Autism Between Synapses and Society: A Cross-Level Review

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Abstract

Autism is investigated across multiple levels, including genetics, synaptic function, neural circuits, behavior, and social theory. Yet these perspectives often operate independently, leading to different and sometimes competing interpretations of what autism represents. This literature review examines how autism is defined and modeled across biological and social frameworks, with a focus on sensory development and heterogeneity. Molecular and animal research highlights altered synaptic plasticity, inhibitory signaling, and sensory processing, while genetic studies demonstrate that autism reflects multiple developmental pathways rather than a single biological mechanism. At the same time, social and theoretical scholarship argues that diagnostic categories are historically shaped and dynamically interpreted. Population-level surveillance data further show that patterns of autism identification change over time, suggesting that prevalence reflects evolving awareness and clinical practice in addition to biology. Taken together, these perspectives indicate that autism cannot be reduced to a singular essence. Instead, it emerges differently depending on the level of analysis and the interpretive frameworks applied. This review argues for a cross-level, humility-based approach that situates biological findings within broader social and developmental contexts. Rather than resolving autism into one definitive explanation, this review highlights the importance of examining how definitions are constructed across scientific and social domains.

Introduction

A central question in autism research is: What is autism? When reviewing the current literature on autism, one may notice a division when comparing social, biological, and clinical literature. This raises a related question that matters just as much: what does autism mean to autistic people, and how does that compare to scientific and clinical literature?

In biological and clinical literature, Autism is typically defined as a heterogeneous neurodevelopmental condition characterized by differences in social communication and restricted or repetitive patterns of behavior (Gadad et al., 2013; Uchino & Waga, 2013). At the same time, research also emphasizes that autism shows remarkable genetic and phenotypic heterogeneity with multiple developmental pathways rather than a single underlying mechanism (Litman et al., 2025). Social and theoretical literature further argues that autism is more than just a biological condition. This scholarship suggests that autism is a category shaped by historical, cultural, and diagnostic factors (Verhoeff, 2012).

Autism is studied across many levels (genes, cells, circuits, behavior, and experience), but these perspectives rarely communicate with each other. In practice, researchers often rely on biological and animal models to represent autism, and then use findings from these models to make broader conclusions about autistic individuals. The problem is not that these models are inaccurate, but that it is not always clear what exactly they are measuring. Are they measuring autism, or are they measuring more general processes like sensory sensitivity, stress, and adaptation? Since autism is still not fully understood, the conclusions drawn from models should be interpreted carefully and with humility.

Population-level data further illustrate how definitions and identification practices shape our understanding of autism. According to the CDC Autism and Developmental Disabilities Monitoring (ADDM) Network, autism prevalence among 8-year-old children in the United States increased from approximately 1 in 150 in 2000 to 1 in 36 in 2020 (CDC ADDM Network, 2022). Over this same period, demographic patterns shifted. Earlier reports showed higher identification rates among White children and children from higher socioeconomic backgrounds, whereas more recent data show increased identification among historically underrepresented groups, including Black and Hispanic children. In 2022, autism prevalence among 8-year-old children was 36.6 per 1,000 among Black children, 33.0 among Hispanic children, and 27.7 among White children (CDC 2025).

The proportion of autistic children with co-occurring intellectual disability has also changed over time. These shifts suggest that autism prevalence reflects not only biology, but also evolving diagnostic practices, awareness, access to services, and clinical interpretation. If the identification markers for autism have changed over time, then the meaning of the category itself cannot be assumed to be static.

Recent work shows both the promise and the complexity of cross-level autism research. Russo and colleagues propose a sensory-first cascading model, arguing that early sensory differences can shape later developmental and social outcomes (Russo et al., 2025). At the same time, Litman and colleagues demonstrate that autism includes multiple phenotypic groupings that map onto different underlying genetic programs, suggesting that there may not be one single biological pathway that explains autism (Litman et al., 2025). These frameworks support the idea that autism cannot be reduced to a single concept or mechanism.

This literature review examines how autism is represented across scientific, clinical, and lived-experience perspectives, with a focus on sensory and developmental models. By synthesizing what is measured in biological research with how autism is described in social theory and experiential frameworks, this review argues for a more careful approach to interpretation, particularly when translating animal models into claims about autistic lives. Qualitative research offers contextual insight into perception, regulation, and social interaction that may not be fully captured in laboratory measures. Including these perspectives does not replace biological research, but it helps situate findings within the broader meanings attached to autism.

Sensory and Developmental Frameworks of Autism

The social perspective in this review centers on theoretical and historical frameworks and social theory that emphasize meaning, context, environment, and function rather than deficit. Scholars in social science and medical humanities have questioned whether autism can or should be treated as a singular biological entity or fixed clinical object (Verhoeff, 2012; Pettit, 2026). Instead, they argue that autism is shaped by historical, cultural, and diagnostic practices (Pettit, 2026). The way autism is defined influences which behaviors are noticed, measured, and labeled as autistic.

Experiential and interpretive literature has emphasized that autism is not only a collection of observable behaviors but also a lived way of perceiving and regulating within particular environments. When social meaning is excluded from scientific models, there is a risk of misinterpreting behaviors that may serve adaptive or regulatory purposes (Verhoeff, 2012). The meaning of autism depends on who is defining behavior and at what level it is being analyzed. Many behaviors categorized as "symptoms" may function as strategies for regulation within specific contexts rather than simple deficits.

Verhoeff critiques the long-standing assumption that autism is a "natural kind" with a single underlying

essence (Verhoeff, 2012). He argues that the significant phenotypic heterogeneity of autism challenges the idea that there is one unifying biological core. Autism presents across a wide range of cognitive profiles, levels of support needs, and behavioral expressions. Diagnostic categories have shifted historically and culturally, which further complicates attempts to locate autism exclusively within a biological framework (Verhoeff, 2012). Efforts to identify a single core deficit overlook the variability found across biomarkers, symptoms, and cognitive traits.

Hacking's concept of "interactive kinds," discussed by Pettit under the framework of historical ontology, further develops this critique (Pettit, 2026). Human science categories are not fixed natural kinds; they are shaped by historical and social processes. Diagnostic labels influence how individuals understand themselves, and individuals, in turn, influence how categories evolve. Autism can be understood through this interactive model, where scientific research, clinical definitions, and lived experiences co-construct the category over time (Pettit, 2026). This perspective challenges strict biological essentialism without rejecting biological research altogether.

Crespi and Badcock propose a different kind of model. They conceptualize autism and psychosis as diametrical disorders of the social brain (Crespi and Badcock, 2008). In their framework, autism involves reduced social-cognitive inference, while psychosis involves exaggerated or hyper-mentalistic tendencies. They draw partly on genomic imprinting theory and discuss biological growth patterns associated with each condition (Crespi and Badcock, 2008). While their model remains biological, it complicates deficit-based interpretations by positioning autism within a broader spectrum of social brain variation rather than framing it as a simple impairment.

Russo and colleagues introduce a cascading sensory model of autism that shifts attention to early sensory processing (Russo et al., 2025). They argue that early sensory differences may influence the later development of social communication abilities. In this framework, early variations in sensory processing influence developmental trajectories, leading to differences in social interaction and behavior (Russo et al., 2025). This model is significant because sensory features were historically underemphasized in autism research, despite being included in DSM-5 criteria, which define autism in terms of differences in social communication and restricted or repetitive patterns of behavior, including atypical sensory responses such as hypersensitivity or reduced sensitivity to environmental stimuli. The inclusion of sensory features reflects growing recognition that sensory processing differences are a core component of the autistic phenotype rather than a secondary feature (Russo et al., 2025). Russo's work suggests that understanding early sensory differences may clarify how later social characteristics emerge.

Litman and colleagues provide further evidence for heterogeneity at the genetic level (Litman et al., 2025). Using mixture modeling, they identify distinct phenotypic classes of autism that correspond to different genetic programs. Their findings suggest that autism does not arise from a single pathway but reflects multiple developmental trajectories with different molecular timing and genetic variation (Litman et al., 2025). This supports a pluralistic view of autism and challenges single-mechanism explanations.

Taken together, these frameworks reveal tension between essentialist models and plural, developmental, and interactive accounts. Autism emerges not only as a neurodevelopmental condition but as a category shaped by biological processes, historical definitions, and lived interpretation. The diversity found in both social theory and genetic evidence makes it difficult to sustain the idea of autism as a singular, unified entity.

Biological Models

Biological scientists have also attempted to answer the question of what autism is by studying it at the molecular, cellular, circuit, and behavioral levels. Many of these

models rely on animal systems, especially rodent models, to investigate neural mechanisms that may underlie sensory reactivity and regulation. However, this raises an important question: are these models measuring "autism," or are they measuring more general processes such as stress, adaptation, or altered development? The interpretation depends on the assumptions made about what autism represents biologically.

One major line of research focuses on Fragile X syndrome (FXS) models. FMR1 knockout mice are frequently used because Fragile X syndrome is one of the most common single-gene conditions associated with autism. These mice lack functional FMRP, which is an RNA binding protein that regulates the translation of synaptic proteins, due to silencing or mutation of the FMR1 gene. Importantly, they model a specific genetic pathway, not autism as a whole.

Because FMRP functions as a regulator of mRNA translation at synapses, its loss is expected to alter synaptic plasticity. Accordingly, Huber et al. (2002) examined synaptic plasticity in FMR1 knockout mice. FMRP had previously been shown to bind subsets of mRNAs and regulate translation. This study investigated how the absence of FMRP affects neuronal function in mammals. They found that mGluR-dependent long-term depression (LTD), which is protein synthesis dependent, was selectively enhanced in FMR1 knockout mice. In contrast, NMDA receptor–dependent LTD remained normal. Rather than showing a simple deficit, the study demonstrated exaggerated mGluR-dependent plasticity. The authors proposed that FMRP plays a critical role in regulating activity-dependent synaptic plasticity and suggested that mGluR antagonists could have therapeutic relevance. This work supports a synaptic dysregulation or plasticity imbalance model rather than a straightforward loss-of-function model.

Patel et al. (2014) further explored synaptic development in FMR1 knockout mice, focusing on cortical connectivity and pruning. Prior hypotheses suggested that hyperconnectivity in FXS and related autistic conditions may result from excessive synapse formation or impaired pruning. Patel and colleagues used simultaneous electrophysiological recordings between neighboring layer 5A pyramidal neurons during postnatal development. Wild-type mice showed normal developmental pruning between postnatal days 15 and 30, reflected in reduced connectivity. FMR1 knockout mice did not show this decrease, indicating persistent connectivity. Connection strength and kinetics were largely unchanged; the primary difference was the presence of connections. The study also observed increased silent NMDA synapses, suggesting delayed pruning rather than overproduction. This shifts the interpretation away from "too many" synapses toward altered developmental regulation of connectivity.

Together, Huber and Patel illustrate that FMRP loss does not produce simple deficits but instead alters synaptic regulation and developmental timing. These findings complicate deficit-based interpretations and instead suggest imbalanced or mistimed plasticity.

A related but distinct mechanism involves inhibitory circuit dysfunction. Kourdougli et al. (2023) investigated parvalbumin (PV) interneurons in FMR1 knockout mice. PV interneurons are key inhibitory cells that regulate cortical excitation and sensory balance. Prior studies suggested reduced PV activity in adult FMR1 knockout mice. Kourdougli examined when this hypoactivity emerges and whether increasing PV activity at different developmental stages could restore circuit and behavioral function. They found that PV interneurons were hypoactive early in development and that this was associated with reduced PV cell density and sensory hyperreactivity. Early activation restored some gene expression patterns but did not fully restore circuit function, whereas activation after the critical period improved behavioral outcomes. This study highlights the importance of developmental timing and suggests that inhibitory dysfunction contributes to

sensory hypersensitivity.

O'Shea et al. (2025) extend circuit-level findings to thalamocortical regulation. Studying lateral geniculate nucleus (LGN) neurons in FMR1 knockout mice, they observed reduced burst firing and a shift toward tonic firing modes. They also found reduced calcium currents at hyperpolarized potentials. Because the thalamus plays a central role in sensory gating and filtering, these findings suggest impaired sensory gating mechanisms. Together with PV interneuron findings, this supports models emphasizing excitation–inhibition imbalance and altered sensory processing rather than isolated social deficits.

Behavioral models attempt to translate these cellular and circuit findings into measurable outcomes. Zeidler et al. (2018) examined the effects of baclofen, a $GABA_B$ agonist, on social behavior in FMR1 knockout mice. Previous work suggested that baclofen could correct certain FXS phenotypes. However, in this study, baclofen treatment worsened performance on behavioral tests such as the automated tube test, used to assess social dominance, and the three-chamber sociability assay, which is commonly used to measure social interaction deficits relevant to autism-like behavior in rodent models. This demonstrates the complexity of translating inhibitory circuit theories into behavioral interventions and suggests that excitation/inhibition balance cannot be reduced to a simple pharmacological correction.

Uchino and Waga (2013) reviewed SHANK3 as an autism-associated gene. SHANK3 encodes a scaffolding protein located at excitatory synapses and is critical for synapse formation and maintenance. Mutations in SHANK3, including those seen in 22q13.3 deletion syndrome, have been associated with autism diagnoses. SHANK3 mutant mice exhibit impaired social interaction and repetitive behaviors. This work reinforces a synaptic model of autism, linking molecular synaptic architecture to behavioral outcomes.

Environmental models further complicate the biological picture. Gadad et al. (2013) investigated prenatal exposure to valproic acid (VPA) as a model of autism. Pregnant rodents exposed to VPA produced offspring that showed reduced social interaction, increased repetitive behaviors, elevated anxiety-like responses, and altered sensory processing relative to controls. The review highlights potential cerebellar involvement and demonstrates how environmental exposure can produce autism-like behavioral phenotypes.

Mihalj et al. (2025) also used a prenatal VPA model in rats. They found delayed motor reflexes, reduced ultrasonic vocalizations, altered cortical neuronal branching, and increased expression of GABAergic markers such as Gad65, Vgat, and Gabrb1. Specifically, they observed reduced cortical branching overall and increased arborization in GABAergic neurons. These findings suggest early developmental disruption and altered inhibitory signaling. However, the assumption that all prenatally exposed animals uniformly model autism raises interpretive questions, particularly given known heterogeneity in genetic and developmental pathways.

Across molecular, circuit, and behavioral levels, biological models do not converge on a single mechanism. Instead, they reveal altered synaptic plasticity, disrupted pruning, inhibitory circuit dysfunction, sensory gating abnormalities, and environmental vulnerability. These findings support mechanistic insights but also highlight heterogeneity. Biological research, much like social theory, does not point to a singular unified essence of autism but instead reveals multiple interacting developmental pathways.

Discussion

Across these models, different scientific sources are telling different stories about autism. Molecular studies tell a story of altered synaptic plasticity and developmental timing. Circuit-level research tells a story of excitation–inhibition imbalance and sensory gating differences. Genetic studies tell a story of heterogeneity and multiple

developmental pathways. Social theory tells a story about categories that are historically constructed and dynamically shaped. It is important to note that these are not contradictory stories, but they are not identical either.

Autism appears differently depending on the level at which it is observed. At the synapse, it may appear as altered mGluR-dependent plasticity. At the circuit level, it may appear as PV interneuron hypoactivity or thalamic gating changes. At the behavioral level, it may appear as repetition or social withdrawal. At the lived level, it may appear as sensory overwhelm, focus, regulation, or adaptation.

This shift in meaning reflects what Fitzgerald (2017) describes in their ethnographic analysis of contemporary neuroscience. In Tracing Autism: Uncertainty, Ambiguity, and the Affective Labor of Neuroscience, Fitzgerald examines how neuroscientists work within uncertainty as they interpret brain signals, models, and measurements. Rather than uncovering fixed truths, researchers must make careful judgments about what counts as meaningful data, while recognizing that these representations are partial and provisional (Fitzgerald, 2017). Similarly, autistic individuals navigate ambiguity in how their behaviors are interpreted and classified. In both cases, meaning is not simply discovered but constructed through interpretation.

Autism, then, is not reducible to any one level. It is relational. It exists between neurons, environments, and interpretations. Biological mechanisms are real, but their meaning is shaped by the frameworks used to interpret them.

The central question becomes not "what is autism?" but "how is autism being defined in this context, and what assumptions are guiding that definition?"

Recognizing this does not invalidate biological research. Instead, it suggests the need for humility. No single model, whether genetic, synaptic, behavioral, or social, captures the full phenomenon.

Implications

If different scientific approaches are telling different stories, then future research must be more intentional about how those stories are constructed.

For scientists, this may mean designing animal models and behavioral assays that account not only for pathology but also for function. Repetitive behaviors, for example, may represent regulatory processes rather than mere dysfunction. Experimental designs could ask what a behavior accomplishes for the organism rather than only whether it deviates from a norm.

For clinicians, this suggests framing support around sensory environments and adaptive strategies rather than focusing exclusively on correcting behaviors. Understanding regulation as a goal may change intervention approaches.

For research collaborations, bridging qualitative and quantitative methods may help align biological findings with lived meaning. Genetic heterogeneity and developmental timing studies already demonstrate pluralism at the molecular level. Incorporating lived accounts may prevent reductionist interpretations of those findings.

Conclusion

The goal of this review is not to define autism once and for all, but to illuminate how definitions are made.

Across molecular, circuit, genetic, and social frameworks, autism does not appear as a singular unified entity. It emerges as a pattern of differences shaped by biology, development, environment, and interpretation.

By examining how neurons, researchers, and autistic individuals each construct meaning around autism, we move toward a science that acknowledges both mechanism and experience.

A humility-based approach does not weaken autism research. It strengthens it by recognizing that complexity is not a flaw in the data but a feature of the phenomenon itself.

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