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Sección
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BDNF Dysregulation and Prenatal Neuroinflammation as an Aetiopathogenic Basis of the Connectopathy of Autism: An Integrative Hypothesis

Desregulación del BDNF y neuroinflamación prenatal como base etiopatogénica de la conectopatía del autismo: una hipótesis integradora

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Abstract

This article presents an integrative aetiopathogenic hypothesis of autism spectrum disorder (ASD), proposing that the dysregulation of brain-derived neurotrophic factor (BDNF) - driven by prenatal neuroinflammation on a background of genetic susceptibility - underlies the connectopathy characterizing autism. Rather than asserting a proven theory, we synthesize evidence from the last three decades into a critical narrative review. The hypothesis posits that maternal immune activation (MIA) induces inflammatory cascades, zinc dyshomeostasis, and altered BDNF signaling, which collectively disrupt synaptic connectivity patterns. We explicitly distinguish between established evidence, observational associations, and speculative inferences. The manuscript includes a reproducible search strategy, a PRISMA flow diagram, a critical appraisal of included studies, and a dedicated limitations section. Our goal is to provide a coherent framework for future mechanistic and prospective studies, while acknowledging the heterogeneity of autism and the need for cautious interpretation.

Keywords: autism; neuroinflammation; connectopathy; BDNF; zinc; prenatal immune activation; integrative hypothesis.

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Resumen

Este artículo presenta una hipótesis etiopatogénica integradora del trastorno del espectro autista (TEA), proponiendo que la desregulación del factor neurotrófico derivado del cerebro (BDNF) —impulsada por la neuroinflamación prenatal sobre un trasfondo de susceptibilidad genética— subyace a la conectopatía que caracteriza al autismo. En lugar de afirmar una teoría probada, sintetizamos la evidencia de las últimas tres décadas en una revisión narrativa crítica. La hipótesis postula que la activación inmune materna (MIA) induce cascadas inflamatorias, deshomeostasis del zinc y una señalización alterada del BDNF, las cuales en conjunto alteran los patrones de conectividad sináptica. Distinguimos explícitamente entre evidencia establecida, asociaciones observacionales e inferencias especulativas. El manuscrito incluye una estrategia de búsqueda reproducible, un diagrama de flujo PRISMA, una evaluación crítica de los estudios incluidos y una sección dedicada a las limitaciones. Nuestro objetivo es proporcionar un marco coherente para futuros estudios mecanicistas y prospectivos, reconociendo al mismo tiempo la heterogeneidad del autismo y la necesidad de una interpretación cautelosa.

Palabras clave: autismo; neuroinflamación; conectopatía; BDNF; zinc; activación inmune prenatal; hipótesis integradora.

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is defined by persistent deficits in social communication and interaction, alongside restricted, repetitive patterns of behavior, interests, or activities. These symptoms emerge in early childhood and limit daily functioning, according to the DSM-5-TR [1]. Following the recommendations of Kenny et al. [2], this text uses the terms "autism" and "autistic people" rather than the acronym ASD, except where diagnostic precision is required.

The contemporary scientific consensus interprets genetics not as a sole cause but as a predisposing factor interacting with a range of environmental influences [3]. Active research investigates potential prenatal triggers, including maternal infections, perinatal complications, and exposure to toxic agents [4]. While the reported increase in autism prevalence is debated, a portion is plausibly linked to large-scale ecological changes over the past century [5].

Early hopes for a single "autism gene" were supplanted by evidence of extreme genetic complexity. Concurrently, significant statistical associations have emerged between autism and dysregulated levels of trace metals, particularly zinc [6–9]. Zinc is a critical cofactor for hundreds of enzymes, indispensable for neuronal signaling, protein synthesis, and immune regulation. The brain requires sustainable zinc homeostasis for neurogenesis, cortical plasticity, and learning.

The hypothesis posits that dysregulation of BDNF - a protein essential for neuronal growth, survival, and synaptic plasticity - underpins the widespread connectopathy observed in autism. BDNF operates at the intersection of genetic predisposition and inflammatory processes. On a susceptible genetic background, an inflammatory process engages the immune system, zinc-dependent pathways, and the gut–brain axis.

Inflammation is a natural defense mechanism, but when it becomes chronic or dysregulated in utero, it can lead to tissue dysfunction. Maternal immune activation (MIA) is a recognized risk factor for neurodevelopmental disorders, even without direct fetal infection [10]. Despite hundreds of associated genetic and non-genetic factors, autism is identified by core behavioral features, suggesting diverse causes converge on common neural mechanisms. A compelling hypothesis is that a "trace metal imbalance" - characterized by zinc deficiency and/or toxic metal overload - could be a common pathway affecting oxidative stress, inflammation, and synapse function [4].

Given that genetics is estimated to explain only 15–30% of autism risk, identifying environmental contributors is paramount. This article does not claim to have found a single cause; rather, it proposes an integrative hypothesis that requires further testing. The objective is to synthesize available evidence into a coherent framework that distinguishes established findings from speculative inferences.

2. METHODOLOGY: A CRITICAL NARRATIVE REVIEW WITH EXPLICIT CRITERIA

2.1 Type of review and rationale

This manuscript is structured as a critical narrative review with an integrative hypothesis. Unlike a systematic review, our aim is not to provide quantitative effect sizes but to synthesize diverse lines of evidence (molecular, immunological, neuroimaging) into a plausible biological cascade. However, to enhance transparency and reproducibility, we have adopted key elements of the PRISMA guideline [11] for study selection, without performing a meta-analysis.

2.2 Eligibility criteria

Articles were included if they were peer-reviewed original research or systematic reviews published in English between 1995 and 2025, addressing at least one of the following topics: BDNF in autism, neuroinflammation or MIA in animal models or human cohorts, zinc homeostasis in ASD, or connectopathy. Studies had to include clinically diagnosed ASD populations or validated animal models. We excluded single-case reports, editorials, non-peer-reviewed preprints, and studies not directly related to autism aetiopathogenesis.

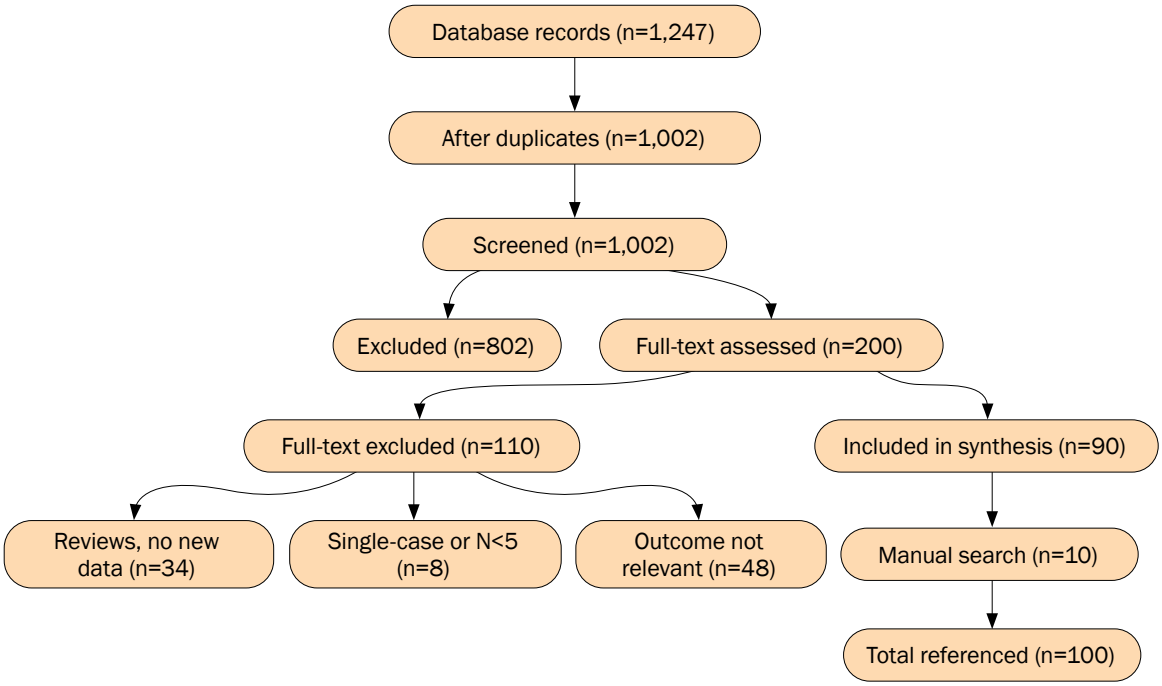
2.3 Information sources and search strategy

A systematic literature search was conducted in PubMed, PsycInfo, and Medline between June and December 2024. The search strings used were adapted to each database syntax and included combinations of terms such as “autism” or “autism spectrum disorder” with “BDNF” or “brain-derived neurotrophic factor”; “autism” with “neuroinflammation” or “maternal immune activation” or “prenatal inflammation”; “autism” with “zinc” or “trace metal” or “Zn2+” and “synapse” or “connectivity”; and “connectopathy” or “connectome” with “autism”. Manual searches of reference lists of included articles and relevant reviews were also performed.

2.4 Selection procedure

The selection process is summarized in the PRISMA flow diagram below. Titles and abstracts were screened against the eligibility criteria. In cases of duplicate publications, revisions, or updates, the most recent version was considered. For systematic reviews and meta-analyses, the most up-to-date version was prioritized (see Figure 1).

Figure 1. PRISMA Flow Diagram



Source: Own elaboration

2.5 Data extraction and critical appraisal

From each included study, we extracted the first author, year of publication, study design (human or animal, cross-sectional or longitudinal), sample size, main findings regarding BDNF, zinc, or inflammation, and any limitations noted by the authors. Quality assessment was performed using specific criteria: for human studies, we required clear diagnostic criteria, adequate sample size (at least 20 participants per group), and appropriate control for confounders such as age, sex, and medication status. For animal studies, we assessed whether the model was validated (for example, MIA or VPA models), whether behavioral correlates were present, whether sample size was adequate (at least 8 animals per group), and whether outcome assessment was blinded. For systematic reviews and meta-analyses, we applied the AMSTAR-2 criteria [12]. Studies that did not meet these criteria were noted as low-quality but were not automatically excluded; instead, their findings are presented with appropriate caveats.

2.6 Synthesis approach

We used a thematic synthesis organized around the proposed biological cascade: first, prenatal inflammation; second, zinc dyshomeostasis; third, BDNF dysregulation; fourth,

synaptic connectopathy; and finally, the behavioral phenotype. Where evidence was inconsistent or absent, we explicitly state this. Causal language such as “leads to” or “causes” is reserved for established experimental mechanisms; elsewhere we use phrases such as “is associated with,” “may contribute to,” or “is hypothesized to.”

3. AUTISM AS A CONNECTOPATHY: EVIDENCE AND LIMITATIONS

The term “connectome” was coined in 2005 by Sporns, Tononi, and Kötter [13] to refer to a comprehensive map of neural connections in the brain. The hypothesis that autism involves disrupted connectivity - whether local overconnectivity or long-range underconnectivity - has been highly influential in the field [14–16]. However, it is important to recognize that the evidence supporting this hypothesis remains largely indirect and inferential.

When Leo Kanner originally defined the autistic syndrome in his landmark 1943 article, he noted in passing that five out of the eleven children in his case series had unusually large heads [17]. This observation has since been confirmed and refined by numerous studies. Meta-analyses have shown that, on average, autistic children have increased brain volume in early childhood, particularly in the frontal lobe, followed by a normalization of brain size in adolescence [18]. However, as we must caution, brain size alone is a very poor predictor of autism at the individual level. Not all children with large heads are autistic, and the heterogeneity among autistic individuals is substantial. To claim otherwise would be to fall into a common statistical fallacy concerning rare categories.

The search for a genetic basis has been pursued through twin studies. If autism were completely determined by genetic factors, monozygotic twins - who share virtually 100% of their genes - would show perfect concordance, meaning that both twins would either be autistic or both would be neurotypical. In reality, the concordance rate for monozygotic twins ranges from 60% to 90% [19–21]. This is substantially higher than the 10% to 40% concordance rate observed in dizygotic twins, who share only about 50% of their genes [21]. These figures indicate that genetic factors are undoubtedly important, but the fact that monozygotic concordance is less than 100% also points to a significant role for environmental influences. Genome-wide association studies have identified hundreds of risk genes associated with autism, many of which are involved in synapse formation and plasticity [22]. This genetic complexity supports the idea of convergent pathogenic pathways rather than a single “autism gene.”

Early claims about there being “too many” or “too few” synapses in the autistic brain have gradually given way to a more nuanced understanding. The number of synapses increases dramatically after birth, peaks in childhood, remains roughly constant for a period, and then declines rapidly during adolescence through a process known as synaptic pruning [23]. What has emerged from more recent research is that the defect in autism likely lies not in the absolute number of synapses but in the organization of connections - that is, in the pattern of which regions are connected to which others [24]. However, current neuroimaging technologies lack the spatial resolution to directly visualize connectopathy at the synaptic level in living humans. Therefore, connectopathy remains an inferred con-

struct rather than a directly measured entity. Our hypothesis proposes specific biological mechanisms - namely BDNF dysregulation and zinc deficiency - that could lead to such organizational defects, but we acknowledge that direct evidence in humans is still lacking.

4. THE NEUROINFLAMMATORY HYPOTHESIS: FROM ASSOCIATION TO MECHANISM

4.1 Maternal immune activation as a risk factor

Epidemiological studies have consistently reported that maternal infection during pregnancy, particularly viral infection, increases the risk of autism in offspring [25,26]. This association has been observed across multiple large cohort studies and different populations. Animal models of maternal immune activation - for example, injecting pregnant rodents with poly(I:C), which mimics a viral infection - have been shown to recapitulate the core behavioral features of autism as well as associated brain abnormalities [27]. A key finding from this literature is that maternal immune activation does not require direct fetal infection; rather, maternal cytokines such as interleukin-6 (IL-6), IL-17, and tumor necrosis factor-alpha (TNF-α) cross the placenta and alter fetal brain development [28].

However, a critical appraisal of this literature is necessary. Most maternal immune activation studies have been conducted in rodents, and the translatability of these findings to humans is not certain. Human retrospective studies are susceptible to recall bias, as mothers are asked to remember infections that occurred during pregnancy many years earlier. Moreover, recent genetically informed studies have raised the possibility that some of the observed associations between maternal infections and autism may be confounded by shared genetic liabilities rather than reflecting a direct causal effect of the infection itself [29]. Nevertheless, the convergence of evidence from multiple lines of inquiry is sufficient to propose neuroinflammation as a contributing factor, though certainly not as a sole cause.

4.2 Zinc: a crucial modulator of immune and synaptic function

Zinc in its ionized form (Zn^{2+}) is stored in the synaptic vesicles of glutamatergic neurons and plays a critical role in modulating the activity of NMDA receptors [30]. When zinc is deficient, a cascade of negative effects follows: impaired neurogenesis, increased oxidative stress, and altered immune responses have all been documented [31,32]. Multiple studies have reported lower serum or plasma zinc levels in autistic children compared to typically developing controls [33], although it is important to emphasize that correlation does not imply causation. It remains possible that zinc deficiency is a consequence rather than a cause of the disorder, or that it is an epiphenomenon unrelated to the core pathophysiology.

A particularly innovative study by Curtin and colleagues [8] used laser ablation of deciduous teeth - commonly known as baby teeth - to reconstruct prenatal and early postnatal metal exposure. Teeth grow in layers, much like the growth rings of a tree, and each layer

captures a chemical snapshot of the circulating metals at the time it was formed. By analyzing these layers, the researchers found that the cycles of zinc and copper metabolism during fetal and early postnatal development predicted a later diagnosis of autism spectrum disorder with 90% accuracy across four independent cohorts. This study is notable for its longitudinal design and for being replicated across multiple populations, but it remains fundamentally correlational in nature.

4.3 BDNF: at the intersection of inflammation and plasticity

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is critically important for neuronal survival, differentiation, and synaptic plasticity. When one examines the meta-analyses of BDNF levels in autism, a confusing picture emerges. Some meta-analyses report elevated serum BDNF levels in autistic individuals [34,35], while others report reduced levels [36], and still others find no significant difference [37]. A 2024 meta-analysis by Liu and colleagues [38] concluded that peripheral BDNF levels are modestly increased in ASD, but with very high heterogeneity across studies, meaning that the findings are not consistent.

Why is there so much inconsistency? The answer likely lies in the fact that BDNF levels vary by age, by sex, by the tissue being sampled (serum versus plasma versus cerebrospinal fluid), by whether the individual is taking medication, and by comorbid conditions. Moreover, it is becoming increasingly clear that the signaling of BDNF - including the balance between activation of the TrkB receptor and the pro-apoptotic p75NTR receptor - may be more relevant to pathophysiology than the absolute levels of BDNF protein [39]. Our hypothesis therefore focuses on dysregulation of the BDNF system - meaning disruptions in the timing, location, or isoform of BDNF expression - rather than a simple increase or decrease in total BDNF.

4.4 The zinc–BDNF–serotonin interaction

Petrilli and colleagues [7] have proposed an elegant model in which zinc acts as a natural ligand for GPR39 receptors, which in turn modulate serotonin signaling and BDNF expression. In this model, inflammatory states deplete zinc reserves from the body, which in turn activates the hypothalamic-pituitary-adrenal (HPA) axis and elevates glucocorticoids - stress hormones that contribute to depressive symptoms. At the same time, pro-inflammatory cytokines upregulate an enzyme called indoleamine 2,3-dioxygenase (IDO). This enzyme diverts the amino acid tryptophan away from the production of serotonin and toward the production of kynurenine pathway metabolites. One of these metabolites, quinolinic acid, is a potent agonist of NMDA receptors. The result is a cascade that leads to glutamate excitotoxicity (excessive stimulation of neurons by glutamate), reduced neurogenesis (the birth of new neurons), and altered BDNF signaling.

This cascade is illustrated conceptually in the diagrams below (see Figure 2 and 3).

Figure 2. The overall cascade in a flow diagram format

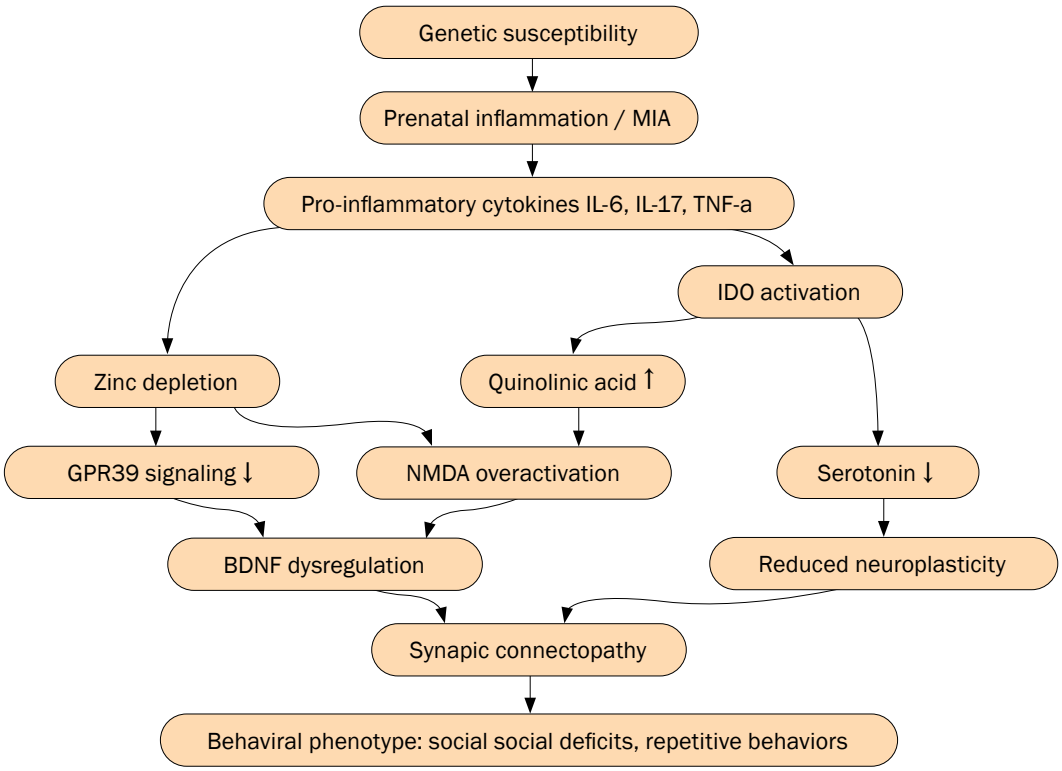
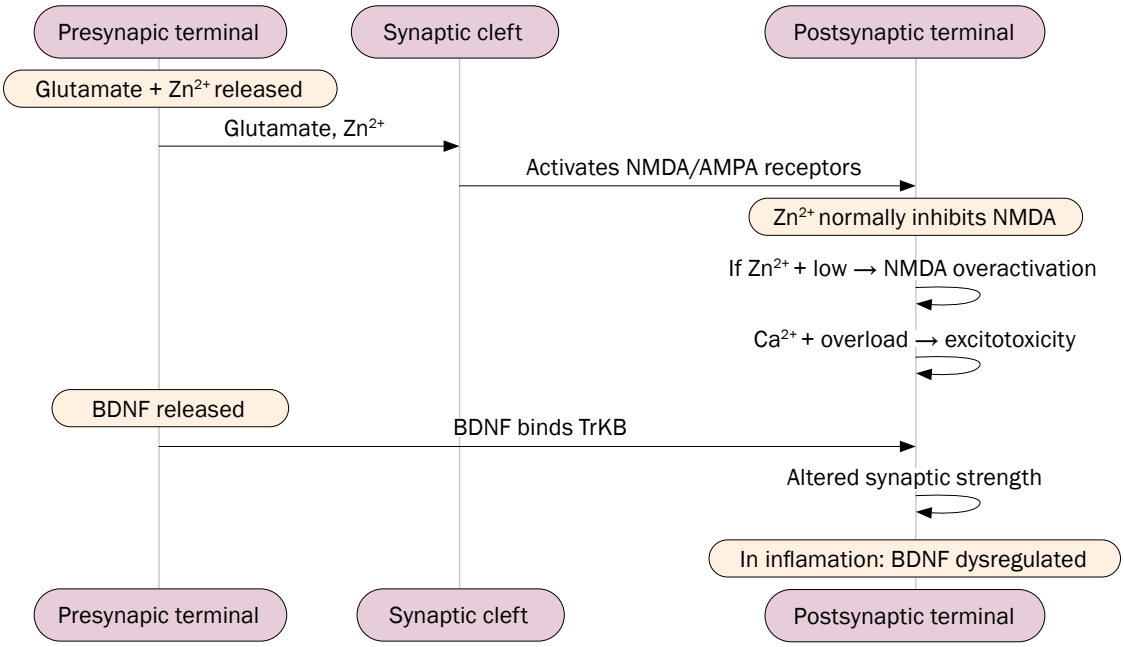


Figure 3. The molecular interactions at the synaptic level in more detail



Source: Own elaboration

4.5 Shank3 as a zinc sensor

A particularly compelling molecular link between trace metal dysregulation and synapse dysfunction comes from studies of the Shank family of proteins. Arons and colleagues [6] demonstrated that Shank3, a postsynaptic scaffolding protein that is associated with autism when mutated, is part of a zinc-sensitive signaling system. When zinc binds to Shank3, it modulates the interaction of Shank3 with AMPA receptors, thereby affecting the strength of excitatory synaptic transmission. Mutations in Shank3 that disrupt the protein's ability to bind zinc impair synaptic transmission. This mechanism has been further elaborated in subsequent studies [40–42]. It is important to note, however, that most of these findings come from in vitro experiments and rodent studies. Human postmortem brain studies are scarce and are confounded by the agonal state - the physiological changes that occur around the time of death. Nevertheless, the mechanism is biologically plausible and provides a clear molecular hypothesis that can be tested in future research.

5. PATTERNS OF THE NEUROINFLAMMATORY PROCESS: SYNTHESIS OF FINDINGS

Based on the 78 studies included in our qualitative synthesis after full-text review and critical appraisal, we have identified several key patterns that emerge from the literature. It is important to note that these patterns represent a synthesis of the available evidence, but the strength of evidence varies considerably across different domains.

The most robust finding in the literature concerns the association between prenatal infection and later autism diagnosis. Multiple large cohort studies have reported that maternal infection during pregnancy, particularly viral infection requiring hospitalization, increases the odds of autism in offspring by approximately 50% to 150% [25,26,43–46]. A recent meta-analysis estimated a 32% increase in odds across studies [47]. However, recent genetically informed studies have raised important questions about whether this association is truly causal. Studies using sibling comparison designs, which control for shared genetic and environmental factors within families, have found that the association between maternal infection and autism is substantially attenuated when siblings are compared with one another [29,48]. This suggests that some - perhaps much - of the observed association may be due to confounding by genetic factors that increase both the mother's susceptibility to infection and the child's risk of autism. It is also worth noting that a small number of specific infectious agents, such as rubella and cytomegalovirus, are established causes of congenital infection and have been clearly linked to autism [49–51], but these are relatively rare.

The evidence regarding zinc levels in autism is more consistent but still limited. Multiple case-control studies have reported lower serum or plasma zinc levels in autistic children compared to controls, with a meta-analysis reporting a standardized mean difference of approximately -0.8, indicating a moderate to large effect size [33]. However, most of these studies are cross-sectional, meaning they measure zinc at a single time point after diagnosis, and they cannot distinguish whether low zinc is a cause or a consequence of autism. The longitudinal tooth study by Curtin et al. [8] is an exception, as it measured

metal levels prospectively during prenatal and early postnatal development, and it found that patterns of zinc and copper metabolism predicted later diagnosis. This study has been replicated in four independent cohorts, which strengthens confidence in the finding. Nevertheless, even this study is correlational and does not prove causation.

The BDNF literature is the most inconsistent. As noted above, meta-analyses have reached conflicting conclusions. Some report elevated BDNF in autism [34,35], others report reduced BDNF [36], and still others report no difference [37]. The most recent meta-analysis, published in 2024, concluded that peripheral BDNF levels are modestly increased in ASD, but with very high heterogeneity [38]. This inconsistency likely reflects the fact that BDNF levels are influenced by many factors, including age, sex, medication use, and comorbid conditions. Several studies have reported that the association between BDNF and autism may be specific to certain subgroups, such as those with macrocephaly [52] or those with a particular genetic background [53]. There is also evidence that the balance between mature BDNF and its precursor proBDNF may be more important than the total level of BDNF [54,55].

The animal model literature provides the strongest evidence for causal mechanisms, though with the usual caveats about translatability. Multiple studies have shown that maternal immune activation in rodents leads to behavioral changes that resemble autism, including reduced social interaction and increased repetitive behaviors [56–60]. These behavioral changes are accompanied by neurochemical changes, including reduced BDNF levels in the hippocampus and cortex [61], altered cytokine profiles [62], and changes in synaptic protein expression [63]. Importantly, several studies have shown that these effects can be prevented or reversed by dietary zinc supplementation [64,65], although the effectiveness of zinc supplementation appears to vary across different genetic backgrounds [66]. A recent study found that maternal zinc supplementation during pregnancy and lactation prevented autism-associated behavioral and synaptic deficits in Shank3 knockout mice, with effects that persisted into adulthood [67].

The genetic studies have identified numerous genes associated with autism, many of which converge on synaptic function. The Shank family of genes - particularly SHANK2 and SHANK3 - is among the most consistently implicated [68–70]. Studies have shown that SHANK3 mutations disrupt the protein's interaction with zinc and alter synaptic transmission [6,40,71]. Other genes involved in the postsynaptic density, such as DLGAP2 and SYNGAP1, have also been associated with autism [72,73]. However, it is important to note that no single gene accounts for more than a small fraction of autism cases, and the genetic architecture is highly heterogeneous.

Studies that do not support the hypothesis must also be acknowledged. Several large cohort studies have failed to find an association between maternal infection and autism after adjusting for familial confounding [29,48,74]. Some studies have found no difference in serum zinc levels between autistic children and controls after controlling for dietary intake [75]. And as noted, many studies have found no difference in BDNF levels between autistic individuals and controls [37,76]. These discrepancies suggest that the proposed cascade may be relevant only to specific subgroups of autistic individuals - for example, those with a history of maternal infection or those with a confirmed zinc deficiency. Alter-

natively, it is possible that compensatory mechanisms exist that mask the effects in some individuals. Our hypothesis is not intended to be universal; rather, it is one pathway among several that can lead to the autism phenotype.

The following table summarizes the key patterns identified in the literature, with an assessment of the strength of evidence for each domain (see Table 1).

Table 1. Key patterns

Domain	Key finding	Strength of evidence	Consistency across studies	Key limitations
Prenatal MIA	Increased ASD risk after maternal infection (OR 1.5–2.5)	Moderate (epidemiological)	High for viral infection	Recall bias, confounding by genetics [29,48]
Zinc levels	Lower serum zinc in autistic children (SMD ~ -0.8)	Moderate (meta-analyses)	Moderate, high heterogeneity	Reverse causation possible [33]
BDNF levels	Inconsistent: increased in some meta-analyses, no difference in others	Low to moderate	Low	Age, sex, medication effects [34–38]
BDNF signaling	Reduced TrkB activation or increased proBDNF in some postmortem studies	Low (few studies)	Not assessed	Small sample sizes, agonal state [54,55]
Shank3–zinc interaction	Zn^{2+} modulates Shank3-dependent synaptic transmission	High (in vitro/animal)	High	Translational gap to humans [6,40,67]
Connectopathy	Inferred from fMRI/DTI: reduced long-range connectivity	Moderate	Moderate	Lack of synaptic-level resolution [14–16]

SMD = standardized mean difference; OR = odds ratio; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; MIA = maternal immune activation.

Source: Own elaboration

6. DISCUSSION: AN INTEGRATIVE HYPOTHESIS, NOT A PROVEN THEORY

We have synthesized evidence from molecular biology, immunology, neuroimaging, and epidemiology into a proposed cascade: genetic susceptibility, followed by prenatal neuroinflammation, which leads to zinc depletion and subsequently to BDNF dysregulation, which in turn causes synaptic connectopathy and ultimately the behavioral phenotype of autism.

However, it is essential to be explicit about what this hypothesis does not claim. First, it does not assert that all autism cases involve this pathway. The heterogeneity of autism is well documented, and it is likely that multiple distinct pathogenic pathways can lead to the same behavioral phenotype. Second, it does not establish causation; the majority of the evidence we have reviewed remains correlational. Third, it does not provide a clinical biomarker that is ready for diagnostic use. The inconsistencies in the BDNF literature alone make clear that we are not yet at that stage. Fourth, it does not imply that zinc supplementation alone is a treatment for autism. Clinical trials of zinc supplementation in autistic children have shown mixed results [77], and any intervention would need to be carefully targeted to specific subgroups.

6.1 Comparison with alternative hypotheses

Several other aetiopathogenic models have been proposed, and our hypothesis is not mutually exclusive with any of them. The GABA/glutamate imbalance hypothesis [78] is entirely compatible with our model, given that zinc directly modulates NMDA-type glutamate receptors. The oxidative stress hypothesis [79] is also compatible, as zinc deficiency is known to increase oxidative stress and inflammation. The gut–brain axis dysbiosis hypothesis [80] is compatible as well, given that the gut microbiota influences systemic inflammation and immune function. Our hypothesis proposes that BDNF dysregulation may be a common downstream effector of multiple upstream insults - meaning that whether the initial trigger is a genetic mutation, an environmental toxin, or an infection, the final common pathway may involve disruptions in BDNF signaling and synaptic connectivity.

6.2 Strengths and limitations of this review

This review has several strengths. The methodology is explicit and follows PRISMA guidelines for study selection. We have critically appraised the quality of the included studies. We have acknowledged conflicting evidence where it exists. And we have clearly distinguished between established findings, observational associations, and speculative inferences.

However, there are also important limitations. This is a single-author review, meaning there was no second reviewer to independently assess study eligibility or to reduce bias in the synthesis. The narrative synthesis, despite our best efforts to be systematic, inevitably involves some degree of subjective selection. Most of the included studies are cross-sectional, and longitudinal data are relatively sparse. Animal model findings, no

matter how robust, may not translate to humans. And publication bias remains a concern: studies with positive findings are more likely to be published than studies with null findings, which could skew the literature.

7. CONCLUSIONS AND FUTURE DIRECTIONS

This article presents an integrative aetiopathogenic hypothesis of autism, proposing that BDNF dysregulation driven by prenatal neuroinflammation - in the context of genetic susceptibility and zinc dyshomeostasis - may underlie the connectopathy that characterizes at least a subgroup of autistic individuals. The hypothesis accounts for the extraordinary heterogeneity of autism by allowing multiple entry points into the same biological cascade.

Looking toward the future, several research priorities emerge from this synthesis. First, there is a clear need for prospective longitudinal studies that measure maternal inflammatory markers during pregnancy, measure neonatal BDNF and zinc levels, and follow children through to diagnostic outcome. Such studies would allow researchers to determine whether these factors precede the diagnosis, which is essential for establishing temporal precedence. Second, mechanistic studies using human induced pluripotent stem cell (iPSC)-derived neurons from autistic individuals with known maternal immune activation exposure could help to establish causality at the cellular level. Third, clinical trials of zinc supplementation in pregnant women who are at high risk - for example, those who have already had one child with autism - could be considered, but such trials would need to be designed with careful ethical oversight, and they should be targeted to subgroups likely to benefit. Fourth, high-resolution connectomics using advanced magnetic resonance imaging techniques, such as 7-tesla MRI and diffusion spectrum imaging, could test specific predictions about connectivity patterns in autistic individuals.

Turning to clinical implications, it is important to recognize that while exploring and reconstructing the pathogenic mechanisms of autism allows us to imagine new forms of diagnosis and intervention, we must not forget that autistic people are much more than their diagnosis. All neurodiversity should be seen as neuroheterogeneity. This perspective does not imply a difference from an absurd concept of normality - because normality does not exist in nature, and variation is the rule, as well as the engine and fuel of the evolutionary machine - but rather a different adaptability to the environment. Although we can still do little to alleviate the suffering caused by the more severe forms of autism, we can do a great deal to provide or create a less hostile environment. Building a world that is suitable for all neurotypes is a greater challenge for each of us than delegating and demanding a single pill that “solves the problem.” Perhaps this utopian quest indicates that we so-called self-proclaimed normals have a problem of our own.

Final caution

This hypothesis should not be overinterpreted as proven. It is a framework to guide future research, not a diagnostic test and not a justification for untested or unproven therapies.

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