Registered in Germany Europa Revue Journal
ISSN: 1862-6564 Vol. 6 No. 9 (2026) Published September 13, 2026

NEURODEVELOPMENTAL FEATURES OF AUTISM SPECTRUM DISORDER: ETIOLOGY, PATHOGENESIS, AND CURRENT NEUROBIOLOGICAL PERSPECTIVES

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Abstract

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder that emerges during early development of the central nervous system and is characterized by persistent differences in social communication and interaction, restricted or repetitive patterns of behavior, interests, or activities, and, in many individuals, atypical sensory processing. From a contemporary neurobiological perspective, ASD cannot be explained by dysfunction of a single brain structure or neurotransmitter system. Rather, its pathogenesis involves complex interactions among genetic and epigenetic factors, prenatal environmental influences, altered neurogenesis and neuronal migration, abnormalities in synaptogenesis and synaptic pruning, dysregulation of excitatory and inhibitory neurotransmission, neuroimmune mechanisms, oxidative stress, mitochondrial dysfunction, and atypical organization of functional brain networks.

Genomic studies have demonstrated the complex polygenic architecture of ASD and have identified numerous risk genes involved in neuronal development, synaptic organization, chromatin remodeling, gene expression, and regulation of neuronal excitability. Large-scale exome sequencing studies have identified numerous ASD-associated genes, many of which are highly expressed during prenatal and early postnatal brain development [1].

Neuroimaging studies have demonstrated heterogeneous structural and functional alterations in individuals with ASD, including atypical patterns of connectivity among distributed neural networks. However, these alterations are not uniform across affected

individuals and currently cannot be considered specific diagnostic biomarkers for ASD [2]. Increasing evidence also suggests that prenatal immune activation, metabolic disturbances, environmental pollutants, and other environmental factors may interact with genetic susceptibility and influence neurodevelopmental trajectories [3,4].

This article reviews the etiology and pathogenesis of ASD from a neurological and neurobiological perspective, integrating contemporary evidence from molecular genetics, developmental neuroscience, neurophysiology, neuroimmunology, neuroimaging, and environmental neuroscience.

Keywords

autism spectrum disorder; neurodevelopmental disorder; central nervous system; neurogenesis; neuroinflammation; synaptogenesis; synaptic plasticity; glutamate; GABA; genetics; epigenetics; neural networks; excitatory-inhibitory balance.

INTRODUCTION. Autism spectrum disorder is one of the most complex conditions investigated in contemporary neurology, developmental neuroscience, neurobiology, and child psychiatry. Clinically, ASD is characterized primarily by persistent differences in social communication and social interaction, restricted or repetitive patterns of behavior and interests, and, in many individuals, atypical responses to sensory stimuli. These features emerge during early development and may vary substantially in their severity and functional consequences throughout the lifespan [5]. The World Health Organization's ICD-11 classifies ASD within the group of neurodevelopmental disorders. This classification does not negate the psychiatric manifestations of ASD but emphasizes that its fundamental biological substrate is closely associated with the development and organization of the central nervous system [6]. From this perspective, considering ASD exclusively as a psychiatric disorder does not fully capture its biological complexity. Contemporary research increasingly conceptualizes ASD as a genetically and biologically heterogeneous disorder of brain development involving alterations in neurogenesis, neuronal migration, axonal guidance, dendritic arborization, synaptogenesis, synaptic pruning, maturation of neurotransmitter systems, and the development of functional neural networks [1,7]. ASD does not have a single etiological cause. Instead, genetic susceptibility may interact with

prenatal and early postnatal environmental factors through multiple molecular pathways, ultimately altering neurodevelopmental processes. Accordingly, ASD is best understood as an etiologically heterogeneous neurodevelopmental disorder characterized by convergence of multiple biological pathways onto partially overlapping neural phenotypes.

1. THE NEURODEVELOPMENTAL NATURE OF AUTISM SPECTRUM DISORDER

Neurodevelopment begins during embryogenesis and continues throughout childhood and adolescence. The proliferation of neural progenitor cells, neuronal differentiation, neuronal migration, axonal growth, dendritic development, synapse formation, and subsequent selective elimination of excessive synapses constitute a highly coordinated sequence of biological processes responsible for establishing functional brain architecture. In ASD, one or more of these processes may be altered as a consequence of genetic variation, epigenetic mechanisms, or interactions between genetic susceptibility and environmental exposures.Therefore, ASD should be distinguished from classical neurodegenerative or destructive neurological disorders. In conditions such as stroke, traumatic brain injury, or neurodegenerative disease, damage to an already developed nervous system is often central to pathogenesis. In ASD, by contrast, the principal abnormality involves an altered developmental trajectory of the nervous system, particularly during critical periods of brain maturation. This distinction is fundamental. Rather than searching for a single "damaged brain center," contemporary neurobiological research focuses on atypical development of distributed neural circuits, synaptic organization, and interactions among brain networks.

2. EPIDEMIOLOGY AND CLINICAL HETEROGENEITY

The reported prevalence of ASD varies substantially across studies according to diagnostic criteria, age groups, geographic regions, surveillance systems, and study methodology. A systematic review and meta-analysis published in 2025, including more than 21 million children across 66 studies conducted between 2008 and 2024, estimated a pooled global prevalence of ASD of approximately 0.77% among children, while emphasizing considerable regional and methodological heterogeneity [8]. Increasing

prevalence estimates over time should not automatically be interpreted as evidence of a proportional increase in biological incidence. Expansion of diagnostic criteria, improved screening, increased awareness, earlier recognition, and identification of individuals with milder phenotypes are important contributing factors [5,8]. The clinical heterogeneity of ASD also reflects substantial biological heterogeneity. Some individuals have preserved intellectual development, whereas others present with intellectual disability, language impairment, epilepsy, motor abnormalities, sleep disturbances, or other neurodevelopmental characteristics. Thus, autism should not be regarded as a single biologically homogeneous disease entity, but rather as a spectrum of phenotypes that may arise through different molecular and neurobiological pathways.

3. GENETIC ETIOLOGY

Genetic factors represent one of the most strongly supported biological components of ASD etiology. Twin and family studies demonstrate a substantial heritable contribution to ASD susceptibility and autistic traits. However, the genetic architecture is highly complex and involves the combined effects of numerous variants rather than a single causative gene [9].Contemporary genomic studies have identified ASD-associated genes belonging to several major functional categories, including:

genes involved in synaptic formation and maintenance;

genes regulating neurotransmission;

genes involved in chromatin remodeling and transcriptional regulation;

genes involved in neuronal differentiation and migration;

genes regulating neuronal excitability and ion channels;

genes involved in intracellular signaling and protein synthesis.

A large-scale exome sequencing study involving more than 35,000 participants, including approximately 12,000 individuals with ASD, identified 102 ASD-associated risk genes. A substantial proportion of these genes are involved in early brain development and neuronal communication [1]. These findings provide strong support for the concept that ASD has a substantial biological and neurodevelopmental basis rather than representing merely a disorder of behavior or social functioning.

4. DE NOVO MUTATIONS AND GENOMIC ALTERATIONS

The genetic architecture of ASD includes both inherited variants and de novo mutations. De novo variants arise during gametogenesis or early embryonic development and may therefore occur even in individuals without a family history of ASD.Whole-genome and exome sequencing studies have demonstrated the contribution of de novo single-nucleotide variants, copy-number variants, and other structural genomic alterations to ASD risk. Some of these variants affect genes involved in chromatin remodeling, neuronal differentiation, synaptic function, and intracellular signaling [10,11]. These mechanisms may explain why ASD can occur in children without an obvious familial history and highlight the importance of early developmental genomic events in its pathogenesis.

5. CHROMATIN REMODELING AND EPIGENETIC MECHANISMS

Neurodevelopment is determined not only by the DNA sequence but also by the precise regulation of gene expression in specific cells and developmental stages. Alterations in genes such as CHD8 and MECP2 can modify chromatin organization, transcriptional regulation, neuronal differentiation, and synaptic development. Such mechanisms represent an important molecular link between genetic variation and the development of abnormal neuronal phenotypes [1,7]. Consequently, ASD pathogenesis can be conceptualized through the following sequence:

genetic variation → epigenetic dysregulation → altered neuronal development → abnormal synaptic organization → atypical neural network development → clinical phenotype.

This framework emphasizes the importance of gene regulation rather than focusing exclusively on structural DNA mutations.

6. ALTERATIONS IN NEUROGENESIS AND NEURONAL MIGRATION

During embryonic brain development, appropriate neuronal positioning and cortical organization are essential for subsequent functional network formation. Several ASD-associated genes identified through genomic studies are involved in neurogenesis, cell-cycle regulation, neuronal differentiation, and migration. Alterations in these pathways may therefore affect cortical microarchitecture and functional organization from prenatal stages of development. This hypothesis provides a biological explanation

for why the earliest manifestations of ASD may become apparent during infancy and early childhood.

7. SYNAPTOGENESIS AND SYNAPTIC PLASTICITY

One of the major areas of contemporary ASD research concerns synaptic biology. Synapses enable communication between neurons, and their number, morphology, receptor composition, and functional strength undergo continuous remodeling throughout development. Genetic alterations involving synaptic proteins, including SHANK, NLGN, and NRXN families, may interfere with synaptic structure and neuronal communication. SHANK3 and NRXN1, for example, participate in molecular complexes essential for normal pre- and postsynaptic function [7]. Synaptic pruning—the selective elimination of excessive or insufficiently functional synaptic connections—is also essential for maturation of neural networks. Both excessive and insufficient pruning may interfere with optimal organization of neural circuits. Therefore, the central issue in ASD is not simply whether the number of synapses is increased or decreased, but whether synapses are formed, maintained, strengthened, and eliminated at the appropriate developmental stage and within the appropriate neural circuits.

8. GLUTAMATERGIC AND GABAERGIC SYSTEMS: EXCITATORY-INHIBITORY BALANCE

The stability of neural activity depends on a dynamic balance between excitatory and inhibitory neurotransmission. Glutamate is the principal excitatory neurotransmitter in the central nervous system, whereas GABA is the major inhibitory neurotransmitter. The excitatory/inhibitory (E/I) balance hypothesis has become an important framework for understanding ASD neurophysiology. According to this model, alterations in the balance between glutamatergic excitation and GABAergic inhibition within specific neural circuits may influence neuronal stability and information processing [12]. A 2023 study investigating glutamate- and GABA-related gene sets, cortical structure, and autistic symptoms provided evidence that alterations in excitatory and inhibitory signaling may be associated with specific ASD phenotypes [12]. However, E/I imbalance should not be interpreted as a universal mechanism underlying all cases of

ASD. Rather, it may represent a convergent neurophysiological mechanism through which diverse genetic and molecular abnormalities influence neural network function.

9. NEURONAL EXCITABILITY AND ION CHANNELS

Neuronal electrical activity depends on the coordinated function of voltage-gated sodium, potassium, calcium, and other ion channels. Variants in genes encoding ion channels, including SCN2A, can alter neuronal excitability and synaptic signaling. Some variants are also associated with epilepsy and other neurodevelopmental phenotypes [11]. This provides a possible biological link between ASD and epilepsy. In individuals with ASD who also develop epileptic seizures, abnormalities in neuronal excitability and network stability may represent important components of the underlying neurophysiology.

10. BRAIN NETWORKS AND FUNCTIONAL CONNECTIVITY

Modern neuroimaging has substantially advanced understanding of ASD neurobiology. Structural MRI, diffusion tensor imaging, functional MRI, EEG, MEG, and multimodal approaches have identified alterations in brain structure and functional connectivity. A 2024 multimodal neuroimaging review incorporating 172 studies demonstrated substantial heterogeneity across structural and functional findings in ASD [13]. This finding is particularly important. ASD cannot be universally characterized as either a disorder of “hypoconnectivity” or “hyperconnectivity.” Some neural circuits may demonstrate reduced connectivity, whereas others may demonstrate increased or atypical connectivity. Current models therefore increasingly emphasize atypical organization and integration of distributed neural networks rather than a single global abnormality in connectivity.

11. NEUROBIOLOGY OF ATYPICAL SENSORY PROCESSING

Atypical responses to sensory stimuli are common in ASD. Individuals may exhibit hypersensitivity or hyposensitivity to auditory, visual, tactile, olfactory, gustatory, or vestibular stimuli. From a neurological perspective, these abnormalities may involve not only peripheral sensory systems but also central processing, integration, filtering, and interpretation of sensory information. Altered interactions between sensory-processing

networks and higher-order cognitive systems may contribute to repetitive behaviors, avoidance responses, and difficulties in adapting to environmental stimuli.

12. NEUROINFLAMMATION AND IMMUNE MECHANISMS

Neuroimmune mechanisms have become an important area of contemporary ASD research. Microglial cells play a central role in immune surveillance within the central nervous system as well as in synaptic pruning and neural circuit maturation. Alterations in microglial activation and immune signaling may influence synaptic plasticity and the development of neural networks. Cytokines and chemokines can influence neuronal development and synaptic function, suggesting that immune signaling may represent one biological pathway contributing to ASD [14]. Nevertheless, an important distinction must be maintained: neuroinflammation has not been established as a universal or primary cause of ASD. Current evidence indicates that immune mechanisms may contribute to specific biological subtypes or developmental trajectories rather than explaining the entire spectrum.

13. PRENATAL IMMUNE ACTIVATION.

Maternal immune activation during pregnancy may influence fetal brain development through inflammatory mediators and alterations in the maternal-placental-fetal interface. Prenatal infections, maternal metabolic conditions, and other inflammatory exposures may alter fetal neurodevelopment through changes in cytokine signaling, placental function, oxidative stress, and neuronal differentiation. Studies investigating prenatal air pollution and maternal immune activation have also reported associations with ASD risk [15]. However, epidemiological association should not automatically be interpreted as direct causality. Because ASD is multifactorial, environmental exposures may influence neurodevelopment differently depending on the individual's underlying genetic susceptibility.

14. PRENATAL AND ENVIRONMENTAL FACTORS

The prenatal period represents a particularly vulnerable window for central nervous system development. Recent reviews have identified maternal infection, gestational diabetes, maternal obesity, certain medication exposures, air pollution, and other environmental factors as potential contributors to ASD risk [3]. Environmental

toxicants, including certain heavy metals, pesticides, and air pollutants, have also been investigated in relation to ASD and other neurodevelopmental disorders [4].

Potential mechanisms include:

environmental exposure → oxidative stress → mitochondrial dysfunction → inflammatory signaling → altered cellular signaling → impaired neurodevelopment. Importantly, none of these environmental factors can independently explain the majority of ASD cases.

15. OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

The brain has exceptionally high metabolic requirements and depends heavily on mitochondrial ATP production to maintain neuronal function. Mitochondrial dysfunction may influence energy metabolism, reactive oxygen species production, calcium homeostasis, and synaptic transmission.

A 2024 systematic review and meta-analysis evaluated biomarkers associated with mitochondrial dysfunction in ASD and provided evidence supporting further investigation of mitochondrial mechanisms in selected individuals [16]. However, mitochondrial abnormalities are currently insufficiently specific to serve as diagnostic biomarkers for ASD.

16. THE GUT-BRAIN AXIS AND MICROBIOTA

The bidirectional relationship between the intestinal microbiota and the central nervous system has emerged as an important area of ASD research. Microbial metabolites, immune mediators, vagal signaling, and metabolic pathways may influence central nervous system function indirectly.

Recent reviews have proposed that alterations in gut microbiota may interact with neuroimmune signaling, cytokine pathways, and microbial metabolites in ASD [17]. Nevertheless, the direction of causality remains uncertain. Microbiome alterations may contribute to neurodevelopmental mechanisms in some individuals, but they may also arise secondarily from dietary patterns, gastrointestinal symptoms, medication exposure, or behavioral characteristics associated with ASD. Therefore, the statement that “autism is caused by gut dysbiosis” is not supported by current scientific evidence.

17. GENE-ENVIRONMENT INTERACTIONS

One of the most important emerging concepts in ASD research is gene-environment interaction.

Genetic susceptibility does not inevitably result in clinical ASD, while environmental exposures do not cause ASD uniformly in all individuals. A conceptual model can therefore be expressed as:

genetic susceptibility + epigenetic vulnerability + prenatal/early postnatal environmental exposure → altered neurodevelopment → synaptic and network dysfunction → individual clinical phenotype. This model helps explain the substantial clinical variability observed across the autism spectrum.

18. AN INTEGRATIVE NEUROBIOLOGICAL MODEL OF ASD PATHOGENESIS

The available evidence supports a multilevel model of ASD pathogenesis.

Level 1 — Genome

Inherited variants, de novo mutations, copy-number variants, and polygenic susceptibility.

Level 2 — Epigenome

Chromatin remodeling, DNA methylation, and altered gene expression.

Level 3 — Cellular level

Neurogenesis, neuronal migration, dendritic development, axonal guidance, and microglial function.

Level 4 — Synaptic level

Synaptogenesis, synaptic pruning, postsynaptic scaffolding, and neurotransmitter receptor function.

Level 5 — Neurotransmitter systems

Functional alterations involving glutamatergic, GABAergic, dopaminergic, and serotonergic signaling.

Level 6 — Neural networks

Atypical structural and functional connectivity and integration among distributed brain regions.

Level 7 — Clinical phenotype

Individual combinations of differences in social communication, sensory processing, repetitive behavior, cognition, and adaptive functioning.

Thus, a contemporary model of ASD neurobiology can be summarized through the following conceptual axis:

gene → synapse → neural network → behavior.

19. DISCUSSION

The major challenge in understanding ASD etiology and pathogenesis is its profound biological heterogeneity. In one individual, the predominant mechanism may involve a mutation affecting synaptic proteins; in another, chromatin remodeling; in another, ion-channel dysfunction or altered intracellular signaling. Different molecular pathways may therefore converge on partially overlapping clinical phenotypes, a phenomenon often described as phenotypic convergence. Conversely, the same genetic variant may produce substantially different clinical manifestations in different individuals. This suggests the involvement of genetic modifiers, epigenetic mechanisms, developmental timing, environmental factors, and individual biological context.

Therefore, future ASD research should move beyond the question:

“What is the cause of autism?”

toward a more precise question:

“Which molecular and neurobiological pathways are altered in a particular individual with ASD?”

Such an approach may provide the foundation for precision medicine, individualized prognosis, molecular stratification, and personalized intervention strategies.

20. NEUROLOGICAL DIAGNOSTIC PERSPECTIVE

There is currently no single laboratory or neuroimaging test capable of diagnosing ASD universally. Diagnosis remains primarily clinical and developmental. Nevertheless, neurological assessment is important for identifying coexisting neurological disorders and potential etiological conditions.

Particular attention should be paid to:

epileptic seizures;

developmental regression;

motor abnormalities;

atypical head-growth trajectories;

abnormal muscle tone;

suspected genetic syndromes;

signs suggestive of neurometabolic disorders;

significant sleep disturbances.

Depending on the clinical context, additional neurological, genetic, metabolic, electrophysiological, or neuroimaging investigations may be appropriate. Importantly, EEG, MRI, metabolic testing, and genetic testing are not universal confirmatory tests for ASD. Their use should be guided by the patient's clinical phenotype and the differential diagnostic question.

21. KEY SCIENTIFIC CONCLUSIONS. The current evidence supports several major conclusions regarding ASD pathogenesis: ASD is primarily a neurodevelopmental disorder involving the development and functional organization of the central nervous system. ASD does not have a single etiological cause. Genetic factors represent major determinants of susceptibility. De novo mutations and copy-number variants contribute substantially to risk in a subset of individuals. Many ASD-associated genes regulate gene expression, chromatin remodeling, neuronal development, and synaptic communication. Altered synaptic plasticity and synaptic pruning represent important pathogenic mechanisms. Alterations in the balance between glutamatergic excitation and GABAergic inhibition may contribute to specific ASD phenotypes.

Structural and functional organization of neural networks is atypical in many individuals with ASD, although the direction and localization of these abnormalities are heterogeneous. Neuroinflammation and microglial dysfunction represent potentially important mechanisms but are not established as universal causes of ASD. Prenatal and environmental factors may interact with genetic susceptibility. Mitochondrial dysfunction and oxidative stress may contribute to selected biological subtypes. The substantial biological heterogeneity of ASD supports a future research strategy based on molecular phenotyping and precision medicine.

CONCLUSION. Autism spectrum disorder should not be conceptualized solely as a psychiatric syndrome but rather as a complex neurodevelopmental disorder involving atypical development and functional organization of the central nervous system. Its pathogenesis is multidimensional and involves interactions among genetic variants, de novo mutations, epigenetic regulation, neurogenesis, neuronal migration, synaptogenesis, synaptic pruning, glutamatergic and GABAergic neurotransmission, neuronal excitability, neuroimmune mechanisms, oxidative and metabolic processes, and the development of distributed neural networks. Current evidence does not support a single pathogenic mechanism capable of explaining the entire autism spectrum. Instead, diverse genetic and environmental factors may converge through multiple molecular pathways to produce overlapping but highly variable neurobiological phenotypes. Accordingly, ASD can be conceptualized as an etiologically heterogeneous, biologically complex, and clinically diverse neurodevelopmental disorder. Future research should therefore focus not on identifying a single universal biomarker or pathogenic mechanism, but on determining the individual molecular, cellular, metabolic, immunological, electrophysiological, and network-level abnormalities present in specific ASD phenotypes. Such an approach may ultimately improve early identification, prognostic stratification, individualized intervention, and the development of precision medicine strategies for autism spectrum disorder.

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