

Review Article

Recent Advances in Autism Spectrum Disorder: Etiological Mechanisms and Integrated Treatment Approaches

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Abstract

Background: Autism Spectrum Disorder (ASD) is a multifaceted neurodevelopmental disorder defined by long-term difficulties in social communication with restricted, repetitive behaviors. The field has recently expanded its understanding of the multifactorial nature of the disorder and broadened therapeutic approaches toward targeted, neurodiversity-affirming interventions. **Etiology:** The architecture of ASD itself is based on a dynamic interaction between heritable genetic risk (including polygenic risk scores, CNVs and de novo mutations) and also environmental effects involving maternal immune activation, advanced parental age, prenatal exposure to chemicals, etc. Pathophysiologically, these contributors converge on synaptic dysregulation, abnormal cortical microcircuitry connectivity, systemic neuroinflammation and gut microbiome dysbiosis. **Therapeutic Paradigms:** Contemporary interventions have transitioned from generic symptom management toward biological, behavioral, and precision-driven modalities:

- **Neuromodulation Therapies:** Non-invasive rTMS and tDCS targeting prefrontal regions to alter neural plasticity and executive function.
- **Microbiota-Gut-Brain (MGB) Axis Interventions:** Dietary modification, targeted pre/probiotics, and Fecal Microbiota Transplantation (FMT) aimed at reducing neuroinflammation.
- **Naturalistic Developmental Behavioral Interventions (NDBIs):** Frameworks like ESDM and JASPER that integrate behavioral learning into child-led, naturalistic contexts.
- **Biomarker-Targeted Pharmacotherapy:** Precision agents addressing pathway-specific mechanisms, such as oxytocinergic regulators and GABAergic modulators.
- **Digital Therapeutics (DTx) & VR:** Virtual reality social training and AI-driven platforms delivering adaptive, tailored skill training in low-anxiety environments.

Conclusion: Bridging etiological insights with multimodal therapeutic paradigms is critical for subgrouping ASD phenotypes, optimizing individual treatment responses, and guiding future clinical research.

1. Introduction

Autism (or Autism Spectrum Disorder, ASD) is characterized by impaired communication and socialization along with repetitive and restricted behaviors that differ in severity among individuals on a graded scale [1]. With promising advancements in autism research came also substantial progress in international policies; beyond the policy actions related to increasing global awareness and advocacy efforts, the field of autism also benefitted from advances on surrounding fields (i.e., human rights, maternal and child health, mental health) [2]. Autism (or autistic disorder) is a neurodevelopmental disorder that mostly involves impairment of verbal or non-verbal communication and social interaction alongside restricted and inflexible interests. It often develops in children before the age of 3, and is more frequent among males. It is a pervasive disorder that affects social skills of children and it is known as “Autism Spectrum Disorder” (ASD). It has been estimated that 3.4 per 1000 boys and girls aged between 3 and 10 years are diagnosed with autism spectrum disorder. The rates of incidence have increased in the last few years, resulting in huge physical and mental health problems for children and impacting families and society at large, a topic that has received great worldwide media attention. Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are highly heritable and frequently co-occurring disorders, but it is challenging to identify genetic variants associated with risk. Despite genetic studies, genome-wide association studies have identified few variants and most findings only support the role of excitatory and inhibitory neurotransmitter systems for aggregating evidence for symptom severity determinants in both ADHD and ASD via multiple marker testing across the genome. Links have been made for the severity of hyperactivity and impulsivity with glutamate, and gamma-aminobutyric acid (GABA) - the principle excitatory and inhibitory neurotransmitters respectively in the brain showing strong association GABA-related genes to inhibitory processes [3]. Sleep disorders are one Common Clinical Symptoms between Children with ASD and it occurs in 50% of this population [4]. Another study associated different neurological and psychiatric disorders with increased serum homocysteine levels such as cognitive impairment [5], and bipolar disorder [6] additionally, these elevated levels asserted to induce oxidative stress, cause mitochondrial dysfunction, and resulted in direct neurotoxicity which are related with autism spectrum disorder [7, 8].

Within this, a population-based Danish study demonstrated that viral infections during the first trimester requiring hospitalisation (influenza, gastroenteritis or other/nonspecified) were associated with a 28-fold increase in risk of autism spectrum disorder, and bacterial infections during the second trimester with 14-fold increased risk of autism spectrum disorder [3].

Maternal immune activation (MIA), triggered by infection or inflammation during pregnancy, has been associated with a range of developmental difficulties in children, including increased risk of speech, language, and motor delays increased behavioral and emotional problems and altered connectivity in brain regions supporting working memory in children. MIA elevates circulating and central Proinflammatory cytokines in animal models, potentially impacting fetal immunity and neurodevelopment.

2. Autism Spectrum Disorder Etiology

The biological landscape of autism spectrum disorder (ASD) is complex and highly diverse. The heritability of ASD is generally estimated to be between 60% and 80% by quantitative genetic research, including comprehensive twin and community panel analyses.

2.1. ASD’s Genetic Architecture microglia’s function in aberrant synaptic pruning

ASD’s Genetic Architecture microglia’s function in aberrant synaptic pruning is one of the subtypes of neuroinflammatory processes. Healthy central nervous system (CNS) wears the microglia worn exome for classic plans. They conserve brain homeostasis over the course of development and adulthood by eliminating attenuated or redundant projections through synaptic pruning [9]. Quantitative genetic studies, such as large twin and family studies, have estimated the heritability of ASD to be 60%–80%. This genetic architecture incorporates both polygenic complexity and rare high-penetrance variants. Some of these key genetic mechanisms include: Polygenic Risk Profiles: Initiates the process via common single nucleotide polymorphisms (SNPs) across multiple gene loci that lead to brain-based changes which, when added together, directly increase baseline vulnerability; Structural Changes and De Novo Mutations: These include rare Copy Number Variations (CNVs) such as chromosomal deletions or duplications, and relatively common de novo protein-truncating mutations hitting synaptic scaffold genes, chromatin remodeling genes, and neural circuit wiring etc. (SHANK3, CHD8; SCN2A). Gene-Environment (GxE) Interactions: Environmental stressors often exert their influence on baseline genetic vulnerabilities through epigenetic alterations—changes in the expression of a gene which do not require modification of its primary sequence such as DNA methylation and histone acetylation. Alternatively, these epigenetic changes lead to dysregulation of neurodevelopmental gene expression during sensitive gestational time intervals.

Polygenic Risk Profiles

Molecular “Eat-Me” and “Don’t-Eat-Me” Cascades: Molecular signaling mechanisms that determine which synapses microglia should engulf are disrupted in abnormal synaptic pruning.

The Complement Cascade (The Classical Pathway): Microglial pruning is mostly carried out by the complement system. In a neuroinflammatory state, cytokines (such as TNF- α and IL-1 β) drive the upregulation and abnormal deposition of complement proteins onto healthy synapses.

C1q and C3 Tagging: Complement component 1q (C1q) acts as the initiator, specifically attaching to synaptic components. This activates a downstream cascade that deposits C3b (an opsonin) onto the membrane, thereby labeling the synapse with a “eat-me” signal [10].

CR3 Receptor Engagement: Microglia express Complement Receptor 3 (CR3), an integrin complex (CD11b/CD18). When CR3 attaches to the opsonized C3b on the synapse, the microglial process initiates actin folding and phagocytic capsule formation, which literally breaks down the synapse [10]. In pathological neuroinflammation, this pathway is over activated, causing the stripping of viable, functional synapses.

Environmental Factors, Epigenetics, and GxE Interactions

Environmental exposures throughout crucial neurodevelopmental periods serve as important modulation factors, whereas genetic architecture provides baseline susceptibility. One of the strongest prenatal risk factors is advanced mother and paternal age, according to accumulated epidemiological information. The development of ASD is significantly influenced by gene-environment interactions. Toxic metals and other environmental contaminants have been connected to de novo mutations and epigenetic changes, which may trigger the development of ASD [11]. Toxic heavy metals have the potential to cause cell death pathways by interacting with cell signaling, interrupting enzyme processes, and causing oxidative stress. Children with ASD often have high levels of mercury and cadmium [12].

2.2. Neuroinflammation and Aberrant Synaptic Pruning

Maternal Immune Activation (MIA) and Aberrant Synaptic Pruning

MIA arises from gestational immune hyper activation triggered by maternal infections, auto inflammatory conditions, or autoimmune diseases, encompassing but not limited to infection-induced inflammatory dysregulation. Maternal immune activation (MIA) during pregnancy has been linked to schizophrenia (SCZ) and autistic spectrum disorder (ASD) [13]. According to the data at hand, the risk for neurodevelopmental disorders (NDDs) is not pathogen-specific and is instead caused by the mother's immune response to a pathogen that may affect the brain's growth and development [14].

Research on animals shows how pro-inflammatory cytokines, such as IL-6 or IL-17, are sufficient to cause NDD-like phenotypes in offspring, and conversely, these traits can be improved by inhibiting cytokines during MIA induction [15] human clinical evidence confirms this association [16] revealed that maternal immune conditions during pregnancy significantly increase the odds of ASD diagnosis in male offspring. According to the “maternal immune activation hypothesis,” neurodevelopmental disorders (NDDs) may be caused by disruptions in immunological interactions during crucial periods of fetal development [17].

Cytokine-Induced Opsonization

Astrocytes and microglia exposed to sustained pro-inflammatory environments increase their synthesis of C1q and C3. This leads to the accidental tagging of active, high-plasticity synapses.

When microglial pruning shifts from a precise scalpel to a blunt instrument, the functional architecture of the brain degrades rapidly:

Nuropsychiatric & Developmental Disorders: Genetic differences (such polymorphisms in the C4 complement gene) lead to increased complement accumulation during adolescent developmental periods in disorders like schizophrenia. This causes the prefrontal cortex to shrink and basic executive processes to change as a result of an excessive wave of microglial pruning.

The Gut-Brain-Microbiota Axis (GBMA), is a highly dynamic, two-directional communication channel that connects the central nervous system (CNS) to the gastrointestinal tract's enteric nerve system (ENS). Although its function is to regulate metabolic states; anxiety, and depression is well-documented, breakthroughs have revealed that the gut microbiome plays a main role in shaping social behavior and prosocial tendencies (such as empathy, helping behaviors, and social bonding), As illustrated in Figure 1.

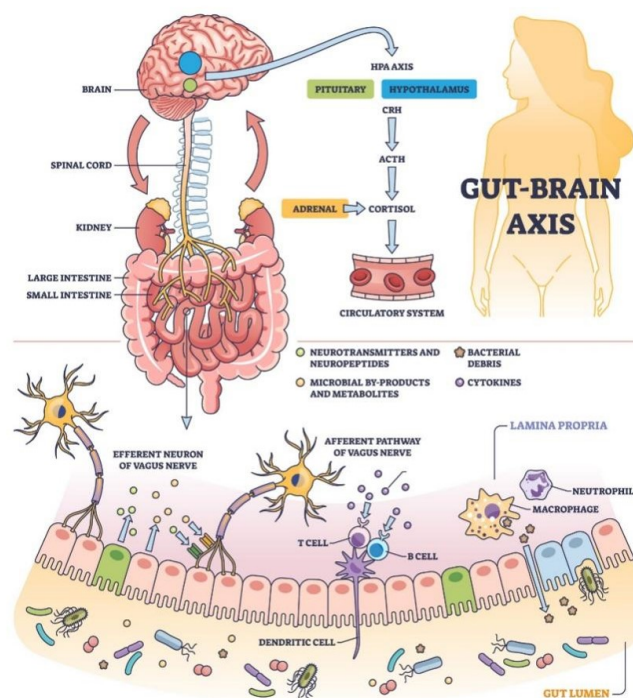


Figure 1: The Gut-Brain Axis: Bidirectional Communication Pathways and Signaling Mechanisms

Mechanisms of Action: How Gut Microbes Talk to the Social Brain

Recent studies have mapped out the precise physiological channels through which microbial shifts directly modify neural circuits dedicated to social interaction [18].

The Vagus Nerve & Oxytocin Signaling

The vagus nerve serves as a direct neural “superhighway.”

- Specific psychobiotics—such as *Lactobacillus reuteri*—stimulate vagal afferent fibers in the gut.
- This signal travels directly to the hypothalamic paraventricular nucleus (PVN), where it causes oxytocin to be secreted and enhanced. The final “social hormone” that is essential for social identification, empathy, and connecting with others [19].

Neurotransmitter and Precursor Synthesis

As tiny chemical factories, gut microorganisms produce neuroactive substances that either penetrate or alter the blood-brain barrier (BBB) [20].

- **Serotonin (5-HT):** Over 90% of the body’s serotonin is synthesized in the gut, heavily mediated by spore-forming microbes. Fluctuations in gut-derived serotonin affect the development of the brain’s reward circuits, altering how reinforcing social interactions feel.
- **Tryptophan Metabolites:** Bacteria metabolize tryptophan into indoles and kynurenine, balancing the availability of precursors required for healthy central neurotransmission.

3. Targeted Metabolite Adsorbents (AB-2004)

Translational human trials have begun targeting the gut-brain axis to treat neurodevelopmental social deficits, particularly in Autism Spectrum Disorder (ASD).

- The medicinal substance AB-2004, a gastrointestinal-restricted adsorbent that is taken orally, was designed to function as a molecular sponge and accurately absorb dangerous bacteria metabolites in the gut, such as 4EPS.
- Clinical investigations shown that lowering systemic 4EPS levels directly reduced participants’ anxiety-like behaviors and core social deficits while also dramatically improving gastrointestinal symptoms [21].

4. Therapeutic Interventions: “Psychobiotics” for Sociability

Understanding that the gut microbiome is highly modifiable introduces targeted, non-invasive therapeutic approaches to enhance social behaviors and manage neurodevelopmental conditions as shown in Table 1 below [22].

Table 1: Microbiota-Gut-Brain Axis Interventions, Mechanisms of Action, and Targeted Behavioral Outcomes

Intervention Type	Mechanism	Target Behavior / Condition
Targeted Probiotics (<i>L. reuteri</i>)	Vagal stimulation leading to hypothalamic oxytocin release.	Enhancing social bonding; mitigating social deficits in ASD.
High-Fiber & Fermented Diets	Boosts SCFA production, optimizing BBB integrity and emotional regulation.	Reducing social anxiety and chronic stress-induced isolation.
Metabolite Adsorbents (AB-2004)	Neutralizes neurotoxic microbial bioproducts (4EPS) within the GI tract.	Managing social avoidance and behavioral irritability.

4.1. Environmental Epigenetics and Neuroendocrine Reprogramming

The Permanent Effects of Toxicant Exposure in Childhood

The human endocrine and central nervous systems are remarkably flexible throughout crucial developmental windows, especially the prenatal and early neonatal stages [23], as cited in [24]. The morphological, biochemical, and molecular pathways of essential organ systems can be irreversibly changed by inadequate exposures during these susceptible stages [25]. This phenomenon forms the bedrock of the **Developmental Origins of Health and Disease (DOHaD)** paradigm [25].

Key Contaminants and Routes of Exposure

EDCs and persistent organic pollutants (POPs) are nearly common in all worldwide ecosystems as a result of modern industrialization [26]. Neonates continue to absorb these chemicals through breastfeeding, dust inhalation, and consumer goods after they easily pass through the placental barrier and build up in fetal tissue [24].

- **Plasticizers and Additives:** Food containers and consumer goods frequently include phthalates, bisphenol A (BPA), and new bisphenol analogs (such as BPS). BPA crosses both the placental barrier and the embryonic blood-brain barrier during critical windows of neurodevelopment, directly impairing fetal neurogenesis, neuronal migration, and synaptogenesis [24, 27].
- **Legacy Industrial Contaminants (POPs):** Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) bioaccumulate efficiently in the food chain despite decades-old bans [24].
- **Heavy Metals:** Lead (Pb), cadmium (Cd), and methylmercury (MeHg) are chronic risks to public health that bioaccumulate through polluted food and water resources [28].

Receptor Interference and Hormone Mimicry

EDCs manipulate cell signaling by structurally mimicking or blocking natural hormones [26]. For example BPA acts as a classic estrogen-mimicking compound [24]. In the developing cerebral cortex, alkyl phenols simulate estrogen and bind to estrogen receptors (ERs), causing aberrant microglial activation and compromised myelination patterns. Heavy metals including mercury, lead, and cadmium build up inside the thyroid gland, causing long-term thyrotoxicity and inhibiting the generation of thyroid hormone [29]. This signaling blockage causes structural neurodevelopmental problems because thyroid hormones are required for embryonic cortical migration and neurogenesis [26, 28] as shown in Table 2.

Table 2: Environmental Pollutants, hormonological Targets and Their Neurobiological Outcomes

Toxicant Class	Principal Biological Targets	Observed Pathological & Phenotypic Outcomes
Bisphenols & Phthalates	Estrogen receptors, Dopaminergic reward circuitry, HPA Axis.	Heightened impulsivity, attentional deficits, anxiety, and elevated vulnerability to addiction [24].
Heavy Metals (Pb, MeHg, Cd)	Thyroid gland, Synaptic organization proteins, Brain-derived neurotrophic factor (BDNF).	Non-monotonic dose responses leading to intergenerational impairments in learning, memory formation, and executive cognition [28].
Alkylphenols & POPs	Microglia, Oligodendrocytes, Thyroid & Gonadal hormone pathways.	Microglial overactivation, neurogenesis defects, myelination failure, and severe reproductive disorders [30].

5. Modern methods of treating autism and their effectiveness

5.1. Neuromodulation Therapies (rTMS & tDCS)

rTMS and tDCS are non-invasive techniques that target the dorsolateral prefrontal cortex (DLPFC). The technique is designed to alter neural plasticity, reduce repetitive and stereotyped behaviors and improve social communication [31], particularly repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS), have emerged as promising therapeutic avenues in ASD management. Using noninvasive/high C/micrometric electrode modality, these focused excitatory/inhibitory strategies allow the modulation of neuroplasticity by restoring the excitation-inhibition balance mainly targeting the dorsolateral prefrontal cortex (DLPFC) among others cortical areas. Recent clinical assessments suggest that protocol-based neuromodulation can robustly diminish RRBs while enhancing executive skills and social communication skills [32].

5.2. Microbiota-Gut-Brain (MGB) Axis Customized Interventions

It will seek to change the gut microbiome — which in turn may have effects on brain immunity processes, including neurological and inflammatory pathways. This will encompass gut microbiota transplantation (FMT), specific probiotics/prebiotics and modified diets aimed at decreasing neuroinflammation in the setting of autism symptoms [33]. Abstract The role of the Microbiota-Gut-Brain (MGB) axis in providing a two-way connection between the central nervous system and gastrointestinal tract has led to paradigms shifts in pathophysiology of ASD. Various targeted approaches that reprogram gut microbiota composition— such as Fecal Microbiota Transplantation (FMT), specific probiotic/prebiotic protocols, and dietary interventions— have emerged as effective therapies in reducing systemic and neuro-inflammation, Interventions that modify short-chain fatty acid (SCFA) production and restore gut barrier integrity simultaneously ameliorate gastrointestinal comorbidities and core behavioral symptoms.

5.3. Naturalistic Developmental Behavioral Intervention (NDBI)

The Newest Generation of Applied Behavior Analysis (ABA) incorporates developmental psychology and behavioral foundations into the child's natural environment. You build on joint attention, speech and spontaneous conversation through methods like the Denver ESDM and Jasper Model [34].

Naturalistic Developmental Behavioral Interventions (NDBIs) build on early principles of Applied Behavior Analysis (ABA), with recent advances in the developmental sciences, to provide child-led, naturalistic treatment approaches. Leading treatments e.g., the Early Start Denver Model (ESDM) and Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER), are based on shared engagement neurodiversity-affirming principles. These aspects are all reflected in clinical trial data demonstrating that NDBIs promote naturalistic language and social reciprocity and adaptive capabilities by increasing the rate of naturally occurring learning opportunities through enhanced interactive coordination during critical sensitive periods of neurodevelopment [35].

5.4. Pharmacotherapy Targeting New Biomarkers

Recent pharmacological investigations in ASD are emphasizing precision over symptom management, using increasingly biomarker-guided approaches. New approaches either target the underlying neurochemical dysregulations (like increasing motivation/social salience with oxytocinergic agents or restoring neural homeostasis with GABAergic modulators, i.e., Bumetanide). These molecularly targeted therapies attempt to target etiology-specific pathways, providing specific biological therapy for a unique patient sub-phenotype [36].

5.5. Digital Therapeutics (DTx), Virtual Reality, and AI

Digital Therapeutics (DTx) and immersive technologies are promising scalable, personalized interventions for cognitive/sensory adaptation in ASD. Data indicates that, Virtual Reality Social-Skill Training (VR-SST) is a low-anxiety setting where the user can practice recognising emotion, dynamic conversation and sensory regulation. In addition, artificial intelligence real-time adaptive feedback and physiological monitoring algorithms that tailor the complexity of tasks to match individual sensory profiles and learning trajectories [37].

6. Synthesis and Future Directions

Recent years have witnessed a structural paradigm shift in Autism Spectrum Disorder (ASD) therapeutic research, from isolated, symptom-reactive interventions to integrated, multimodal care models. The alignment between biological strategies, including non-invasive neuro-modulation, gut brain axis modulation, and biomarker-driven pharmacotherapy, with developmentally grounded behavior models (NDBIs) and digital therapeutics (DTx) represents a paradigm shift towards integrated translational psychiatry. Rather than acting in silos of core features, modern frameworks engage neuroplasticity during windows of critical development and simultaneously address neurobiological and systemic physiological dysregulations that underlie these fear circuits.

The next step for ASD therapy is focused on clinical personalization and biomarker validation. Conclusion Future studies should aim to differentiated heterogeneous patient populations into defined biological sub-phenotypes by utilizing a combination of multi-omics disease profiling, functional neuroimaging and electromagnetic signals. Prospective clinical trials are also needed to test the efficacy of these biological agents in combination with adaptive digital skills platforms. Ultimately, in order to translate these precision therapeutic approaches into clinical practice, the need for standardised neurodiversity-affirming outcome metrics will remain a significant challenge.

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