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Review

Microglia, cerebellar inflammation, and autism spectrum disorders: Developmental mechanisms and therapeutic perspectives

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ABSTRACT

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by deficits in social interaction and communication, as well as restricted and repetitive behaviors. These conditions often co-occur with medical issues linked to synaptic alterations, which compromise synaptic integrity and are associated with brain circuit dysfunction. Both human and animal studies have identified cerebellar structural and functional alterations in subsets of ASD cases, with evidence of abnormal morphology and disrupted connectivity correlating with symptom severity. Numerous studies further suggest that neuroinflammation and microglia dysfunction may contribute to atypical cerebellar development during critical postnatal windows and may be associated with ASD-like phenotypes. However, the timing and mechanisms underlying the onset of these processes remain unclear, and a primary causal role in human ASD has not been established. This review synthesizes current knowledge on microglia in early stages of cerebellar development and discusses how cerebellar inflammation could be linked to ASD-related phenotypes. A better understanding of these pathological processes and their behavioral correlates may reveal opportunities for early-life intervention strategies.

Introduction

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental conditions characterized by deficits in social interaction, verbal and nonverbal communication, and repetitive and stereotyped behaviors. ASD is often associated with cognitive deficits and epilepsy (American Psychiatric Association, 2013). Diagnosis typically occurs in early childhood, with symptoms (that can vary from one individual to another) often becoming apparent within the first two years of life; however, in several cases, symptoms may not be fully apparent or recognized until later (American Psychiatric Association, 2013). According to the most recent epidemiological estimates, the global prevalence is about 1 in 100 individuals, with an increasing trend in recent years, and a 4:1 prevalence in males compared to females. The causes of this different prevalence are mostly unknown, but it has been hypothesized they might include exposure to prenatal steroid and social factors (Halladay et al., 2015; Ferri et al., 2018), a female protective effect (females show resilience to risk factors for ASD; Zwaigenbaum et al., 2012), as well as a female-specific tendency to mask or compensate for their autistic behaviors in social settings ("social camouflaging"; Cancino-Barros et al., 2025). The heterogeneity of the disorder makes it difficult to identify its precise causes, yet it offers numerous points of experimental study. ASD is considered a multifactorial condition, so several factors contribute to its pathogenesis. Over 1,000 genes have been associated with autism, mainly involved in transcription/translation control, synaptic plasticity, neural development, and neuronal

Abbreviations: ADHD, attention deficit-hyperactivity disorder; ASD, autism spectrum disorders; AST, astaxanthin; BBB, blood–brain barrier; CNS, central nervous system; *Cntnap2*, contactin associated protein-like 2; CSF1R, colony stimulating factor 1 receptor; E/I, excitation/inhibition: *En2*, Engrailed-2; Glx, glutamate/glutamine; GSH, glutathione; IL, interleukin; iPSC, induced pluripotent stem cell; MIA, maternal immune activation; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; NAC, N-acetylcysteine; PET, positron emission tomography; SCZ, schizophrenia; *Shank3*, SH3 and multiple ankyrin repeat domains 3; TNF, tumor necrosis factor; VPA, valproic acid.

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connectivity (https://gene.sfari.org). Several ASD-associated genes are expressed in the neocortex (Parikshak et al., 2013; Willsey et al., 2013) and other brain structures implicated in ASD pathogenesis; for example, the amygdala expresses 80 ASD genes validated across species; this expression profile directly links to deficits in social-emotional processing (Herrero et al., 2020).

Growing evidence indicates that the cerebellum is also a crucial site for the expression of ASD-associated genes (Menashe et al., 2013). While traditionally recognized for its role in sensorimotor control (such as balance, coordination, and sensory integration), the cerebellum is increasingly understood to facilitate higher-order cognitive and affective functions, including language, attention, and social cognition (Fatemi et al., 2012; Stoodley, 2016). Thus, disruptions in cerebellar gene expression may contribute to both motor and social impairments characteristic of ASD. Recent studies have identified mutations in genes controlling cerebellar development (such as EN2, SHANK3, and CNTNAP2) in individuals with ASD, further supporting the hypothesis (emerging from mouse studies) that altered cerebellar structure and connectivity, whether arising from genetic or environmental insults, may impact on the behavioral symptoms observed in ASD (Provenzano et al., 2014; Wang et al., 2014; Gibson et al., 2022). Thus, the convergence of genetic, anatomical, and functional evidence from both human and animal studies highlights the importance of cerebellar pathways in ASD, warranting further research into how these molecular mechanisms contribute to the onset and progression of this condition.

Alongside a strong genetic component, several environmental factors (such as maternal infections, prenatal exposures to toxic substances, and subsequent immune alterations) have been associated with increased risk of ASD. Several animal studies indicate that immune dysfunction and neuroinflammation, often accompanied by altered states of microglia (the brain's resident immune cells) at prenatal and postnatal stages, are associated with ASD-relevant phenotypes, particularly in the cerebellum (Estes and McAllister, 2016; Stoodley and Tsai, 2021). The vulnerability of the cerebellum during early postnatal stages and the critical role of microglia in shaping synaptic refinement suggest that early-life inflammatory events might persistently alter cerebellar circuitry and contribute to ASD-like behaviors (Mastenbroek et al., 2024). Therefore, understanding how inflammation impacts cerebellar development represents a fundamental challenge in ASD research. In this review, we will summarize current knowledge of the role of microglia in early stages of cerebellar development and offer a novel perspective on the potential relationship between cerebellar inflammation and ASD pathogenesis.

The role of the cerebellum in ASD

The cerebellum is a brain structure located in the posterior cranial fossa under the cerebral hemispheres. Structurally, it consists of distinct lobules, each with specific functional properties and organized in a cerebellar cortex, which includes the molecular (external), Purkinje cell (intermediate), and granular (deep) layers; deep cerebellar nuclei are located within the white matter. Cerebro-cerebellar circuits, which link the cerebellum with prefrontal and limbic regions, serve as the primary neural substrate for cerebellar social processing (Fatemi et al., 2012; Stoodley, 2016).

The involvement of the cerebellum in ASD is supported by multiple pieces of evidence. Structural abnormalities including cerebellar hypoplasia, disrupted cerebellar cortical organization, volumetric differences, loss of Purkinje cells, aberrant synaptic connectivity, and gliosis have been consistently found in various cerebellar subregions in postmortem samples from individuals with ASD (Kemper and Bauman, 1998; Bauman and Kemper, 2005; Fatemi et al., 2012; Stoodley et al., 2017; Mapelli et al., 2022; Sydnor and Aldinger, 2022; Mastenbroek et al., 2024). Damage to the posterior cerebellum in humans results in deficits in executive function, working memory, abstract reasoning, and emotional processing (Schmahmann and Sherman, 1998; Schmahmann et al., 2021). In mice, cerebellar lesions can result in impaired attention, behavioral flexibility, and social interactions (Badura et al., 2018; Stoodley, 2016). Specifically, interfering with rodent crus I (a cerebellar region structurally altered in humans with ASD), results in repetitive behaviors as well as deficits in social interactions and cognitive flexibility.

Mutations in genes controlling cerebellar development have been reported in individuals with neurodevelopmental conditions, including ASD (Wang et al., 2014). Similarly, mice bearing mutations in genes that control cerebellar morphogenesis show altered formation of cerebellar circuits, accompanied by cognitive and behavioral difficulties resembling those observed in ASD (Provenzano et al., 2014; Gibson et al., 2022). Overall, these findings support an association between altered cerebellar structure and connectivity with ASD-related behavioral phenotypes. In the following paragraphs, we will elaborate on this hypothesis by addressing developmental mechanisms of cerebellar inflammation that may contribute to ASD pathogenesis.

Peripheral and central inflammation in ASD

Inflammation is a highly coordinated immune response initiated by various triggers, such as infection, physical trauma, or metabolic stress. In the periphery, this process involves the mobilization of immune cells and the release of cytokines, which collectively restore tissue homeostasis and support recovery from injury or disease (Medzhitov, 2008).

Immune dysfunction is often linked to high levels of systemic inflammation in individuals with ASD (Croonenberghs et al., 2002; Ashwood et al., 2011; Masi et al., 2017). Studies found elevated levels of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, IL-12p40, tumor necrosis factor (TNF), and IL-17, in the plasma of children with ASD who were not taking medication (Ashwood et al., 2011). Further studies confirmed higher levels of peripheral inflammation markers (e.g., IL-1β, IL-6, IL-17) in the plasma of children with ASD and interictal epileptiform activity, indicating the co-occurrence of immune system dysfunction and hyperexcitability in ASD (Inga Jácome et al., 2016).

When inflammation occurs in the brain, it is called neuroinflammation. This form of inflammation typically engages specialized neural immune cells, namely microglia, which act to protect and maintain the neural environment. These cells coordinate the brain's immune response, highlighting both the similarities and unique aspects of inflammation in the central nervous system compared to the rest of the body. Within the brain, microglia constitute the predominant cell type of the innate immune system. Unlike the adaptive immune system, which generates antigen-specific responses, the innate immune system develops non-specific responses that recognize conserved structures expressed by pathogens. Microglia are estimated to account for approximately 80% of all brain immune cells, comprising 10%–15% of the total brain cell population (Pangrazzi et al., 2020; Pangrazzi et al., 2025b).

Neuroinflammation, even when mild or transient, can disrupt synaptic maturation, alter neurotransmitter homeostasis, and impair neuronal development (Thion et al., 2018). During sensitive developmental windows, especially the early postnatal period, these disruptions can have long-lasting consequences. An example that links neuroinflammation to ASD is maternal immune activation (MIA), a condition that refers to excessive immune system activity during pregnancy. Maternal infection and activation of the maternal immune system have been associated with an increased risk for neurodevelopmental disorders in human offspring (Mastenbroek et al., 2024); the occurrence of ASD (Jiang et al., 2016) and schizophrenia (SCZ) (Brown and Patterson, 2011; Khandaker et al., 2013) also correlates with MIA. Accordingly, prenatal inflammation in rodent models of MIA primes the offspring microglia for exaggerated responses, inducing ASD-like behaviors (Enayati et al., 2012). Postnatal studies in mouse models of MIA confirmed that elevated pro-inflammatory cytokines and microglial

reactivity correlate with behavioral deficits (Golan et al., 2006).

Importantly, MIA should be interpreted primarily as a model of early developmental vulnerability rather than as direct evidence that chronic neuroinflammation and persistent microglial activation are causally linked to ASD in humans. Epidemiological studies support an association between maternal infection during pregnancy and a modestly increased risk of ASD in offspring (with risk estimates varying according to the type, timing, and severity of the infectious exposure), but these data remain correlational and do not establish a causal inflammatory mechanism in the child's brain (Hall et al., 2023). Preclinical MIA paradigms are therefore most useful for investigating how transient prenatal or perinatal immune challenges can alter fetal brain development, microglial maturation, and later behavioral outcomes, while their translation to the heterogeneous human ASD phenotype remains uncertain and context-dependent. Accordingly, MIA provides a mechanistic framework for studying how early inflammatory perturbations may increase neurodevelopmental risk, while the extent to which these processes translate to the heterogeneous human ASD phenotype remains uncertain and likely context-dependent.

Cerebellar inflammation in ASD

Clinical and preclinical studies often highlight cerebellar dysfunction as a key factor in ASD, connecting structural and functional changes in the cerebellum with challenges in behavioral and cognitive regulation that are typical of ASD. Disruptions in the cerebellum's predictive and adaptive functions align with ASD symptoms; these disruptions may be influenced by immune responses and inflammation, which can affect cerebellar activity (Tsai, 2016; Kelly et al., 2021). Markers of neuroinflammation have been detected in ASD cerebella (Vargas et al., 2005; Wei et al., 2011; Suzuki et al., 2013; McCarthy and Wright, 2017; Kern et al., 2016). Additionally, patients with ASD frequently show imbalances in redox processes and their immune systems, including higher levels of pro-inflammatory molecules and evidence of oxidative stress in both the brain and blood (Shpyleva et al., 2014; Pangrazzi et al., 2020). Collectively, this research suggests that cerebellar inflammation is one aspect of a complex landscape in which genetic risk factors, oxidative stress, and dysfunctions of the peripheral and central immune systems combine to affect how ASD begins and progresses (Pangrazzi et al., 2020).

Studies performed in BTBR mice confirmed the presence of oxidative stress in the cerebellum of a widely used ASD model (Shpyleva et al., 2014). Moreover, rat and mouse studies suggest that, within the cerebellum, microglia dysfunction may contribute to ASD pathogenesis: failure of microglia activation during the development of cerebellar white matter, cortex, and other regions, may trigger the formation of impaired cerebellar circuits and neuronal activity associated with ASD (Yamamoto et al., 2019). More recent studies from our laboratory reported cerebellar neuroinflammation accompanied by microglia dysfunction in both *Cntnap2*$^{-/-}$ (Pangrazzi et al., 2025a) and *Shank3b*$^{-/-}$ (Pangrazzi et al., 2024; Madhavan et al., 2026) adult mice, two robust models of syndromic ASD. Our preliminary data also indicate that cerebellar inflammation is present in *Cntnap2*$^{-/-}$ and *Shank3b*$^{-/-}$ mice as early as the first postnatal week. Other studies performed in mice suggest that inflammatory signaling may interact directly with genetic factors linked to ASD during cerebellar development. For example, dysregulation of *Engrailed-2* (*En2*), a key transcription factor for Purkinje cell differentiation and cerebellar patterning, can heighten Purkinje cells' vulnerability to inflammation; experimental evidence indicates that pro-inflammatory stimuli worsen dendritic abnormalities in Purkinje cells depending on *En2*, possibly via microglia-driven TNF-α signaling (Bahaaeldin et al., 2024). These preclinical findings suggest that neuroinflammatory signaling can actively interact with developmental genetic mechanisms and potentially amplify cerebellar circuit alterations. These gene–immune interactions offer insight into how cerebellar susceptibility, altered neural connectivity, and behavioral features typical of ASD are interconnected.

However, a note of caution is warranted when interpreting these findings: several factors indicate that a direct causal link between cerebellar inflammation and ASD pathogenesis remains elusive. First, neuroinflammation may not represent a primary driver of pathology but rather a downstream or compensatory response to excitation/inhibition (E/I) imbalance (resulting from altered neuronal activity, synaptic imbalance, or developmental miswiring), which has been proposed to contribute to ASD (Rubenstein and Merzenich, 2003; Nelson and Valakh, 2015). In this view, microglial activation could reflect attempts to restore homeostasis rather than the initiation of dysfunction. Similarly, disrupted cerebellar function might arise from intrinsic neuronal or circuit-level alterations, including Purkinje cell loss or synaptic deficits, independent of immune mechanisms (Fatemi et al., 2012; Wang et al., 2014). Second, monogenic mouse models (e.g., *Shank3*, *Cntnap2*, *Fmr1*, *Nlgn3*, *Tsc1/2* mutants, and others) provide valuable mechanistic insights, but capture only a small fraction of ASD cases, while ASD is predominantly idiopathic and highly heterogeneous in humans (Lord et al., 2020). In addition, environmental animal models of ASD (e.g., MIA, prenatal valproic acid exposure) and human-based systems such as induced pluripotent stem cell (iPSC)-derived neurons and brain organoids (Dixon and Moutri, 2023; Michels et al., 2025; Tenreiro and Muotri, 2026) clearly indicate that several different primary drivers may contribute to ASD. These models often recapitulate distinct, and sometimes non-overlapping, aspects of ASD pathophysiology, ranging from synaptic dysfunction and E/I imbalance to altered neurodevelopmental trajectories independent of inflammation (or that might involve inflammation only secondarily), underscoring that no single model fully captures the disorder.

Species-specific differences in microglial biology, immune responses, and cerebellar development further limit translational generalizability (Masuda et al., 2020). At present, the role of microglial responses in ASD and their involvement in pathogenic mechanisms remains unclear. Microglial activation within the CNS appears to play a dual role in brain inflammatory responses, acting both as a direct mediator of injury and as a neuroprotective factor (Nguyen et al., 2002). It is not yet well understood how or when microglia become activated in the brains of individuals with ASD; however, given that microglial activation represents the primary cellular response to CNS dysfunction, it is plausible that abnormal microglial activity is closely linked to ASD. Although a direct causal relationship has not been established, cerebellar inflammation and altered microglial activity may represent one developmental mechanism contributing to ASD-related phenotypes in a subset of cases, potentially through effects on synaptic pruning, neuronal maturation, and circuit refinement. In the following section, we will address the developmental contribution of microglia to cerebellar inflammation.

Microglia and cerebellar inflammation: A developmental perspective

Microglial ontogeny and cerebellar development. The cerebellum, including its microglial component, undergoes active development during both embryonic and postnatal stages. Microglia originate from yolk sac erythromyeloid progenitors and colonize the CNS early in embryogenesis. In the cerebellum, microglia are already present and active during early postnatal days, where they play essential roles in synaptic pruning, trophic signaling, and circuit refinement.

Mouse studies showed that microglia are critical regulators of CNS development, contributing to axonal sculpting, synaptic remodeling through the elimination of unused synapses, maintenance of neuronal homeostasis, and immune surveillance as brain-resident macrophages (Paolicelli et al., 2011). Their distribution, morphology, and transcriptional profile remain highly dynamic throughout early postnatal life: cerebellar microglia undergo a protracted maturation trajectory, with substantial transcriptional remodeling between postnatal days 3 and 21 in the mouse. Functionally, microglia continuously sense environmental signals via pattern-recognition receptors and shift between ramified

(surveying) and amoeboid (activated) states in response to developmental and physiological demands. When microglial maturation is impaired by genetic or environmental factors, or when their activation becomes excessive or persistently dysregulated, synaptic pruning, growth factor regulation, and cellular homeostasis can be disrupted. Several animal studies support the crucial role of microglia in shaping cerebellar circuitry (Stoessel and Majewska, 2021): as an example, impaired microglial maturation alters cerebellar synaptic refinement and leads to abnormal behavioral phenotypes (Pinto et al., 2024), while excessive early postnatal microglial activation creates an inflammatory environment that disrupts functional cerebellar network formation (Paolicelli and Ferretti, 2017). These data indicate that (at least in rodents) early-life microglial dysfunction alters cerebellar connectivity, subsequently affecting behavior.

Cerebellar development during the perinatal and early postnatal period. In both rodents and humans, cerebellar development occurs primarily during the perinatal and early postnatal periods and involves tightly coordinated processes, including neuronal migration, granule cell proliferation, synapse formation, Purkinje cell maturation, and the establishment of cerebellar circuitry. This developmental window represents a period of heightened vulnerability, during which environmental or biological insults can produce long-lasting alterations in cerebellar architecture and connectivity. Disruptions caused by inflammatory events, oxidative stress, metabolic stress, or exposure to toxins can interfere with neuronal differentiation, synaptogenesis, and long-range connectivity, ultimately compromising cerebellar contributions to motor and cognitive functions. Supporting this view, early-life oxidative stress has been shown to impair Purkinje cell maturation and synaptic density in rodents, while perinatal neuroimmune activation alters microglial maturation patterns within the cerebellum, leading to enduring deficits associated with ASD-like phenotypes (Belletti et al., 2022; Liu et al., 2023). Collectively, these findings highlight that early postnatal cerebellar development is highly sensitive to pathological insults, with long-lasting consequences for neurodevelopment.

Microglia, astrocytes, and cerebellar inflammation. Postnatal cerebellar inflammation can arise from a range of biological conditions, including perinatal infection, MIA, hypoxia–ischemia, environmental toxicity, and inherited vulnerability. When these events occur during early developmental stages, they can prematurely activate microglia, driving them toward a pro-inflammatory state characterized by excessive cytokine production, oxidative stress, and metabolic dysfunction. These processes negatively affect neuronal migration, neurogenesis, and the formation and refinement of cerebellar circuits. The newborn brain is particularly sensitive to inflammatory molecules.

Post-mortem studies of cerebellar tissue from individuals with ASD further reveal increased microglial activation and elevated pro-inflammatory cytokines (Vargas et al., 2005; Suzuki et al., 2013), while animal models consistently link excessive microglial activation to ASD-like behaviors (Zhan et al., 2014; Yuan et al., 2016; Coomey et al., 2020). Interestingly, mouse studies showed that cerebellar microglia exhibit a more pronounced immunogenic transcriptional profile as compared to their cortical counterparts, including elevated expression of genes involved in immune responses and pathogen detection (C-type lectin-like receptors Clec4e and Clec7a), interferon signaling (Stat1, Stat4, Irf7), antigen presentation (MHC I and II), and nucleic acid recognition (Zbp1) (Grabert et al., 2016). As a result, cerebellar microglia may be particularly sensitive to systemic inflammation, oxidative stress, and local insults. A large series of animal studies clearly indicates that aberrant microglial activation leads to the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-4), reactive oxygen species, chemokines, and matrix-modifying enzymes, profoundly altering the local brain environment. This inflammatory milieu interferes with normal brain development, neuronal survival, synaptic pruning, and plasticity, ultimately leading to structural abnormalities and functional deficits (Haruwaka et al., 2019).

In addition, activated microglia can induce astrocytes to adopt a neurotoxic phenotype, further amplifying inflammation and perpetuating a self-sustaining cycle of neuroinflammatory damage (Luo and Wang, 2024). Indeed, under inflammatory conditions, reactive astrocytes undergo phenotypic changes (astrogliosis) and release pro-inflammatory mediators, including cytokines, nitric oxide, glutamate, and matrix metalloproteinases, which disrupt tight junctions and increase blood–brain barrier (BBB) permeability (Gullotta et al., 2023). This highlights the significant role of astrocytes and the BBB as central regulators of cerebellar inflammatory processes, acting through tightly coordinated mechanisms within the neurovascular unit (Heithoff et al., 2021). Astrocytic branches envelop cerebellar microvessels and actively maintain BBB integrity by promoting tight junction formation, regulating transporters, and releasing trophic factors such as sonic hedgehog (SH) and retinoic acid that stabilize endothelial function (Heithoff et al., 2021). During neuroinflammation, astrogliosis may cause breakdown of the BBB, facilitating the infiltration of peripheral immune cells into the cerebellum and amplifying local neuroinflammation. Concurrently, BBB endothelial cells themselves contribute to inflammation by producing immune signaling molecules and regulating leukocyte trafficking, acting as an active interface rather than a passive barrier (Acioglu and Elkabes, 2025). In the cerebellum (where precise microenvironmental control is essential for sensorimotor and cognitive functions), these alterations can profoundly affect neuronal circuits. Importantly, astrocytes exhibit a dual role: they can form secondary barrier-like structures and limit immune cell entry when endothelial integrity is compromised, highlighting their context-dependent protective versus detrimental effects during neuroinflammation (Gullotta et al., 2023). Together, astrocyte–BBB interactions represent a dynamic system that both regulates and propagates cerebellar inflammatory responses, with dysfunction in this crosstalk being a key contributor to neurodevelopmental and neurodegenerative disorders.

Early detection of inflammatory signatures: opportunities and limitations

Collectively, evidence from both animal and human studies supports the hypothesis that early postnatal or even embryonic cerebellar inflammation may occur in ASD, underscoring the need for early diagnostic strategies capable of detecting neuroimmune activation during the earliest stages of development and for proposing therapeutic interventions at very early time points in life. Early detection could enable therapeutic intervention during periods of heightened neuroplasticity, thereby potentially reducing the severity or likelihood of ASD symptom emergence.

Although research in this area remains at an early stage, one promising approach is to identify, in both preclinical and clinical settings, early-life time points of inflammation onset and to determine how inflammation influences neurobiological and behavioral phenotypes. Within this framework, the following considerations should be interpreted as key hypotheses and future research directions rather than conclusions supported by current evidence. In particular, experimental strategies aimed at inducing inflammation or depleting microglia in young rodents represent a promising but still largely untested avenue. The systemic injection of lipopolysaccharide (LPS, a component of Gram-positive bacterial membranes and a powerful activator of the innate immune system; Alexander and Rietschel, 2001) enables the simulation of an acute inflammatory insult and the study of its effects at the brain and behavioral levels. While LPS has been widely used to model maternal immune activation and induce neuroinflammation, relatively few studies have specifically investigated its effects on immune cell activation and behavior in established genetic or environmental ASD models, and the available evidence remains limited and sometimes conflicting (Manjeese et al., 2021; Zhang et al., 2023). Similarly, no study has yet systematically and comparatively examined, in rodent models of ASD, the effects of pharmacological microglial depletion via inhibition of the CSF1R receptor (essential for microglial and macrophage survival, proliferation, and differentiation; Meng et al.,

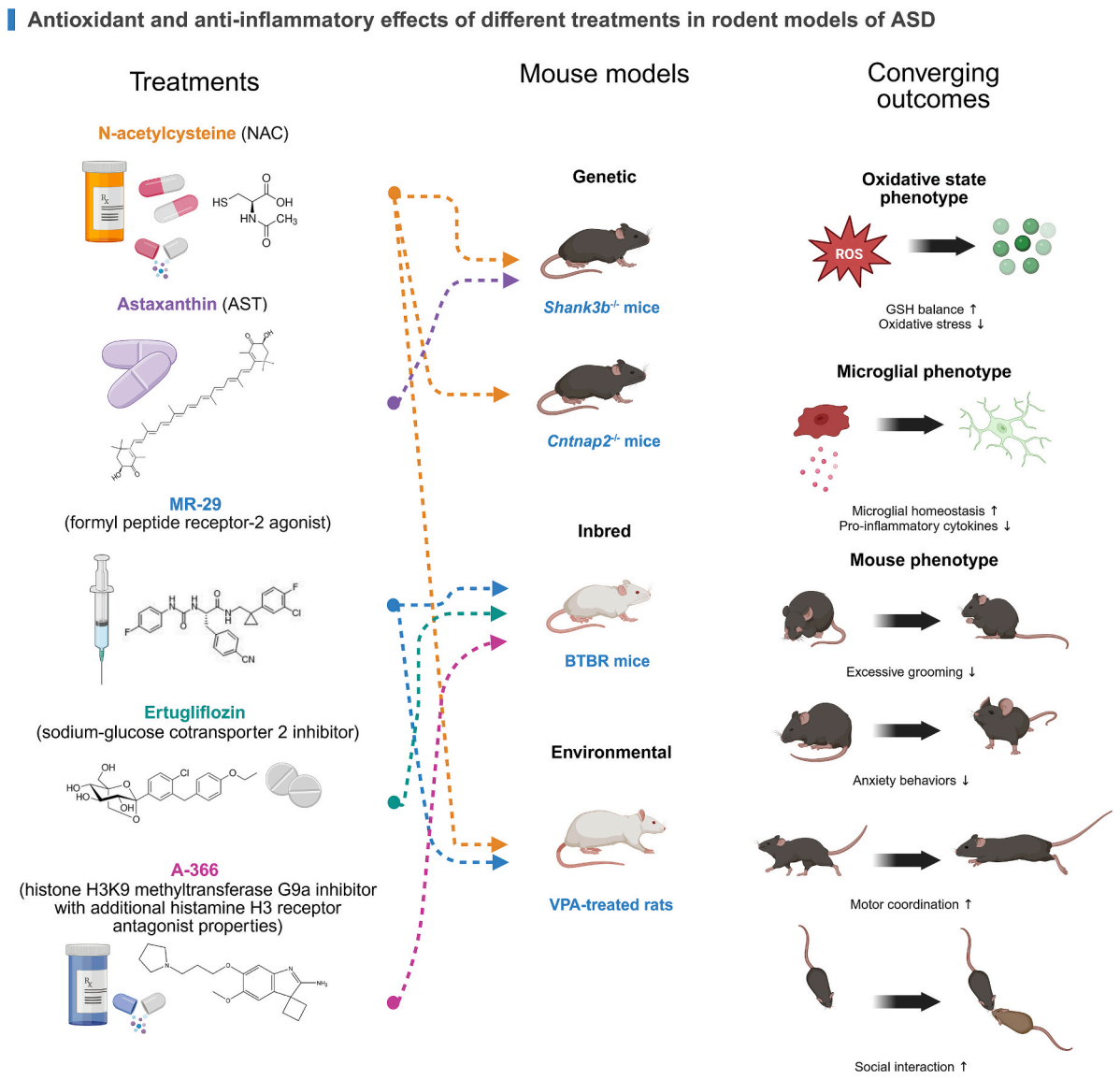

Fig. 1. Antioxidant and anti-inflammatory treatments successfully mitigate neuroinflammation and associated behavioral traits in genetic, inbred, and environmental rodent models of ASD (see Table 1 for references). Abbreviations are as in the text. Figure created in BioRender. Casarosa, S. (2026) https://BioRender.com/4wqec64.

2024) using PLX5622; thus, whether microglia play an active role in determining behavioral phenotypes or whether they represent a secondary response to pre-existing disease processes remains to be elucidated.

Likewise, the use of a wide range of techniques to identify early diagnostic markers of cerebellar inflammation in human subjects also opens promising but still largely untested avenues. Screening the expression of inflammatory cytokines within the cerebellum could help determine whether and when inflammatory processes occur. In addition, biomarkers derived from blood, cerebrospinal fluid, or neuroimaging approaches are increasingly investigated as potential indicators of microglial activation or oxidative stress in infants (Van Camp et al., 2022). For instance, elevated inflammatory cytokines in neonatal plasma have been reported to correlate with altered cerebellar morphology as early as one year of age (as detected by magnetic resonance imaging, MRI), and positron emission tomography (PET) tracers have been highlighted as useful tools for identifying microglial activation in pediatric neurological disorders (Evans et al., 2022; Martínez-Sosa et al., 2023).

Among available neuroimaging techniques, *in vivo* magnetic resonance spectroscopy (MRS) is a complementary, non-invasive modality for examining neurochemical changes associated with neuroinflammation in the developing brain. Although current MRS studies in ASD are limited and somewhat heterogeneous, they have identified alterations in metabolites related to neuronal integrity and glial function, such as decreased N-acetylaspartate (NAA) and fluctuations in glutamate/glutamine (Glx) levels, indicating potential E/I imbalance and glial-related metabolism (Page et al., 2006; Kubas et al., 2012; Horder et al., 2018; Oya et al., 2023). While these observations are not universally consistent across studies due to differences in developmental stage and the brain regions examined, they offer valuable *in vivo* links between peripheral immune markers and postmortem findings. Integrating MRS with other biomarker methodologies may enhance early detection strategies and facilitate identification of neuroinflammatory signatures during critical periods of cerebellar development.

Therapeutic perspectives: Current treatments to reduce cerebellar inflammation and improve autistic symptoms

At present, no standardized treatment specifically targeting

Table 1
Antioxidant and anti-inflammatory effects of different treatments in monogenic, inbred, and environmental rodent models of ASD.

Treatment	Model(s)	Primary outcomes & mechanisms	References
N-acetylcysteine *(NAC)*	*Shank3b*$^{-/-}$ mice	Rescues cerebellar and peripheral inflammation; improves social interaction deficits	Pangrazzi et al., 2024
	Cntnap2$^{-/-}$ mice	Normalizes cerebellar oxidative stress and microglial dysfunction; reverses motor and social impairments	Pangrazzi et al., 2025a
	VPA-treated rats	Ameliorates social deficits and anxiety; restores glutathione (GSH) balance and synaptic gene expression; restores E/I imbalance by metabotropic glutamate receptor-dependent mechanisms	Chen et al., 2014Zhang et al., 2017Schiavi et al., 2022
Astaxanthin *(AST)*	*Shank3b*$^{-/-}$ mice	Improves social interaction, repetitive grooming, and motor coordination; reduces cerebellar pro-inflammatory cytokines and microglial hyperactivation	Pangrazzi et al., 2024
MR-39 *(formyl peptide receptor-2 agonist)*	BTBR & VPA mice	Reduces hippocampal inflammatory markers and restores neuronal plasticity; improves social phenotypes	Cristiano et al., 2022
Ertugliflozin *(sodium-glucose cotransporter 2 inhibitor)*	BTBR mice	Reduces repetitive behaviors and anxiety; inhibits microglial activation and oxidative stress in the hippocampus and prefrontal cortex	Wang et al., 2026
A-366 *(histone H3K9 methyltransferase G9a inhibitor with additional histamine H3 receptor antagonist properties)*	BTBR mice	Reduces pro-inflammatory cytokines; restores social behaviors and reduces repetitive behaviors	Hajar et al., 2026

cerebellar inflammation and microglial dysfunction in ASD has been established. Consequently, there is a pressing need to identify more effective anti-inflammatory and microglia-targeting therapeutic compounds. Emerging therapeutic strategies largely rely on anti-inflammatory and antioxidant agents, immune modulators, and behavioral or neuro-modulatory interventions, most of which remain at the preclinical stage.

Natural antioxidants and anti-inflammatory molecules have emerged as promising candidates for counteracting core ASD symptoms both in humans and rodents. Such treatments may involve the administration of compounds such as vitamin C, vitamin E, astaxanthin (AST), glutathione, and N-acetylcysteine (NAC), either by intraperitoneal injection, oral supplementation, or dietary intake of nutraceutical-rich plant, fish, and crustacean-derived foods that target inflammation and oxidative stress (Pangrazzi et al., 2020). Evidence from both animal and human studies indicates that these molecules, in addition to their anti-inflammatory properties, exhibit neuroprotective potential by preserving cognitive function (Suswidiantoro et al., 2026).

Recent studies from our laboratory showed that treatment with NAC was able to lower cerebellar neuroinflammation, correct microglial dysfunction, and improve ASD-like social behaviors in adult *Cntnap2*$^{-/-}$ mice (Pangrazzi et al., 2025a). Similarly, AST treatment markedly reduced cerebellar neuroinflammation, microglial dysfunction, and motor and social behaviors in adult *Shank3b*$^{-/-}$ mice (Madhavan et al., 2026). Antioxidant and anti-inflammatory drugs also showed efficacy in lowering inflammation, oxidative stress, and ASD-like deficits in inbred and environmental models of ASD in rodents (Chen et al., 2014; Zhang et al., 2017; Schiavi et al., 2022; Cristiano et al., 2022; Hajar et al., 2026; Wang et al., 2026). Fig. 1 and Table 1 summarize the major outcomes of antioxidant and anti-inflammatory treatments in monogenic, inbred, and environmental rodent models of ASD.

In humans, clinical studies suggest that immunomodulatory and anti-inflammatory treatments (e.g., prednisolone, pregnenolone, celecoxib, minocycline, NAC, sulforaphane, and/or omega-3 fatty acids) may be beneficial for the management of core (e.g., stereotypies) and associated (e.g., irritability, hyperactivity, lethargy) symptoms in individuals with ASD (Lee et al., 2021; Arteaga-Henríquez et al., 2023). Nevertheless, well-designed randomized clinical trials are still required to evaluate the efficacy and long-term outcomes of these interventions.

Although these interventions showed therapeutic promise, their safety profiles and long-term effects are not yet fully understood. Antioxidants are generally regarded as safe when used appropriately; however, excessive doses may result in serious adverse effects. For example, NAC is well tolerated and has shown improvements in irritability and repetitive behaviors among individuals with ASD, though side effects such as gastrointestinal disturbances and variable efficacy have been reported (Wink et al., 2016). Likewise, antioxidant agents including AST and vitamins C and E are considered safe at standard dosages, but concerns persist regarding chronic administration, optimal dosing, and the possibility of off-target effects, such as disruption of physiological redox signalling (Bjelakovic et al., 2012; Pangrazzi et al., 2020). Additionally, immunomodulating therapies may entail risks of excessive immunosuppression or alterations in neurodevelopment, particularly when administered during critical periods of brain maturation (Estes and McAllister, 2016). In the near future, it will be therefore important to conduct longitudinal studies and clinical trials to evaluate the efficacy, safety, tolerability, and developmental outcomes of antioxidant and anti-inflammatory treatments, thereby determining the potential for these interventions to be translated into safe and effective clinical strategies for ASD.

Unresolved questions

Despite growing evidence linking cerebellar inflammation to ASD, it is still unclear whether inflammatory features described in the cerebellum are specific to ASD pathogenesis or instead reflect a broader vulnerability shared across neurodevelopmental disorders. Disruptions in cerebellar function, possibly caused by inflammation, are observed across a range of human neurodevelopmental conditions: postmortem and imaging studies indicate that cerebellar neuroinflammation (characterized by microglial activation and cytokine dysregulation) is a common feature across ASD, attention deficit-hyperactivity disorder (ADHD), and SCZ, raising the possibility that immune alterations are not disorder-specific but rather indicative of a common response to developmental perturbations (Vargas et al., 2005; Stoodley, 2016; Estes &

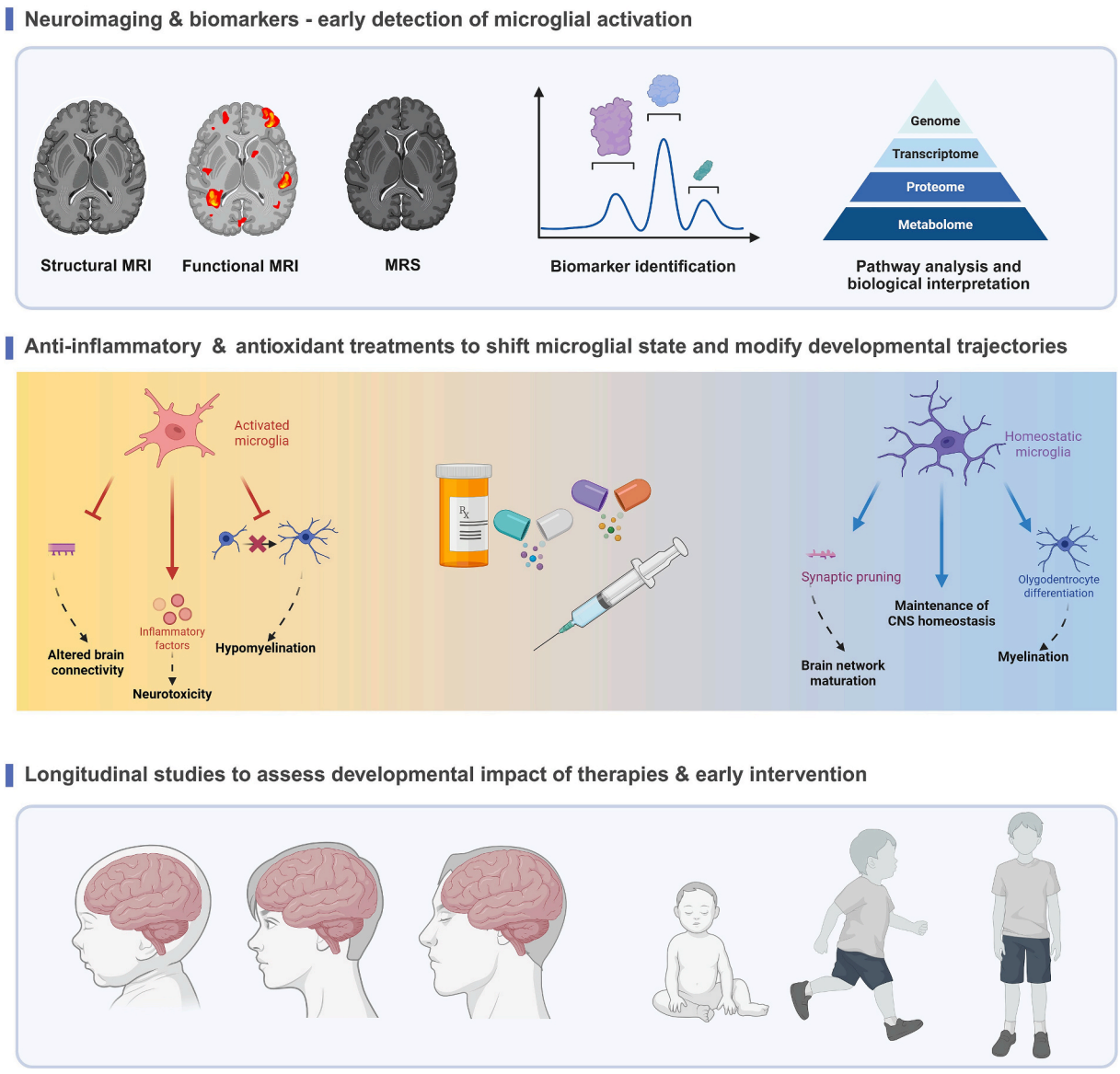

Fig. 2. Emerging diagnostic and microglia-targeted therapeutic strategies for early intervention in ASD. Abbreviations are as in the text. Figure created in BioRender. Casarosa, S. (2026) https://BioRender.com/4wqec64.

McAllister, 2016). Comparative studies across disorders, particularly at early developmental stages, will be essential to disentangle specificity from shared pathology.

Another unresolved issue concerns the functional role of microglial activation in the cerebellum, as it remains uncertain whether it is primarily pathogenic or represents a compensatory response to underlying circuit abnormalities. Classical studies in mice showed that microglia play a critical role in synaptic pruning and circuit refinement during development, and that their dysregulation can directly contribute to altered connectivity (Paolicelli et al., 2011; Schafer et al., 2012). However, microglial activation may also arise in response to neuronal dysfunction or environmental insults, potentially contributing to protective or homeostatic functions (Salter and Stevens, 2017). Distinguishing between these possibilities will require longitudinal, cell-type-specific approaches capable of establishing causality.

Finally, the temporal dynamics of cerebellar inflammation remain poorly defined in humans. It is not yet established whether immune alterations emerge early in development and contribute to ASD onset, or whether they arise later as a consequence of ongoing neural dysfunction. Evidence from the MIA mouse model suggests that early-life inflammatory events can have lasting effects on cerebellar development and ASD-like behaviors (Shi et al., 2009; Hsiao et al., 2012), but direct translation to human ASD remains limited. Addressing this gap will require integrating human longitudinal data with mechanistic insights from animal models.

Clarifying these unresolved questions will be critical for defining the precise role of cerebellar inflammation in ASD and for determining whether targeting neuroimmune pathways represents a viable therapeutic strategy.

Conclusions and future perspectives

Evidence reported in this review supports the view that ASD is a multifactorial condition in which inflammation and microglial dysfunction may contribute to the pathophysiology, at least in a specific subset of cases (Bozzi, 2025). While the cerebellum has been traditionally associated with sensorimotor control, it is now recognized as playing a key role in cognition and social behavior (Fatemi et al., 2012; Stoodley, 2016), making cerebellar pathology particularly relevant to the study of ASD.

Postmortem studies and animal models have reported glial activation and cerebellar inflammatory signatures (altered cytokine profiles) in association with ASD-related phenotypes, often occurring alongside Purkinje cell loss and disrupted synaptic architecture (Fatemi et al., 2012; Mastenbroek et al., 2024). Because the cerebellum continues to develop during the neonatal period, inflammatory insults during this stage could alter neuronal networks and behavioral trajectories; however, the extent to which this contributes to human ASD remains uncertain, as these signatures are present only in a proportion of individuals. Consequently, cerebellar inflammation should be viewed as a contributing factor in specific cases rather than a universal underlying mechanism.

Future research efforts should focus on improving diagnostic precision and expanding therapeutic strategies that target these neuroimmune pathways. Advances in neuroimaging techniques (such as PET, MRI, and MRS), along with plasma biomarker profiling, may help identify markers of microglial activation early in life, though their reliability and specificity are still being established. There is also growing interest in developing microglia-targeted therapies and utilizing antioxidant or anti-inflammatory interventions (e.g., NAC and AST) to shift microglial phenotypes from pro-inflammatory to neuroprotective states.

The success of these approaches will depend on preclinical and clinical longitudinal studies designed to identify the appropriate therapeutic windows and the specific subpopulations most likely to benefit (Fig. 2). Furthermore, current research must address the limitations of many preclinical models, which often fail to account for the multifactorial nature of ASD, including gene-environment interactions and sex differences. An integrative approach (combining human-derived systems, diverse model organisms, and comprehensive phenotyping) is essential to link early neuroimmune alterations with later behavioral outcomes. By clarifying whether, when, and in which ASD subgroups neuroinflammation contributes to disease-relevant mechanisms, researchers can move these strategies from theoretical potential to clinically actionable interventions.

Declaration of generative AI in scientific writing

Generative artificial intelligence (AI) and AI-assisted technologies (Chat-GPT, Google Gemini) were used in the writing process solely to improve readability and language of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Martina Schiano-Visconte: Writing – original draft. **Luigi Balasco:** Writing – review & editing, Writing – original draft. **Simona Casarosa:** Writing – review & editing, Funding acquisition. **Yuri Bozzi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Acioglu, C., Elkabes, S., 2025. Innate immune sensors and regulators at the blood brain barrier: focus on toll-like receptors and inflammasomes as mediators of neuroimmune crosstalk and inflammation. J. Neuroinflammation 22, 39. https://doi.org/10.1186/s12974-025-03360-3.

Alexander, C., Rietschel, E.T., 2001. Bacterial lipopolysaccharides and innate immunity. J. Endotoxin Res. 7, 167–202.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Publishing, Washington DC.

Arteaga-Henríquez, G., Gisbert, L., Ramos-Quiroga, J.A., 2023. Immunoregulatory and/or anti-inflammatory agents for the management of core and associated symptoms in individuals with autism spectrum disorder: a narrative review of randomized, placebo-controlled trials. CNS Drugs 37, 215–229. https://doi.org/10.1007/s40263-023-00993-x.

Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J (2011) Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav Immun 25:40–45. doi:10.1016/j.bbi.2010.08.003.

Badura, A., Verpeut, J.L., Metzger, J.W., Pereira, T.D., Pisano, T.J., Deverett, B., Bakshinskaya, D.E., Wang, S.S., 2018. Normal cognitive and social development require posterior cerebellar activity. Elife 7, e36401. https://doi.org/10.7554/eLife.36401.

Bahaaeldin, M., Bülte, C., Luelsberg, F., Kumar, S., Kappler, J., Völker, C., Schilling, K., Baader, S.L., 2024. Engrailed-2 and inflammation convergently and independently impinge on cerebellar Purkinje cell differentiation. J. Neuroinflammation 21, 306. https://doi.org/10.1186/s12974-024-03301-6.

Bauman, M.L., Kemper, T.L., 2005. Neuroanatomic observations of the brain in autism: a review and future directions. Int. J. Dev. Neurosci. 23, 183–187. https://doi.org/10.1016/j.ijdevneu.2004.09.006.

Belletti, D., Riva, D., Cattaneo, A., 2022. Early-life oxidative stress alters cerebellar development and synaptic maturation. Neurobiol. Dis. 165, 105620. https://doi.org/10.1016/j.nbd.2022.105620.

Bjelakovic, G., Nikolova, D., Gluud, L.L., Simonetti, R.G., Gluud, C., 2012. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst. Rev. 2012 (3), CD007176. https://doi.org/10.1002/14651858.CD007176.pub2.

Bozzi, Y., 2025. Unraveling white matter alterations in autism: the role of oligodendrocytes, microglia, and neuroinflammation. Cereb. Cortex 35, bhaf094. https://doi.org/10.1093/cercor/bhaf094.

Brown, A.S., Patterson, P.H., 2011. Maternal infection and schizophrenia: implications for prevention. Schizophr. Bull. 37, 284–290. https://doi.org/10.1093/schbul/sbq158.

Cancino-Barros, I., Villacura-Herrera, C., Castillo, R.D., 2025. A meta-analytic review of quantification methods for camouflaging behaviours in autistic and neurotypical individuals. Sci. Rep. 15, 22885. https://doi.org/10.1038/s41598-025-06137-z.

Chen, Y.W., Lin, H.C., Ng, M.C., Hsiao, Y.H., Wang, C.C., Gean, P.W., Chen, P.S., 2014. Activation of mGluR2/3 underlies the effects of N-acetylcysteine on amygdala-associated autism-like phenotypes in a valproate-induced rat model of autism. Front. Behav. Neurosci. 8, 219. https://doi.org/10.3389/fnbeh.2014.00219.

Coomey, R., Stowell, R., Majewska, A., Tropea, D., 2020. The role of microglia in neurodevelopmental disorders and their therapeutics. Curr. Top. Med. Chem. 20, 272–297. https://doi.org/10.2174/1568026620666200221172619.

Cristiano, C., Volpicelli, F., Crispino, M., Lacivita, E., Russo, R., Leopoldo, M., Calignano, A., Perrone-Capano, C., 2022. Behavioral, anti-Inflammatory, and neuroprotective effects of a novel FPR2 agonist in two mouse models of autism. Pharmaceuticals 15, 161. https://doi.org/10.3390/ph15020161.

Croonenberghs, J., Bosmans, E., Deboutte, D., Kenis, G., Maes, M., 2002. Activation of the inflammatory response system in autism. Neuropsychobiology 45, 1–6. https://doi.org/10.1159/000048665.

Dixon, T.A., Muotri, A.R., 2023. Advancing preclinical models of psychiatric disorders with human brain organoid cultures. Mol. Psychiatry 28, 83–95. https://doi.org/10.1038/s41380-022-01708-2.

Enayati, M., Solati, J., Hosseini, M.H., Shahi, H.R., Saki, G., Salari, A.A., 2012. Maternal infection during late pregnancy increases anxiety- and depression-like behaviors with increasing age in male offspring. Brain Res. Bull. 87, 295–302. https://doi.org/10.1016/j.brainresbull.2011.08.015.

Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353, 772–777. https://doi.org/10.1126/science.aag3194.

Evans, A.C., Collins, D.L., Mills, S.R., Brown, E.D., Kelly, R.L., Peters, T.M., 2022. Neuroimaging biomarkers of neuroinflammation in early neurodevelopmental disorders. Neuroimage Clin 35, 103078. https://doi.org/10.1016/j.nicl.2022.103078.

Fatemi, S.H., Aldinger, K.A., Ashwood, P., Bauman, M.L., Blaha, C.D., Blatt, G.J., Chauhan, A., Chauhan, V., Dager, S.R., Dickson, P.E., Estes, A.M., Goldowitz, D., Heck, D.H., Kemper, T.L., King, B.H., Martin, L.A., Millen, K.J., Mittleman, G., Mosconi, M.W., Persico, A.M., Sweeney, J.A., Webb, S.J., Welsh, J.P., 2012. Consensus paper: pathological role of the cerebellum in autism. Cerebellum 11, 777–807. https://doi.org/10.1007/s12311-012-0355-9.

Ferri, S.L., Abel, T., Brodkin, E.S., 2018. Sex differences in autism spectrum disorder: a review. Curr. Psychiatry Rep. 20, 9. https://doi.org/10.1007/s11920-018-0874-2.

Gibson, J.M., Howland, C.P., Ren, C., Howland, C., Vernino, A., Tsai, P.T., 2022. A critical period for development of cerebellar-mediated autism-relevant social behavior. J. Neurosci. 42, 2804–2823. https://doi.org/10.1523/JNEUROSCI.1230-21.2021.

Golan, H., Lev, V., Hallak, M., Sorokin, Y., Huleihel, M., 2006. Alterations in behavior in adult offspring mice following maternal inflammation during pregnancy. Dev. Psychobiol. 48, 162–168. https://doi.org/10.1002/dev.20116.

Grabert, K., Michoel, T., Karavolos, M.H., Clohisey, S., Baillie, J.K., Stevens, M.P., Freeman, T.C., Summers, K.M., McColl, B.W., 2016. Microglial brain region-dependent diversity and selective regional sensitivities to aging. Nat. Neurosci. 19, 504–516. https://doi.org/10.1038/nn.4222.

Gullotta, G.S., Costantino, G., Sortino, M.A., Spampinato, S.F., 2023. Microglia and the blood-brain barrier: an external player in acute and chronic neuroinflammatory conditions. Int. J. Mol. Sci. 24, 9144. https://doi.org/10.3390/ijms24119144.

Hall, M.B., Willis, D.E., Rodriguez, E.L., Schwarz, J.M., 2023. Maternal immune activation as an epidemiological risk factor for neurodevelopmental disorders: considerations of timing, severity, individual differences, and sex in human and rodent studies. Front. Neurosci. 17, 1135559. https://doi.org/10.3389/fnins.2023.1135559.

Halladay, A.K., Bishop, S., Constantino, J.N., et al., 2015. Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority. Mol. Autism 6, 36. https://doi.org/10.1186/s13229-015-0019-y.

Hajar, M., Jayaprakash, P., Stark, H., Sadek, B., 2026. The dual G9a inhibitor and histamine H3 receptor antagonist a-366 improves repetitive and social behaviors and attenuates neuroinflammation in BTBR T+tf/J mice. Sci. Rep. 16, 7105. https://doi.org/10.1038/s41598-026-38481-z.

Haruwaka, K., Ikegami, A., Tachibana, Y., Ohno, N., Konishi, H., Hashimoto, A., Matsumoto, M., Kato, D., Ono, R., Kiyama, H., Moorhouse, A.J., Nabekura, J., Wake, H., 2019. Dual microglia effects on blood-brain barrier permeability induced by systemic inflammation. Nat. Commun. 10, 5816. https://doi.org/10.1038/s41467-019-13812-z.

Heithoff, B.P., George, K.K., Phares, A.N., Zuidhoek, I.A., Munoz-Ballester, C., Robel, S., 2021. Astrocytes are necessary for blood-brain barrier maintenance in the adult mouse brain. Glia 69, 436–472. https://doi.org/10.1002/glia.23908.

Herrero, M.J., Velmeshev, D., Hernandez-Pineda, D., Sethi, S., Sorrells, S., Banerjee, P., Sullivan, C., Gupta, A.R., Kriegstein, A.R., Corbin, J.G., 2020. Identification of amygdala-expressed genes associated with autism spectrum disorder. Mol. Autism 11, 39. https://doi.org/10.1186/s13229-020-00346-1.

Hsiao, E.Y., McBride, S.W., Chow, J., Mazmanian, S.K., Patterson, P.H., 2012. Modeling an autism risk factor in mice leads to permanent immune dysregulation. PNAS 109, 12776–12781. https://doi.org/10.1073/pnas.1202556109.

Horder, J., Petrinovic, M.M., Mendez, M.A., Bruns, A., Takumi, T., Spooren, W., Barker, G.J., Künnecke, B., Murphy, D.G., 2018. Glutamate and GABA in autism spectrum disorder - a translational magnetic resonance spectroscopy study in man and rodent models. Transl. Psychiatry 8, 106. https://doi.org/10.1038/s41398-018-0155-1.

Inga Jácome, M.C., Morales Chacòn, L.M., Vera Cuesta, H., Maragoto Rizo, C., Whilby Santiesteban, M., Ramos Hernandez, L., Noris García, E., González Fraguela, M.E., Fernandez Verdecia, C.I., Vegas Hurtado, Y., Siniscalco, D., Gonçalves, C.A., Robinson-Agramonte, M.L., 2016. Peripheral inflammatory markers contributing to comorbidities in autism. Behav Sci (basel) 6, 29. https://doi.org/10.3390/bs6040029.

Jiang, H.Y., Xu, L.L., Shao, L., Xia, R.M., Yu, Z.H., Ling, Z.X., Yang, F., Deng, M., Ruan, B., 2016. Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. Brain Behav. Immun. 58, 165–172. https://doi.org/10.1016/j.bbi.2016.06.005.

Kelly, E., Escamilla, C.O., Tsai, P.T., 2021. Cerebellar dysfunction in autism spectrum disorders: deriving mechanistic insights from an internal model framework. Neuroscience 462, 274–287. https://doi.org/10.1016/j.neuroscience.2020.11.012.

Kemper, T.L., Bauman, M., 1998. Neuropathology of infantile autism. J. Neuropathol. Exp. Neurol. 57, 645–652.

Kern, J.K., Geier, D.A., Sykes, L.K., Geier, M.R., 2016. Relevance of neuroinflammation and encephalitis in autism. Front. Cell. Neurosci. 9, 519. https://doi.org/10.3389/fncel.2015.00519.

Khandaker, G.M., Zimbron, J., Lewis, G., Jones, P.B., 2013. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol. Med. 43, 239–257. https://doi.org/10.1017/S0033291712000736.

Kubas, B., Kułak, W., Sobaniec, W., Tarasow, E., Lebkowska, U., Walecki, J., 2012. Metabolite alterations in autistic children: a 1H MR spectroscopy study. Adv. Med. Sci. 57, 152–156. https://doi.org/10.2478/v10039-012-0014-x.

Lee, T.M., Lee, K.M., Lee, C.Y., Lee, H.C., Tam, K.W., Loh, E.W., 2021. Effectiveness of N-acetylcysteine in autism spectrum disorders: a meta-analysis of randomized controlled trials. Aust. N. Z. J. Psychiatry 55, 196–206. https://doi.org/10.1177/0004867420952540.

Liu, L., Qi, X., Cheng, S., Meng, P., Yang, X., Pan, C., Zhang, N., Chen, Y., Li, C., Zhang, H., Zhang, Z., Zhang, J., Cheng, B., Wen, Y., Jia, Y., Liu, H., Zhang, F., 2023. Epigenetic analysis suggests aberrant cerebellum brain aging in old-aged adults with autism spectrum disorder and schizophrenia. Mol. Psychiatry 28, 4867–4876. https://doi.org/10.1038/s41380-023-02050-4.

Lord, C., Brugha, T.S., Charman, T., Cusack, J., Dumas, G., Frazier, T., Jones, E.J.H., Jones, R.M., Pickles, A., State, M.W., Taylor, J.L., Veenstra-VanderWeele, J., 2020. Autism spectrum disorder. Nat. Rev. Dis. Primers 6, 5. https://doi.org/10.1038/s41572-019-0138-4.

Luo, Y., Wang, Z., 2024. The impact of microglia on neurodevelopment and brain function in autism. Biomedicines 12, 210. https://doi.org/10.3390/biomedicines12010210.

Madhavan, A., Schiano-Visconte, M., Dutton, L., Cantalupo, M., Balasco, L., Mavillonio, A., Chelini, G., Bozzi, Y., Pangrazzi, L., 2026. Astaxanthin improves behavioural and immune dysfunction in the Shank3b mouse model of autism spectrum disorder. Biomed. Pharmacother. 195, 119051. https://doi.org/10.1016/j.biopha.2026.119051.

Manjeese, W., Mvubu, N.E., Steyn, A.J.C., Mpofana, T., 2021. *Mycobacterium tuberculosis*-induced maternal immune activation promotes autism-like phenotype in infected mice offspring. Int. J. Environ. Res. Public Health 18, 4513. https://doi.org/10.3390/ijerph18094513.

Mapelli, L., Soda, T., D'Angelo, E., Prestori, F., 2022. The cerebellar involvement in autism spectrum disorders: from the social brain to mouse models. Int. J. Mol. Sci. 23, 3894. https://doi.org/10.3390/ijms23073894.

Martínez-Sosa, P., Gómez-Fernández, A., Llorente, R., 2023. Early inflammatory biomarkers and neurodevelopmental outcomes in infancy. Brain Behav. Immun. 112, 45–56. https://doi.org/10.1016/j.bbi.2023.02.014.

Masi, A., Glozier, N., Dale, R., Guastella, A.J., 2017. The immune system, cytokines, and biomarkers in autism spectrum disorder. Neurosci. Bull. 33, 194–204. https://doi.org/10.1007/s12264-017-0103-8.

Mastenbroek, L.J.M., Kooistra, S.M., Eggen, B.J.L., Prins, J.R., 2024. The role of microglia in early neurodevelopment and the effects of maternal immune activation. Semin. Immunopathol. 46, 1. https://doi.org/10.1007/s00281-024-01017-6.

Masuda, T., Sankowski, R., Staszewski, O., Prinz, M., 2020. Microglia heterogeneity in the single-cell era. Cell Rep. 30, 1271–1281. https://doi.org/10.1016/j.celrep.2020.01.010.

McCarthy, M.M., Wright, C.L., 2017. Convergence of sex differences and the neuroimmune system in autism spectrum disorder. Biol. Psychiatry 81, 402–410. https://doi.org/10.1016/j.biopsych.2016.10.004.

Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428–435. https://doi.org/10.1038/nature07201.

Menashe, I., Grange, P., Larsen, E.C., Banerjee-Basu, S., Mitra, P.P., 2013. Co-expression profiling of autism genes in the mouse brain. PLoS Comput. Biol. 9, e1003128. https://doi.org/10.1371/journal.pcbi.1003128.

Meng, J., Pan, P., Guo, G., Chen, A., Meng, X., Liu, H., 2024. Transient CSF1R inhibition ameliorates behavioral deficits in Cntnap2 knockout and valproic acid-exposed mouse models of autism. J. Neuroinflammation 21, 262. https://doi.org/10.1186/s12974-024-03259-5.

Michels, S., Mali, A., Jäntti, H., Rezaie, M., Malm, T., 2025. Microglial involvement in autism spectrum disorder: insights from human data and iPSC models. Brain Behav. Immun. 130, 106071. https://doi.org/10.1016/j.bbi.2025.106071.

Nelson, S.B., Valakh, V., 2015. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. Neuron 87, 684–698. https://doi.org/10.1016/j.neuron.2015.07.033.

Nguyen, M.D., Julien, J.P., Rivest, S., 2002. Innate immunity: the missing link in neuroprotection and neurodegeneration. Nat. Rev. Neurosci. 3, 216–227. https://doi.org/10.1038/nrn752.

Oya, M., Matsuoka, K., Kubota, M., Fujino, J., Tei, S., Takahata, K., Tagai, K., Yamamoto, Y., Shimada, H., Seki, C., Itahashi, T., Aoki, Y.Y., Ohta, H., Hashimoto, R. I., Sugihara, G., Obata, T., Zhang, M.R., Suhara, T., Nakamura, M., Kato, N., Takado, Y., Takahashi, H., Higuchi, M., 2023. Increased glutamate and glutamine levels and their relationship to astrocytes and dopaminergic transmissions in the brains of adults with autism. Sci. Rep. 13, 11655. https://doi.org/10.1038/s41598-023-38306-3.

Page, L.A., Daly, E., Schmitz, N., Simmons, A., Toal, F., Deeley, Q., Ambery, F., McAlonan, G.M., Murphy, K.C., Murphy, D.G., 2006. In vivo 1H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. Am. J. Psychiatry 163, 2189–2192. https://doi.org/10.1176/appi.ajp.163.12.2189.

Pangrazzi, L., Balasco, L., Bozzi, Y., 2020. Oxidative stress and immune system dysfunction in autism spectrum disorders. Int. J. Mol. Sci. 21, 3293. https://doi.org/10.3390/ijms21093293.

Pangrazzi, L., Cerilli, E., Balasco, L., Dall'O', G.M., Chelini, G., Pastore, A., Weinberger, B., Bozzi, Y., 2024. N-acetylcysteine counteracts immune dysfunction and autism-related behaviors in the Shank3b mouse model of autism spectrum disorder. Antioxidants (basel) 13, 1390. https://doi.org/10.3390/antiox13111390.

Pangrazzi, L., Cerilli, E., Balasco, L., Khurshid, C., Tobia, C., Dall'O', G.M., Chelini, G., Perini, S., Filosi, M., Barbieri, A., Ravizza, T., Vezzani, A., Provenzano, G., Pastore, A., Weinberger, B., Rubert, J., Domenici, E., Bozzi, Y., 2025a. The interplay between oxidative stress and inflammation supports autistic-related behaviors in Cntnap2 knockout mice. Brain Behav. Immun. 127, 57–71. https://doi.org/10.1016/j.bbi.2025.02.030.

Pangrazzi, L., Weinberger, B., Bozzi, Y., 2025b. Brain-resident immune cells in neurodevelopmental disorders. Adv. Exp. Med. Biol. 1477, 265–280. https://doi.org/10.1007/978-3-031-89525-8_10.

Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. Science 333, 1456–1458. https://doi.org/10.1126/science.1202529.

Paolicelli, R.C., Ferretti, M.T., 2017. Function and dysfunction of microglia during brain development: consequences for synapses and neural circuits. Front. Synaptic Neurosci. 9, 9. https://doi.org/10.3389/fnsyn.2017.00009.

Parikshak, N.N., Luo, R., Zhang, A., Won, H., Lowe, J.K., Chandran, V., Horvath, S., Geschwind, D.H., 2013. Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell 155, 1008–1021. https://doi.org/10.1016/j.cell.2013.10.031.

Pinto, M.J., Ragozzino, D., Bessis, A., Audinat, E., 2024. Microglial modulation of synaptic maturation, activity, and plasticity. Adv Neurobiol 37, 209–219. https://doi.org/10.1007/978-3-031-55529-9_12.

Provenzano, G., Pangrazzi, L., Poli, A., Pernigo, M., Sgadò, P., Genovesi, S., Zunino, G., Berardi, N., Casarosa, S., Bozzi, Y., 2014. Hippocampal dysregulation of neurofibromin-dependent pathways is associated with impaired spatial learning in engrailed 2 knock-out mice. J. Neurosci. 34, 13281–13288. https://doi.org/10.1523/JNEUROSCI.2894-13.2014.

Rubenstein, J.L., Merzenich, M.M., 2003. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav. 2, 255–267. https://doi.org/10.1034/j.1601-183x.2003.00037.x.

Salter, M.W., Stevens, B., 2017. Microglia emerge as central players in brain disease. Nat. Med. 23, 1018–1027. https://doi.org/10.1038/nm.4397.

Schafer, D.P., Lehrman, E.K., Kautzman, A.G., Koyama, R., Mardinly, A.R., Yamasaki, R., Ransohoff, R.M., Greenberg, M.E., Barres, B.A., Stevens, B., 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74, 691–705. https://doi.org/10.1016/j.neuron.2012.03.026.

Schiavi, S., La Rosa, P., Petrillo, S., Carbone, E., D'Amico, J., Piemonte, F., Trezza, V., 2022. N-Acetylcysteine mitigates social dysfunction in a rat model of autism normalizing glutathione imbalance and the altered expression of genes related to synaptic function in specific brain areas. Front. Psych. 13, 851679. https://doi.org/10.3389/fpsyt.2022.851679.

Schmahmann, J.D., Pierce, S., MacMore, J., L'Italien, G.J., 2021. Development and validation of a patient-reported outcome measure of ataxia. Mov. Disord. 36, 2367–2377. https://doi.org/10.1002/mds.28670.

Schmahmann, J.D., Sherman, J.C., 1998. The cerebellar cognitive affective syndrome. Brain 121, 561–579. https://doi.org/10.1093/brain/121.4.561.

Shi, L., Smith, S.E., Malkova, N., Tse, D., Su, Y., Patterson, P.H., 2009. Activation of the maternal immune system alters cerebellar development in the offspring. Brain Behav. Immun. 23, 116–123. https://doi.org/10.1016/j.bbi.2008.07.012.

Shpyleva, S., Ivanovsky, S., de Conti, A., Melnyk, S., Tryndyak, V., Beland, F.A., James, S. J., Pogribny, I.P., 2014. Cerebellar oxidative DNA damage and altered DNA methylation in the BTBR T+tf/J mouse model of autism and similarities with human post mortem cerebellum. PLoS One 9, e113712. https://doi.org/10.1371/journal.pone.0113712.

Stoessel, M.B., Majewska, A.K., 2021. Little cells of the little brain: microglia in cerebellar development and function. Trends Neurosci. 44, 564–578.

Stoodley, C.J., 2016. The cerebellum and neurodevelopmental disorders. Cerebellum 15, 34–37. https://doi.org/10.1007/s12311-015-0715-3.

Stoodley, C.J., D'Mello, A.M., Ellegood, J., Jakkamsetti, V., Liu, P., Nebel, M.B., Gibson, J.M., Kelly, E., Meng, F., Cano, C.A., Pascual, J.M., Mostofsky, S.H., Lerch, J. P., Tsai, P.T., 2017. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat. Neurosci. 20, 1744–1751. https://doi.org/10.1038/s41593-017-0004-1.

Stoodley, C.J., Tsai, P.T., 2021. Adaptive prediction for social contexts: the cerebellar contribution to typical and atypical social behaviors. Annu. Rev. Neurosci. 44, 475–493. https://doi.org/10.1146/annurev-neuro-100120-092143.

Suzuki, K., Sugihara, G., Ouchi, Y., Nakamura, K., Futatsubashi, M., Takebayashi, K., Yoshihara, Y., Omata, K., Matsumoto, K., Tsuchiya, K.J., Iwata, Y., Tsujii, M., Sugiyama, T., Mori, N., 2013. Microglial activation in young adults with autism spectrum disorder. JAMA Psychiat. 70, 49–58. https://doi.org/10.1001/jamapsychiatry.2013.272.

Suswidiantoro, V., Tang, K.S., Rahman, K., Ariestanti, D.M., James, R.J., Yan, C.C., Kato, M., Saputri, F.C., 2026. Natural compounds as multitarget agents in Alzheimer's diseases: evidence from in vivo and in vitro models. Front. Pharmacol. 17, 1766470. https://doi.org/10.3389/fphar.2026.1766470.

Sydnor, L.M., Aldinger, K.A., 2022. Structure, function, and genetics of the cerebellum in autism. J. Psychiatr. Brain Sci. 7, e220008. https://doi.org/10.20900/jpbs.20220008.

Tenreiro, M.F., Muotri, A.R., 2026. Reconstructing human corticogenesis: Insights from cerebral organoids into neurodevelopment and disease modeling. Dev. Cell 61, 720–743. https://doi.org/10.1016/j.devcel.2026.02.018.

Thion, M.S., Low, D., Silvin, A., Chen, J., Grisel, P., Schulte-Schrepping, J., Blecher, R., Ulas, T., Squarzoni, P., Hoeffel, G., Coulpier, F., Siopi, E., David, F.S., Scholz, C., Shihui, F., Lum, J., Amoyo, A.A., Larbi, A., Poidinger, M., Buttgereit, A., Lledo, P.M., Greter, M., Chan, J.K.Y., Amit, I., Beyer, M., Schultze, J.L., Schlitzer, A., Pettersson, S., Ginhoux, F., Garel, S., 2018. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell 172, 500–516.e16. https://doi.org/10.1016/j.cell.2017.11.042.

Tsai, P.T., 2016. Autism and cerebellar dysfunction: evidence from animal models. Semin. Fetal Neonatal Med. 21, 349–355. https://doi.org/10.1016/j.siny.2016.04.009.

Van Camp, N., Lavisse, S., Roost, P., Gubinelli, F., Hillmer, A., Boutin, H., 2022. TSPO imaging in animal models of brain diseases. Eur. J. Nucl. Med. Mol. Imaging 49, 77–109. https://doi.org/10.1007/s00259-021-05379-z.

Vargas, D.L., Nascimbene, C., Krishnan, C., Zimmerman, A.W., Pardo, C.A., 2005. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann. Neurol. 57, 67–81. https://doi.org/10.1002/ana.20315.

Wang, S.S., Kloth, A.D., Badura, A., 2014. The cerebellum, sensitive periods, and autism. Neuron 83, 518–532. https://doi.org/10.1016/j.neuron.2014.07.016.

Wang, X., Zhao, Z., Sun, L., Gao, C., Wang, L., Mei, D., Hao, C., Zhao, S., Yan, X., Liu, J., Liu, L., Guo, B., Zhang, Y., 2026. Ertugliflozin improves animal behaviours associated with oxidative stress and inflammation in a BTBR *T*$^{+}$*Itpr3tf/J* mouse model of autism. Brain Commun. 8, fcag083. https://doi.org/10.1093/braincomms/fcag083.

Wei, H., Zou, H., Sheikh, A.M., Malik, M., Dobkin, C., Brown, W.T., Li, X., 2011. IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. J. Neuroinflammation 8, 52. https://doi.org/10.1186/1742-2094-8-52.

Willsey, A.J., Willsey, A.J., Sanders, S.J., Li, M., Dong, S., Tebbenkamp, A.T., Muhle, R. A., Reilly, S.K., Lin, L., Fertuzinhos, S., Miller, J.A., Murtha, M.T., Bichsel, C., Niu, W., Cotney, J., Ercan-Sencicek, A.G., Gockley, J., Gupta, A.R., Han, W., He, X., Hoffman, E.J., Klei, L., Lei, J., Liu, W., Liu, L., Lu, C., Xu, X., Zhu, Y., Mane, S.M., Lein, E.S., Wei, L., Noonan, J.P., Roeder, K., Devlin, B., Sestan, N., State, M.W., 2013. Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell 155, 997–1007. https://doi.org/10.1016/j.cell.2013.10.020.

Wink, L.K., Adams, R., Wang, Z., Klaunig, J.E., Plawecki, M.H., Posey, D.J., McDougle, C. J., Erickson, C.A., 2016. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Mol. Autism 7, 26. https://doi.org/10.1186/s13229-016-0088-6.

Yamamoto, M., Kim, M., Imai, H., Itakura, Y., Ohtsuki, G., 2019. Microglia-triggered plasticity of intrinsic excitability modulates psychomotor behaviors in acute cerebellar inflammation. Cell Rep. 28, 2923–2938.e8. https://doi.org/10.1016/j.celrep.2019.08.078.

Yuan, L., Liu, S., Bai, X., Gao, Y., Liu, G., Wang, X., Liu, D., Li, T., Hao, A., Wang, Z., 2016. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. J. Neuroinflammation 13, 77. https://doi.org/10.1186/s12974-016-0531-3.

Zhan, Y., Paolicelli, R.C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., Vyssotski, A.L., Bifone, A., Gozzi, A., Ragozzino, D., Gross, C.T., 2014. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat. Neurosci. 17, 400–406. https://doi.org/10.1038/nn.3641.

Zhang, Y., Cui, W., Zhai, Q., Zhang, T., Wen, X., 2017. N-acetylcysteine ameliorates repetitive/stereotypic behavior due to its antioxidant properties without activation of the canonical Wnt pathway in a valproic acid-induced rat model of autism. Mol. Med. Rep. 16, 2233–2240. https://doi.org/10.3892/mmr.2017.6787.

Zhang, L., Bang, S., He, Q., Matsuda, M., Luo, X., Jiang, Y.H., Ji, R.R., 2023. SHANK3 in vagal sensory neurons regulates body temperature, systemic inflammation, and sepsis. Front. Immunol. 14, 1124356. https://doi.org/10.3389/fimmu.2023.1124356.

Zwaigenbaum, L., Bryson, S.E., Szatmari, P., et al., 2012. Sex differences in children with autism spectrum disorder identified within a high-risk infant cohort. J. Autism Dev. Disord. 42, 2585–2596. https://doi.org/10.1007/s10803-012-1515-y.