitive, and social experiences. They further proposed that environmental

enrichment could serve as a potential therapeutic approach for children with autism, possibly reducing the manifestation of ASD symptoms through neural compensatory processes stimulated by enriched environments.

In this context, Leon and colleagues conducted a series of studies where EE was used as a therapy for autistic children. Their studies involved providing EE to children diagnosed with autism, consisting of approximately three dozen novel sensory exercises administered in the morning and evening. In addition to conventional treatment, the ASD group exposed to enriched environments for 6 months (4 to 7 days per week, approximately 30 min per day) received sensory–motor stimulation from their parents, which activated different combinations of sensory systems, including olfactory, tactile, thermal, auditory, visual, and motor systems. For example, activities included handling objects with various textures, exposure to specific scents, and exercises involving body movements and changes in temperature. Baseline assessments and follow-up evaluations were conducted after six months by psychologists who were blinded to the group assignments. The results showed clinical reductions in autism symptom severity in the enriched group. Additionally, cognitive improvements were observed in the enriched group compared to the control group, including a decrease in autism severity as assessed with the Childhood Autism Rating Scale, an increase in IQ scores, a decline in atypical sensory responses, and an improvement in receptive language performance [8].

Furthermore, a randomized controlled trial by Woo et al. [9] investigated the effects of sensorimotor enrichment administered at home by parents over a six-month period. Children aged 3 to 6 years who received daily sensorimotor enrichment (similar to previous studies [8]), in addition to standard care, demonstrated significant gains in IQ scores, reductions in atypical sensory responses, and improvements in receptive language performance compared to the control group receiving standard care alone. Notably, 21% of the children in the enrichment group improved to the extent that they no longer met the criteria for classic autism, whereas none of the children in the control group exhibited comparable improvements.

These findings were further supported by a large-scale study in which 1002 children with ASD received daily Sensory Enrichment Therapy administered by their parents (it employed the same paradigm as previous studies [8,9], following personalized therapy instructions provided through an online platform). Over a period of up to seven months, parents assessed their children's symptoms every two weeks. The results demonstrated significant improvements across multiple domains, including learning, memory, anxiety, attention span, motor skills, sensory processing, communication, and social interactions. Notably, symptom amelioration was observed across different age groups, genders, and levels of initial symptom severity, reinforcing the potential of environmental enrichment as a scalable and cost-effective therapeutic approach for ASD [10].

These studies underscore the potential of environmental enrichment interventions, particularly those implemented in home settings and facilitated by parents, as accessible and cost-effective therapeutic strategies for children with ASD. In this context, Marcotte et al. [115] explored how an enriched home environment can promote independence in autistic adolescents and adults. Using walking interviews with 10 dyads of autistic individuals and their parents in Quebec, the researchers identified six key factors contributing to an enriched environment: parental support, social network assistance, a physically adapted living space, clear time indicators, opportunities to develop life skills in multiple settings, and professional support. Participants provided concrete strategies for modifying home environments, emphasizing the importance of structured spaces, appropriate sensory elements, and autonomy-promoting features. This study highlights that an enriched environment not only fosters independence but also enhances overall well-being in

autistic individuals. These findings underscore the need for tailored home adaptations that align with individual preferences and needs, offering a foundation for future interventions aimed at optimizing home environments to support autistic individuals in leading more autonomous and fulfilling lives.

4. Discussion

The impact of EE on ASD has garnered increasing attention in recent years, primarily due to its potential to induce significant neural and behavioral improvements, both in animal models [6,7] and humans [8–10]. Traditional therapeutic approaches for ASD, such as behavioral interventions and pharmacological treatments, often focus on mitigating the core symptoms of the disorder, such as deficits in social communication, repetitive behaviors, and sensory sensitivities. While these approaches can be effective to some extent, they do not fully address the underlying neural mechanisms driving ASD symptoms [5,76,79–86]. Consequently, there has been growing interest in exploring how environmental factors, particularly those that enhance neuroplasticity, could serve as a complementary therapeutic strategy.

EE have demonstrated promising effects in improving various behaviors associated with autism both in animal models and human studies. These enriched settings include a variety of novel stimuli, such as new objects, increased exercise opportunities, and social interaction. The primary goal of EE is to promote brain plasticity by facilitating the reorganization and restoration of neural circuits that are compromised, particularly in brain regions involved in social, emotional, and cognitive functions [6,7,111,112].

In animal models of autism induced by prenatal exposure to VPA, EE has shown positive effects in improving various behaviors, such as enhancement of the performance in spatial memory tasks, as well as in object recognition tasks [6]. Furthermore, EE also facilitated improved exploration and social interaction, suggesting a restoration of social and cognitive abilities impaired by prenatal VPA exposure [111,112].

Studies on EE in animal models have paved the way for investigations exploring its therapeutic potential in humans, particularly in the treatment of Autism Spectrum Disorder (ASD). Given the considerable heterogeneity of ASD in humans, the application of EE as a therapeutic adjunct may offer significant benefits. Unlike interventions targeting specific deficits, EE focuses on the holistic enhancement of cognitive, emotional, motor, and social skills. Similar to animal models, EE in humans could involve exposure to novel sensory, cognitive, and social stimuli, potentially promoting neural reorganization and compensating for the areas of the brain affected by ASD. This broad-based approach may facilitate improvements across multiple domains, supporting the development of skills and abilities in individuals with autism [8–10,114].

Central to this evolving discourse is the emerging role of glial cells, which have historically been regarded as passive support cells for neurons, providing metabolic support, structural stability, and immune defense. However, recent research has redefined glial cells as active participants in brain function, particularly in processes related to neuroplasticity. Glial cells, including astrocytes, microglia, and oligodendrocytes, have been found to influence synaptic activity, neuronal communication, and even the remodeling of neural circuits. This reclassification of glial cells as critical modulators of neural activity challenges the traditional view of them as merely auxiliary components of the nervous system [71].

The role of glial cells in neuroplasticity is particularly relevant in the context of ASD, where alterations in glial function have been implicated in the disorder's pathophysiology [71,72]. On the other hand, EE has been found to induce morphological and functional changes in glial cells, with astrocytes playing a critical role in enhancing synaptic com-

munication. This aligns with the idea that glial cells are not passive elements but active contributors to the neural changes induced by probably enriched environments [12].

The evidence from both animal and human studies strongly suggests that exposure to EE leads to significant changes in glial function, with these changes being closely linked to the observed neural and behavioral improvements. For instance, in animal models of ASD, EE exposure has been shown to modulate glial activity, resulting in enhanced synaptic plasticity [105]. These functional changes are believed to underlie the improvements in social behavior and cognitive function observed in these animals. Furthermore, similar findings have been reported in human studies, where children with autism who participated in sensory-rich therapeutic interventions exhibited improvements in both behavioral symptoms and cognitive abilities [8–10]. These findings indicate that EE may act as a therapeutic tool that enhances neuroplasticity, which is probably promoted by glial-mediated mechanisms, potentially mitigating some of the cognitive and behavioral impairments observed in individuals with ASD.

In this regard, a plausible glial-mediated mechanism underlying the beneficial effects of EE involves both macroglia and microglia [12]. Glial cells are crucial for regulating synaptic transmission and modulating neurotransmitter levels—processes that are often disrupted in ASD [71]. In enriched environments, astrocytes appear to contribute to synaptic remodeling by promoting the formation of new synaptic connections and enhancing the efficiency of existing ones. EE has been shown to upregulate glial cell line-derived neurotrophic factor, which is essential for synaptic plasticity [100]. The elevated presence of this factor may drive structural modifications in synapses, increase dendritic complexity, and improve overall network connectivity, thereby fostering compensatory effects that mitigate ASD-related synaptic deficits [100,101].

Glial plasticity following EE exposure is further supported by increased gliogenesis and notable improvements in glial morphology in the motor cortex [104] and hippocampus [105]. These morphological adaptations, characterized by a more stellated astrocytic phenotype, are likely linked to increased synaptic density and improved synaptic function [105].

Moreover, microglial modulation also plays a role in EE-induced neural remodeling. In ASD, microglial dysfunction is associated with altered synaptic pruning and chronic low-grade neuroinflammation [67]. EE appears to shift microglia from a pro-inflammatory to a neuroprotective phenotype, reducing excessive synaptic pruning and restoring a more balanced excitatory/inhibitory (E/I) synaptic connectivity [101].

These glial and synaptic modifications are not only fundamental to neuroplasticity but have also been associated with improvements in cognitive functions. For instance, Soffié et al. [106] showed that EE reversed aging-related deficits in short-term memory and reduced astrocyte hypertrophy in aged rats, further underscoring the capacity of EE to counteract both neurobiological and cognitive impairments. Thus, through mechanisms that promote neurotrophic support, glial remodeling, and microglial modulation, EE not only enhances synaptic function but also contributes to the restoration of disrupted neural networks, ultimately leading to improvements in cognition, social behaviors, and overall neurodevelopmental outcomes in ASD models. Therefore, a compensatory-like effect may occur through EE-driven glial and synaptic modifications, potentially reducing the manifestation of ASD symptoms via neural compensatory processes [12,114].

5. Conclusions

Autism Spectrum Disorder is a highly complex neurodevelopmental condition with an etiology that involves genetic, environmental, and epigenetic mechanisms. These factors collectively alter brain development, resulting in impairments across various functions,

including cognitive processes. Despite the availability of various therapeutic approaches, such as pharmacological and behavioral interventions, the heterogeneity of the disorder has impeded the identification of a universal treatment strategy for the affected population.

In this context, the use of enriched environments as an adjunctive therapy for children with ASD emerges as a promising approach, supported by findings in both animal models and human studies. Numerous studies have shown that exposure to an enriched environment not only alleviates autism symptoms but also induces significant changes in glial processes. Glial cells, traditionally considered as support cells for neurons, have gained recognition as potential compensatory agents in the neuroplasticity associated with enriched environments.

It has been proposed that the sensory, cognitive, and motor stimuli characteristic of these environments modify glial activity, enhancing the formation of new synapses and improving neuronal communication. This process may be a key mechanism underlying the observed improvements in behavior and cognitive abilities in children with ASD.

Therefore, this review suggests that enriched environments provide not only direct benefits for neuroplasticity but also act as modulators of the cerebral microenvironment, promoting glial function and synaptic regeneration. These findings highlight the importance of incorporating innovative approaches into existing therapies for children with ASD, with glial cells emerging as a potential target for future research and therapeutic strategies. However, it is crucial to acknowledge that the application of enriched environments in humans requires further experimentation and evidence-based support, as significant gaps in knowledge still exist.

6. Future Directions

One of the primary future directions is to determine whether the observed improvements in neural and behavioral outcomes are mediated by glial processes, both in animal models and humans. However, defining what constitutes "enrichment" for human beings presents greater challenges. Controlled experiments are not feasible, and human brains are inherently unique. Individuals differ significantly in their genetic backgrounds and environmental influences. Additionally, what is considered an enriching environment for one person may differ substantially for another, reflecting the diversity of human experiences and needs.

A crucial point to consider is that most studies evaluating the effects of enriched environments on the autistic population do not account for the disorder's heterogeneity. Therefore, future research could focus on designing and assessing individualized enrichment protocols tailored to the specific needs, preferences, and abilities of everyone. This involves identifying the sensory, cognitive, or motor stimuli most effective for enhancing neuroplasticity and glial function in diverse subpopulations within the autism spectrum. Such personalized approaches could lead to more precise and impactful therapeutic strategies.

Finally, another promising direction could involve investigating the long-term effects of enriched environments. Exploring whether the observed neural and behavioral improvements are sustained over time and how these changes influence broader life outcomes—such as social integration, academic performance, or quality of life—would provide critical insights into the durability and practical implications of this approach.

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Abbreviations

The following abbreviations are used in this manuscript:

ABA	Applied Behavior Analysis
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autistic Spectrum Disorder
ATP	Adenine Triphosphate
BDNF	Brain-derived neurotrophic factor
Ca^{2+}	Calcium cation
CA1	Cornu Ammonis 1
CBT	Cognitive–behavioral therapy
CNS	Central nervous system
DG	Dentate gyrus
DNA	Deoxyribonucleic acid
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EAAT1	Excitatory amino acid transporter 1
EAAT2	Excitatory amino acid transporter 2
EE	Environmental enrichment
fMRI	Functional magnetic resonance imaging
GABA	Gamma Aminobutyric Acid
GDNF	Glial-derived Factor
GFAP	Glial Fibrillary Acidic Protein
iPSCs	Induced Pluripotent Stem Cells
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-18	Interleukin-18
MBP	Myelin basic protein
MEA	Multi-electrode array
MRI	Magnetic resonance imaging
NLs	Neuroligins
Olig2	Oligodendrocyte transcription factor 2
PLC-IP_3	Phospholipase C–Inositol 1,4,5–Triphosphate
RNA	Ribonucleic acid
TEACCH	Treatment and Education of Autistic and related Communication Handicapped Children
VPA	Valproic acid

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