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REVIEW

The Neuroimmunology of Autism

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Abstract
Alterations and maladaptations of the immune system remain some of the most controversial concepts in autism spectrum disorder (ASD). Nonetheless, intensifying evidence confirms that much of what ASD involves is related not to a static encephalopathy-based model of autism but rather to the consequences of environmental insult and complex and dynamic psychological and physiological processes involving the interdependence of the nervous, immune, and host microbiome. This narrative review provides a conceptual framework, focuses on clinical research, and is written for specialists and non-specialists. To provide access to multi- and interdisciplinary perspectives with wide-ranging cutting-edge implications for all people with ASD. Beginning with historical, epidemiological, and etiological underpinnings, we elaborate on a contemporary understanding of the immune system in the pathophysiology of ASD. Theoretical and scientific discourse on the relationship of the immune system with the nervous system and host microbiota in homeostasis/allostasis, neurodevelopment, and psychological and physiological health and disease is also provided. As a basis for conceptual advances detailing the interconnection, interdependence**,** and interference with or subjugation (as would be the case for autoinflammatory and autoimmune conditions) of the nervous system and host microbiota by the immune system, and the role of these interactions in the pathogenesis of ASD. This gives us a platform for not only examining the role of the immune system in the etiology, pathogenesis, and pathophysiology of ASD but also understanding social and higher-level processes of consciousness for individuals on the spectrum. Finally, taking a neuroimmunological perspective, we highlight the need for a multi-scale, holistic approach to understanding and developing future therapeutic modalities to address the core symptoms of ASD that go beyond the current reductionist and "*magic-bullet*" medical paradigm.

Keywords Autism spectrum disorder · Immune system · Neuroimmunology · Gut-brain axis · Bioregulatory systems medicine

Introduction

In the 1910 s, the Swiss psychiatrist Eugen Bleuler introduced the term autism to refer to what he identified as one of the symptoms of schizophrenia [63]. A fundamental description of autism spectrum symptoms was later developed in the 1920 s by Sucharew [496] followed by systematic case reports by Kanner [262] and Asperger [30] in the 1940s. Kanner and Asperger laid the foundation to make the distinction between autism and childhood schizophrenia [552], later clarified in the 1980 s with the 3rd edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [20, 455]. Over time, the apparent heterogeneous nature of autism in clinical presentation, etiology, underlying neurobiology, and degree of severity led to the adoption and common usage of the term autism spectrum disorder (ASD) [347]. This conveys a shift from categorical concepts of autistic syndromes to a dimensional concept within the larger framework of neurodevelopmental disorders (NDD). The current consensus, according to the National Institute of Mental Health (NIMH), defines ASD as "*a neurological and developmental disorder that affects how people interact with others, communicate, learn, and behave*" [394]; while the current diagnostic criteria for ASD according to DSM-V [19] state that a child must have persistent deficits in areas of social communication and interaction plus restricted repetitive behaviors and interests. Other disorders that share

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features with ASD include Asperger's disorder, Rett's disorder, Landau-Kleffner Syndrome, Fragile X syndrome, childhood disintegrative disorder (Heller's syndrome), and pervasive developmental disorder not otherwise specified [247].

ASD is broadly characterized as a neuropsychiatric disorder, while its manifestation is that of a psychiatric syndrome [464]. Its most severe manifestation could indicate, as Eugen Bleuler first identified, "*a neonate's tendency to turn away from reality and retire into a subjective world"* [64]. Current real-world evidence documents that, in a significant number of cases, parents witness the occurrence of ASD behavioral phenotypes in normal babies who have reached all previous developmental milestones [38, 181, 324, 327, 575]. While former studies suggested that regressive forms of onset were not common in ASD, more recent investigations indicate that the rates are quite high and may be under-reported. For example, Ozonoff et al. [405] report an 88% regressive ASD phenotype in a systematic investigation of infants with and without a family history of ASD. Changes in the postnatal or early developmental periods include dramatic abnormalities in social interaction and withdrawal (i.e., lack of pair-bonding, "*avert eyes*" [111], and lack of neonatal imitation [452]), impairments in verbal and non-verbal communication, and a restricted repertoire of interests and activities [42], as well as seeking and finding comfort in repetitive behaviors. Babies, adolescents, and adults with ASD are also reported to have difficulties in emotion processing, in particular, problems with recognizing and discriminating emotions in others [83].

Growing evidence shows that much of what ASD involves is related not to a static or fixed encephalopathy-based model of autism, but rather to the consequences of an allostasis systems malfunction [491], principally mediated through environmental insult and deficiencies, leading to maladaptation and pathology of the immune system as well as metabolic processes. Response to acute or chronic stress promotes allostasis or adaptation and promotes survival by protecting the body from damage and adaptive responses for which it has immunologic memory [356]. However, when the allostatic systems are overworked beyond a "*tipping point*", the capacity to respond acutely and appropriately functions poorly and, if the immunologic memory is for an inflammatory or autoimmune response within the nervous system, the shorter-term stress effect could exacerbate into a chronic disease process [357], generating heterogeneous ASD behavioral phenotypes with heterogeneity deriving from interindividual systems differences.

This review aims to move beyond genetic determinism to epigenetic regulation and its modulation by acute and chronic environmental toxic exposure and insult to the immune system in individuals with ASD. Historically, the documentation of psychological features largely preceded the documentation of physiological components of ASD. However, the pathological mechanisms on which we elaborate involve interacting sets of complex "*whole-body*" psychological and physiological processes along the gut-brain axis (GBA), working through individuals with ASD at different rates, with different equilibria or set points when compared to neurotypical people. Real-world and clinical evidence of fever has been reported from the onset of ASD symptoms [359], which would indicate an inflammatory response in its etiology. Several immunological abnormalities have been detected both in the peripheral and central nervous system (CNS) for the pathogenesis of ASD [178]. The role of toxic compounds and their accumulation in the CNS and their role in neurodegenerative and NDDs has been acknowledged for many decades [266]. However, ASD was not thought to be associated with any loss or maladaptation of the function of the immune system, as a malfunction in the CNS, which was thought to be the source and locus of autism, was understood to be shielded from immune influences by barriers.

If the critical role of environmental insult in the pathogenesis of ASD is taken a priori, and the contributions of such insults to immune dysfunction must be acknowledged, the role of the immune system becomes paramount in its pathophysiology. This has been reviewed from the 2000 s by Pardo and coworkers [410, 411], Anderson et al. [24], Patterson [414], and Ashwood and coworkers [29, 403], among others. Nonetheless, alterations and maladaptation of the immune system, including both adaptive and innate systems, still remain some of the most controversial concepts in ASD [428]. Building on this pioneering work, this review provides an updated and current commentary on the roles of the immune system and neuroimmunology within a broader environmental "*exposome*" framework in the pathology and pathophysiology of ASD. Indeed, since the 1960´s the brain was almost axiomatically viewed as an immune-privileged site [473]. However, over the last decade, mounting evidence has uncovered the substantial role of the immune system in CNS health and functioning and disease.

This paper focuses on clinical research and is written for specialists and non-specialists to provide access to multi- and interdisciplinary perspectives with wide-ranging cutting-edge implications for all individuals with ASD. This development is a result of an interplay between the expansion of tools for observation, investigation, experimentation, and frames of reference, as well as major changes in social and environmental life conditions, and a significant increase in autism prevalence. We highlight the current state-of-the-art, detailing the interconnection, interdependence**,** and interference with or subjugation (as would be the case for autoinflammatory and autoimmune conditions) of the nervous system and host microbiota by the immune system and the role of these interactions in the pathogenesis of ASD. We begin with the epidemiological, genetic, and environmental

underpinnings of vulnerability to ASD, and on this basis, turn our attention to the current scientific discourse regarding the relationship of the immune system with the nervous system and host microbiota in homeostasis/allostasis, neurodevelopment, and psychological and physiological health and disease. This gives us a platform for not only examining the role of the immune system in the etiology, pathogenesis, and pathophysiology of ASD but also understanding social and "*higher-level processes of consciousness*" such as cognition, sentence, and self-consciousness in individuals on the autistic spectrum.

We also highlight the need for a multi-scale holistic approach to understanding and developing future therapeutic modalities for ASD [219], which can be greatly facilitated through multidimensional omics technology and a bioregulatory systems (BrSYS) approach. Considering the heterogeneous nature of ASD and the vulnerable nature of individuals on the spectrum, we also endorse and highlight non-pharmacological, nutritional, botanical, and "*mind–body*" therapeutic modalities, particularly considering the growing body of scientific literature documenting the impacts of many of these approaches on neuroplasticity, immune function, and the GBA. Optimally, multiple interventions with low-risk profiles would be synergistically woven into an individualized dynamic strategy tailored to the specific, usually multisystem, set of vulnerabilities of each person, so as to not only provide exceptional safety profiles but also go beyond a reductionist pharmacological medical paradigm, with the capacity to not only ameliorate the symptoms of ASD but also reverse its core phenotypes.

Epidemiological Preambles of ASD

ASD has complex heterogeneous clinical manifestations [45], a strong bias toward males, and a broad crossover with numerous neuropsychiatric disorders. ASD phenotypes (social-communication impairments and restricted, repetitive patterns of behavior) are commonly associated with intellectual disabilities, anxiety, depression, epilepsy, attention deficit hyperactivity disorder (ADHD), sleep disorders, dyspraxia, and lack of verbal communication [40]. The significant occurrence of physiological comorbidities in ASD is also highlighted [276] by reports of increased rates of chronic physical health conditions across all organ systems in autistic children, adolescents, and adults [565]. This can be broadly sub-grouped as related to gastrointestinal [74] and metabolic disorders [174]; immune disorders (allergies, infections, primary immunodeficiency, and autoimmune) [240]; and motor/coordination disorders [368].

ASD is not strictly associated with mental retardation, and some people on the ASD spectrum are exceedingly brilliant. Nonverbal people with ASD can also be articulate and expressive through assistance and technologies that facilitate spelling and typing [250]. While a person unable to speak may be assumed to lack the capacity for symbolic thought that underlies language, verbal speech is only one means of expressive language, and literacy by non-verbal means has been extensively reported in nonspeaking people with ASD [250]. For example, some have learned to communicate by pointing to alphabet letters. This method remains controversial because it requires the assistance of another person who could theoretically cue them to point to letters [316]. A study published in 2020 by Jaswal et al. [251] used head-mounted eye-tracking to investigate communicative agency in a sample of nine non-speaking autistic individuals. Researchers measured the speed and accuracy with which individuals looked at and pointed to letters as they responded to novel questions. Participants pointed to about one letter per second, rarely made spelling errors, and visually fixated on most letters for about half a second before pointing to them. Additionally, their response times reflected planning and production processes characteristic of fluent spelling in non-autistic typists. These findings by Jaswal et al. would render a cueing account of participants' performance unlikely and a blanket dismissal of assisted autistic communication unwarranted.

While ASD can involve exquisite gifts and unusual qualities of perception and thought, the condition can also involve a great deal of suffering for individuals on the spectrum as well as family and the wider community. In a descriptive study, Weitlauf et al. [571] report that up to 25% of 726 participants with ASD have severe disabilities and require substantial support and 24-h-a-day care. Siegel et al. [486] report that 11% of children with ASD are psychiatrically hospitalized in the USA before age twenty-one, and Lui et al. [317] report that adolescents with ASD accessed emergency department services four times as often as adolescents without ASD. Depending on the degree of severity and intervention strategies accessed, some children with ASD may develop into independent and interdependent adults with full-time employment and self-sufficiency; however, this is seldom the case. Moreover, a clear need also becomes apparent, not only to address the core characteristics but also deeper existential suffering and loneliness for a growing and vulnerable adult population with ASD [227], and issues may relate to psychosocial burden[1] [103, 286].

ASD remained a relatively unknown disorder affecting less than 1 in 2,500 children up until the 1980 s [388]. Current estimates by the CDC [331, 484] and national

[1] For example, loss and change, freedom of choice versus loss of control, the dignity of the self, a sense of fundamental aloneness, altered quality of relationships, searching for meaning, mystery of what seems unknowable, and death anxiety.

and state estimates of adults by Dietz et al. [121] indicate that in the USA, up to 1 in 31 children and 1 in 45 adults have ASD, respectively. This apparent dramatic increase in ASD prevalence by CDC surveillance studies [338] over the past five decades has provoked a heated debate in the academic and medical community. While the broad clinical manifestations of ASD have remained largely unchanged since Kanner's and Asperger's first descriptions. children born from the mid-to-late 1990s were particularly more likely to be identified with ASD, with a broadening of the autistic spectrum by the new DSM-IV (1994) [449] and DSM-5 (2013) criteria [39], increased autism awareness among the public and health professionals [65], and expanded diagnosis and differing methodological factors in observational and epidemiological studies [389]. Based on Autism cases identified from 1990 through 2006 in databases of the California Department of Developmental Services. Hertz-Picciotto et al. estimated that changing age at diagnosis explained a 12% increase or a 56% increase, with the inclusion of milder cases [225].

A rising prevalence of ASD also coincides with an epidemic of chronic childhood diseases in the USA, each of which has its own set of diagnostic criteria. At present, the CDC reports that up to 2 in 5 US students aged 6 to 17 have chronic health conditions such as asthma, diabetes, or epilepsy [84]. This again represents a dramatic increase from estimates of 18 in 1000 children reported to have such conditions sufficiently severely to interfere with usual daily activities in the 1960 s [424] and estimates of 1 in 100 to 1 in 25 children under 16 to have a severe chronic illness in the 1980 s [202]. In 2011, based on a 2007 National Survey of Children's Health, Bethell et al. estimated that 54% of US children had at least 1 of 20 chronic health conditions and/or were at risk for developmental delays [55]. Based on surveys Ullah and Kaelber [545] conducted between 2016 and 2018, an estimated 40% of children and adolescents have at least one chronic disease, including obesity, eczema, asthma, food allergies, ADHD, and hypertension.

A rising, often medically complicated, and aging global population with ASD also has economic implications. For the individuals with ASD identified from 1990–2019, the lifetime social (medical, educational, productivity, and care) cost for the US was estimated to be more than $7 trillion in 2019 dollars [80]. As discussed by Cakir et al. [80], even if one assumes that the rate of increase in the prevalence of ASD is static for the next decade (2020–2029), the projected cost estimate for ASD in the US will increase to $11.5 trillion in 2019 dollars. These numbers are not unique to the USA. Autism is often regarded internationally as the most expensive disability [244]. In the United Kingdom, the total annual cost for children with ASD is $4.3 billion, while for adults it is reported to be $40.5 billion [288]; and the national cost of ASD in Australia is estimated to range from $4.5 to $7.2 billion [236].

Underpinnings of ASD: from Genetic to Environmental and Gene/Environment Etiologies

The ongoing debate on the rise and prevalence of ASD over nearly half a century can be associated with the central scientific dogma that ASD is a highly heritable genetic disease of the brain. Indeed, the current professional standard of care emanates from the genetic narrative's static encephalopathy-based model of autism. Yet, although over $1 billion has been spent on genetic research in autism over the past 10 years by the NIH, Autism Speaks, and the Simons Foundation, unequivocal evidence that a genetic association is "*hardwired*" has not been established [218]. Moreover, genetic investigations have failed to yield a single therapy to treat the core symptoms. Concordance (shared diagnosis) of 90% of monozygotic (identical twins) and 10% of dizygotic (fraternal twins), published in the 1970 s, was initially used to justify an intensive focus on genetics to the exclusion of environmental influence [150]. These findings have yet to be corroborated. For example, in 2011, Hallmayer et al. [195] reported on the largest twin study to date and reported a lower monozygotic concordance and higher dizygotic concordance. Their results yielded a smaller gap between autism rates in identical as compared with fraternal twins, with 55% of the variance for strict autism and 58% for ASD explained by shared environmental factors, with moderate genetic heritability of 37–38% [195]. In 2014, using an epidemiological sample from Sweden, Gaugler et al. [166] concluded that autism's genetic architecture has a narrow-sense heritability of ≈52.4%, with most due to the common variations and rare de novo mutations.

Genome-wide association studies (GWAS) using large cohorts and dense datasets, including the Autism Genetic Resource Exchange, Simons Simplex Collection, Autism Genome Project, Autism Case–control, and Autism Center of Excellence, have revealed a myriad of genes implicated in autism [179]. On review of GWAS, Glessner et al. [179] report that de novo variants, although exceedingly rare to find recurrently, play a strong role but should be placed in the context of the gene-based mutation rate and conclude that: "*the reality that hundreds of modest, common, and rare/strong impact/partially penetrant variants abound in each genome.*" A recent study of Zhang et al. [598] found developmental trajectories and polygenic architecture of autism to vary with age at diagnosis. These findings could

partly explain the varying genetic correlations among the different GWASs of autism and between autism and various mental-health conditions.

Taken as a whole, these findings would indicate that environmental factors could complement, rather than replace genetic factors, in further assessment of etiological risk for ASD [568]. Indeed, a growing body of evidence implicates a strong interplay between environmental insults and epigenetics [118] in the pathophysiology of ASD [189, 536], with chronic and acute multifactorial xenobiotic exposure occurring during peri- or postnatal or even preconception periods. Fuller et al. [159] report that up to nine million deaths per year (16% of all deaths worldwide) are attributed to air, water, and soil pollution alone. This is unsurprising when one considers that today's typical contemporary diet and lifestyle are corrupted by ultra-processed and nutrient-poor food [309, 362], and new-to-nature exposures through chemicals in cosmetics, home-care products, household construction materials, agrochemicals, aerosols, and pharmaceuticals, as well as electromagnetic exposures in the home, school, and workplace.

Scientific literature spanning many decades implicates exposure to non-metabolic heavy metals such as mercury [53, 167, 273] and aluminum [138, 139, 482]. Recent meta-analysis by Stojsavljević et al. [504] and O'Connor et al. [399] indicates Hg concentrations were higher in children with ASD than those without in case–control studies; however, large-scale longitudinal data were lacking. Both have a long environmental legacy from mining in North America and have had widespread applications as adjuvants in biologics recommended during pregnancy and to infants [53, 62, 99, 168, 235, 273, 274]. Other heavy metals implicated, again with no metabolic function in the human body, include cadmium, lead, and arsenic [123], which are all found in contaminated Superfund sites. All these metals are highly neurotoxic and are known to cause neurodevelopmental deficits [602]. Energy, porphyrin, and neurotransmitter homeostasis are the key metabolic pathways affected by heavy metal exposure. Various pharmaceuticals taken by mothers during pregnancy are implicated in the etiology of ASD and detailed in systematic reviews and meta-analyses include: antibiotics based on twelve studies (6,264,831 patients), when taken in all trimesters [335]; acetaminophen, based on five studies (2,647,536 patients), especially in the third trimester [256]; antidepressants from 10 studies including a meta-analysis on 6 case–control studies (117737 patients) in all trimesters or before pregnancy [361]; and anticonvulsants (10 studies, 54,747 patients), particularly valproate, carbamazepine, and oxcarbazepine [304].

Fetal and neonatal exposure to toxins can also occur from industrial chemicals [60]. Duque-Cartagena et al. [130] provide a systematic review of 27 studies and a meta-analysis of 22 studies. These studies included 1,289,183 participants and 129 environmental pollutants and indicated positive associations for nitrogen dioxide, copper, mono-3-carboxypropyl phthalate, monobutyl phthalate, and PCB 138, and the development of ASD. Systematic review and meta-analysis have also implicated polyfluorinated substances [21], polychlorinated biphenyls [360], and plasticizers like phthalates [252] and bisphenol A [595]. All these chemicals are known to be endocrine-disrupting chemicals and can disrupt normal immune function in the brain, leading to chronic or excessive neuroinflammation. The effects of their early-life exposure on neurodevelopment merit further study, particularly the cumulative effects of prenatal and postnatal exposures, with appropriate attention to exposure assessment and relevant pre- and post-natal confounders. More research is also needed to explore sensitive subgroups or potential mitigating factors such as breastfeeding and nutrient intake, which will require larger, more diverse samples.

Organophosphorus (OP) compounds are a class of acetylcholinesterase inhibitors used in agrochemicals (pesticides, insecticides, herbicides, and fungicides) and have a long history in chemical warfare as neurotoxins [435]. Some chronic illnesses that manifest symptomatology overlapping with ASD, such as Gulf War Illness, have (at least in part) been attributed to OP exposure [248, 534, 593]. A proposed etiological role of glyphosate for ASD has recently been proposed by Seneff, Kyriakopoulos, and Nigh [475] and González et al. [183]. Glyphosate is a widely used active ingredient in agricultural herbicides, inhibiting the biosynthesis of aromatic amino acids in plants by targeting their shikimate pathway [461]. The shikimate pathway is not present in mammals per se; however, the pathway is present in gut bacteria [468]. Walsh, Hill, and Ross [562] further hypothesize and explore the potential of glyphosate to inhibit the growth or functionality of beneficial microbes in the gut. Moreover, glyphosate can substitute for glycine in protein synthesis, creating potential havoc [476].

Studies spanning many decades have shown that exposure to low-level, low-frequency electromagnetic radiation (EMF) can break DNA chains, damage proteins, even increase the blood–brain barrier permeability, disturb sleep, and cause fatigue, memory, and concentration (ADHD) problems [498]. Herbert and Sage [220, 221] reviewed the pathophysiological damage to core cellular processes that are associated both with ASD and with the biological effects of EMF exposures that contribute to chronically disrupted homeostasis and human health [386]. Epidemiological studies have also shown a clear association between maternal immune activation (MIA) and schizophrenia or autism in the progeny [137]. Maternal autoimmune disorders, allergies, asthma, acute stress, and exposure to environmental pollutants have been linked to an enhanced risk of ASD and

schizophrenia [137]. Emerging evidence suggests similar links for disorders like cerebral palsy and aging-associated neurodegenerative diseases, positioning MIA as a factor in the brain's responsiveness to cumulative lifetime exposure to environmental insults [290].

The Immune and Nervous Systems: "*Systems of Relations*"

In an abstract sense, the current dogma states that the immune system is tasked to monitor and interpret insults and potential threats (i.e., toxins, pathogens, and wounds) from the external world and mount appropriate defensive actions. This would include a sophisticated innate and adaptive defense system to counter environmental insults successfully. At the same time, it also monitors the states of self of internal organs, including the nervous system, facilitates resistance to stress and maintenance of homeostasis, and has an essential role in allostasis and healing responses [438]. Of note, a general evolutionary trend indicates an inverse correlation between the ability to regenerate damaged/lost body parts and the development of an advanced immune system [3]. The same abstract framing of the immune system also applies to the nervous system, particularly the CNS, which processes information from the external and internal worlds and commands reactions to external and internal stimuli to maintain homeostasis, allostasis, and survival.

Homeostasis involves the maintenance and defense of vital physiological variables such as blood pressure and blood sugar. Walter Cannon first defined this concept in 1929 as the principle underlying physiological regulation [149]. Later, in the late 1980 s, Sterling and Eyer coined the term allostasis to reflect the process whereby adaptive organisms must be able to change the defended levels of one or more regulated parameters as needed to adjust to new or changing environments [357]. Allostatic systems promote adaptation to stressful experiences and are generally most useful when rapidly mobilized and terminated. However, when they are prolonged without resolution, potentially irreversible disease states can arise. Allostatic processes can undermine mental and physical health, primarily because of their effects on brain plasticity, immune, microbiome, and metabolic pathophysiology [489]. Singletary [491] provides an integrative model of ASD as a disorder of allostatic overload, amplifying the neurobiological vulnerabilities generally considered to make primary contributions to the development of autism. In addition, the HPA axis has traditionally been the focus of stress pathophysiology research in ASD; however, the evidence for HPA axis dysregulation in autism is inconsistent [520]. Makris et al. [334] provide an up-to-date summary of the findings regarding stress system alterations in ASD, including the pivotal role of the immune system, HPA axis–ANS coordination, and the possible role of early life stress in the dysregulation of the stress system.

Homeostasis in the nervous tissue is controlled by glial cells (astrocytes, microglia) and mast cells, resident and invasive immune cells (e.g., T-cell and B-cell lymphocytes, neutrophils, dendritic cells, macrophages, mast cells); and immune signaling and inflammatory regulators (e.g., chemokines and cytokines). The immune system is essential for normal healthy functioning and the neuroinflammatory response [1] and tumor immunosurveillance [495]. However, it can also act as a double-edged sword and exhibit complementary and inhibitory functions [592]. For example, the chronic activation of the immune system has been highlighted to trigger self-reinforcing disease processes through failed shut-off of stress-responsive hormone systems [136]. Immune dysfunction and neuroinflammatory components are also associated with several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease [214, 300].

Following on and as reviewed by Hiller-Sturmhöfel and Bartke [232], the CNS and the glandular endocrine system are intimately connected, forming the neuroendocrine system. Hormones can be produced by endocrine glands in the hypothalamus, pituitary gland, adrenal glands, and gonads [287]. In this system, the "*neural part*" can recognize its environment, memorize it, and influence the endocrine system, which acts as the "*biochemical executor*" [101]. In tandem with the neuroendocrine system, immune cells also synthesize, store, and secrete various hormones identical to those secreted by endocrine glands. These include the proopiomelanocortin hormones (e.g., endorphin), the thyroid system hormones, growth hormones, prolactin, melatonin, histamine, serotonin, and catecholamines [101]. In the immune-endocrine axis, immune cells can recognize and store the information (immune memory) and execute the commands provoked by the recognition. Immune cells are also mobile, meaning they can appear in any place in the organism, under local factors that attract them, e.g., in the case of inflammation. Blalock further theorizes that the immune system can be deemed a "*sensory organ*" that uses the same signals and receptors as the neuroendocrine system [61] to inform the brain about its wider external and internal environment, including parasites and toxins. Indeed, neuroimmunology has established that the nervous and the immune systems are two functionally related physiological and complementary "*systems of relations*" that work closely together [105]. This is comparable to profound functional relationships between other systems, such as structure (skeletal, muscular) and metabolic/physiological maintenance (digestive, respiratory, renal, endocrine, cardiovascular, hemopoietic, and reproductive).

Finally, the nervous system and the immune system are found to be correspondingly controlled by and engaged in controlling a complex, dynamic, and diversely composed microbiota with residence in various niches of the human body, which would include not just the gastrointestinal system but also the oral cavity, nasal passages, lungs, skin, hair, bladder, and vagina [97]. Not only do immune cells and the microbiota help control infections and malignancy, but the extraordinary plasticity and motility of immune cells and their reliance on the highly dynamic microbiota also bridge virtually all physiological systems, making the immune system and microbiota central regulators of host homeostasis [27].

Interdependence of the Immune, Gastrointestinal, and Neural Systems

An appreciation of the role of microorganisms in disease gave rise to "*germ theory*", which was established in the nineteenth century [306], and the central role of microorganisms in childhood morbidity and mortality during the Industrial Revolution is well documented [231]. Infectious diseases in this period were principally mediated through poor sanitation, inadequate waste disposal systems, and water supply, poverty, and deprivation [243, 294]. In juxtaposition, more recent discoveries over the last three decades have revealed that the human body harbors a diverse ecosystem of symbiotic microorganisms, including bacteria, viruses, and fungi, collectively known as the microbiota or microbiome, that are vital for normal health and well-being and for the prevention of disease [119]. The ability of microorganisms to selectively colonize the human niche reflects their evolutionary adaptation and results in reciprocal interacting processes that form a single unified process [37] and superorganism (or "*holobiont*") [67, 340, 501]. The most studied microbiome of the human body resides in the gastrointestinal (GI) tract. GI mucosal surfaces are intimately associated with the most abundant and diverse microbial communities in the human body [328]. The current consensus implicates four prominent bacterial *phyla* in the gut. i.e., *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroides* [97]. Stress can sway the balance of the microbiome away from homeostasis. Of note, while many triggers to disease have been identified, far less is known about the triggers of a natural return to homeostasis [444]. The immune system learns to tolerate the dynamic evolution of commensal microbiota and respond appropriately to pathogens and antigens; in turn, the host microbiota is integral to educating the immune system to function correctly [342]. From this viewpoint, the immune-microbial systems interactions represent the most conspicuous set of anti-exploitation adaptations involved in human–microbial symbiosis [119]. There is still debate and controversy regarding which mechanisms underlie the acquisition of microbial communities. It remains unclear whether pioneer colonization starts during fetal life (i.e., *"*in utero *colonization"* hypothesis) or whether it occurs during birth and the early postnatal period (i.e., *"sterile womb paradigm"*) [423, 502, 503]. Furthermore, maternal antibodies are emerging as a key player in shaping initial interactions with the microbiota [27].

The GBA [100, 301, 350] provides an essential link between two important systems of the nervous system–namely, the CNS and the enteric nervous system (ENS), and the gut microbiome and metabolome [440]. The ENS represents an interdependent and extensive network of nerve cells within the gut. Its local complement component acts as a vigilant sentinel to a dynamic and evolving environment in the GI tract [586]. Even though it is now considered a third branch of the autonomic nervous system (ANS), the ENS has been referred to as the "*second brain*" [171], based on its size, complexity, and similarity in neurotransmitters and signaling molecules with the brain [171]. Since ENS neurons do not extend into the intestinal lumen, their ability to sense the microbiota is indirect, accomplished either by microbial molecules that have penetrated the epithelial barrier or by sensing through epithelial cells themselves [330]. The ENS is viewed as a peripheral extension of the limbic system into the gut, where it is exposed closely to our complex internal environment, including powerful mechanical, (bio)chemical, and microbial influences [584]. The GBA essentially represents the bidirectional communication between the CNS and the ENS, linking the emotional and cognitive centers of the brain with peripheral intestinal functions. The GBA has a critical role in the integration of external and internal changes in the environment and the maintenance of bodily homeostasis. Indeed, there is growing recognition that the GBA is a critical regulator of neurological functions and an intermediary to neurotoxicity by environmental stressors such as drugs, environmental contaminants, and dietary factors [115]. Interactions represent a system with bidirectional communication channels and multiple feedback loops. GBA crosstalk occurs via multiple channels, with rapid neuronal signaling primarily by the vagus nerve, as well as the gut connectome (via the semi-autonomous ENS), with more delayed feedback being achieved through neuroendocrine and neuroimmune signals into the circulation [351, 506] in the form of gut-derived neurotransmitters (dopamine (DA), serotonin (5-HT), GABA, and histamine), hormones, and inflammatory mediators (i.e., cytokines). 90% of vagal fibers between the gut and brain are afferent, suggesting that the brain is more of a receiver than a transmitter concerning brain-gut communication [54].

Nonetheless, preclinical studies indicate the destabilization of microbial diversity and disturbed microbiome (called dysbiosis) after acute brain trauma and chronic physiological

stress [264, 270], suggesting the CNS is a critical player in this GBA interplay. The GBA is not only of importance for well-being but also a bridge to our understanding of homeostasis, adaptation, disease, and the body–mind connection [506]. Mounting evidence implicates the GBA in the pathogenesis of multiple chronic diseases, including inflammatory bowel disease, coeliac disease, allergies, asthma, metabolic syndrome, cardiovascular disease, and obesity [51], and the pathology of numerous neurological and psychiatric disorders. GI dysbiosis is also implicated in the etiology of ASD [437, 560], and children with ASD often experience chronic GI symptoms (e.g., diarrhea, constipation, bloating, and gastroesophageal reflux [561]). Moreover, a strong positive correlation has been observed between the severity of GI symptoms and the severity of ASD symptoms [533]. Indeed, in 2010, an expert panel of the American Academy of Pediatrics strongly recommended further investigation into the role of GI abnormalities in the pathophysiology of ASD [74].

However, epidemiological association is not proof of causation. Zhao et al. [599] underscore the need for large-scale targeted mechanistic studies, such as longitudinal gut-microbiome profiling, in vivo models of α-synuclein propagation, and integrated immune–metabolite analyses, to elucidate pathways along the gut–brain axis. A notable pilot study by Fouquier et al. [152] investigated study-site effects and longitudinal analyses of behavior change with the gut microbiome in autism with neurotypical controls in Arizona and Colorado. Researchers reported that the gut microbiome in individuals with ASD was affected by study-site location as well as GI symptom severity and that non-ASD-related study site differences in gut microbiome composition may contribute to inconsistent results in the literature regarding the association between gut microbiome composition and ASD.

Two important boundaries in the CNS and GBA are the blood–brain barrier (BBB) and the gut-blood barrier (GBB) [330]. The integrity of both GBB and BBB has been reported to be impaired in ASD individuals [526]. The BBB constitutes the largest interface between the blood and the brain, separating the brain interstitial fluid from blood plasma [2]. In disease states, BBB breakdown and dysfunction lead to leakages of inappropriate as well as harmful blood components into the CNS, cellular infiltration, and aberrant transport and clearance of molecules. BBB breakdown can lead to neurotoxic accumulations of fibrin, thrombin, and plasmin, and red blood cell extravasation, the release of hemoglobin and ferrous iron, causing reactive oxygen species (ROS), which can all injure dopaminergic neurons [513]. Like any other organ, the brain is vascularized from the surrounding vascular plexus during embryogenesis, and the BBB is tempered by the body's immune system from embryonic development [513]. Both the arteriolar and capillary vessel walls are covered by astrocytic end feet and glia limitans. Components of the neurovascular unit, including smooth muscle cells, pericytes (mural cells), and astrocytes, all have neuronal innervation. Sweeney et al. [513] extensively review the involvement of BBB breakdown and dysfunction in neurological deficits and other pathologies, including chronic conditions (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis), as well as acute CNS disorders such as stroke, traumatic brain injury, spinal cord injury, and epilepsy. The GBB, i.e., the intestinal epithelium, is a highly dynamic structure, is estimated to completely self-renew every 4–7 days, and plays an important role in homeostasis [400]. Weakened intestinal epithelial barrier function has been suggested as a possible source of chronic inflammation in schizophrenia [400] and ASD [208] and the development of autoimmune diseases [23]. However, there are still major gaps in our understanding of how specific microbial compounds influence human conditions. The associations between circulating metabolite levels and brain function are difficult to interpret without knowledge of at least BBB permeability. In addition, many of the currently proposed mediators of microbiota-gut-brain signaling have no known receptors in the CNS.

The Pathophysiology of ASD

From a pathophysiological perspective, maladaptation of inflammation processes is a common feature of many acute and chronic neurodegenerative diseases [22, 213] and NDDs [254]. Immune abnormalities were first described in individuals with ASD in 1977 by Stubbs et al. [509]. Since then, a growing body of research spanning nearly half a century has implicated oxidative stress, mitochondrial dysfunction, and inflammatory processes, as well as chronic and systemic immune dysregulation in the pathophysiology of ASD. These can be broadly characterized as neuroinflammation (encephalitis) and autoimmune encephalitis, involving the innate and adaptive immune systems respectively [140, 358, 403, 467] (Fig. 1). Alongside this, a growing body of evidence indicates the influence of the gut microbiota and microbial signaling molecules and metabolites (e.g., bile acids, short-chain fatty acids, and tryptophan metabolites) on neurodevelopment and behavior. Many studies have shown that early colonization, mode of delivery, and antibiotic usage significantly affect the development of the gut microbiome and the onset of ASD [516]. Many authors speculate that gut-microbiota dysbiosis may be central to the etiology and pathogenesis of ASD [74, 207, 234, 241, 417, 436, 507, 516]. However, as discussed by White [578] and Beopoulos [52], an alternative (or perhaps complementary) hypothesis also explored here is that it may be a secondary consequence of immune pathology in the GI tract and ENS [73, 395, 398].

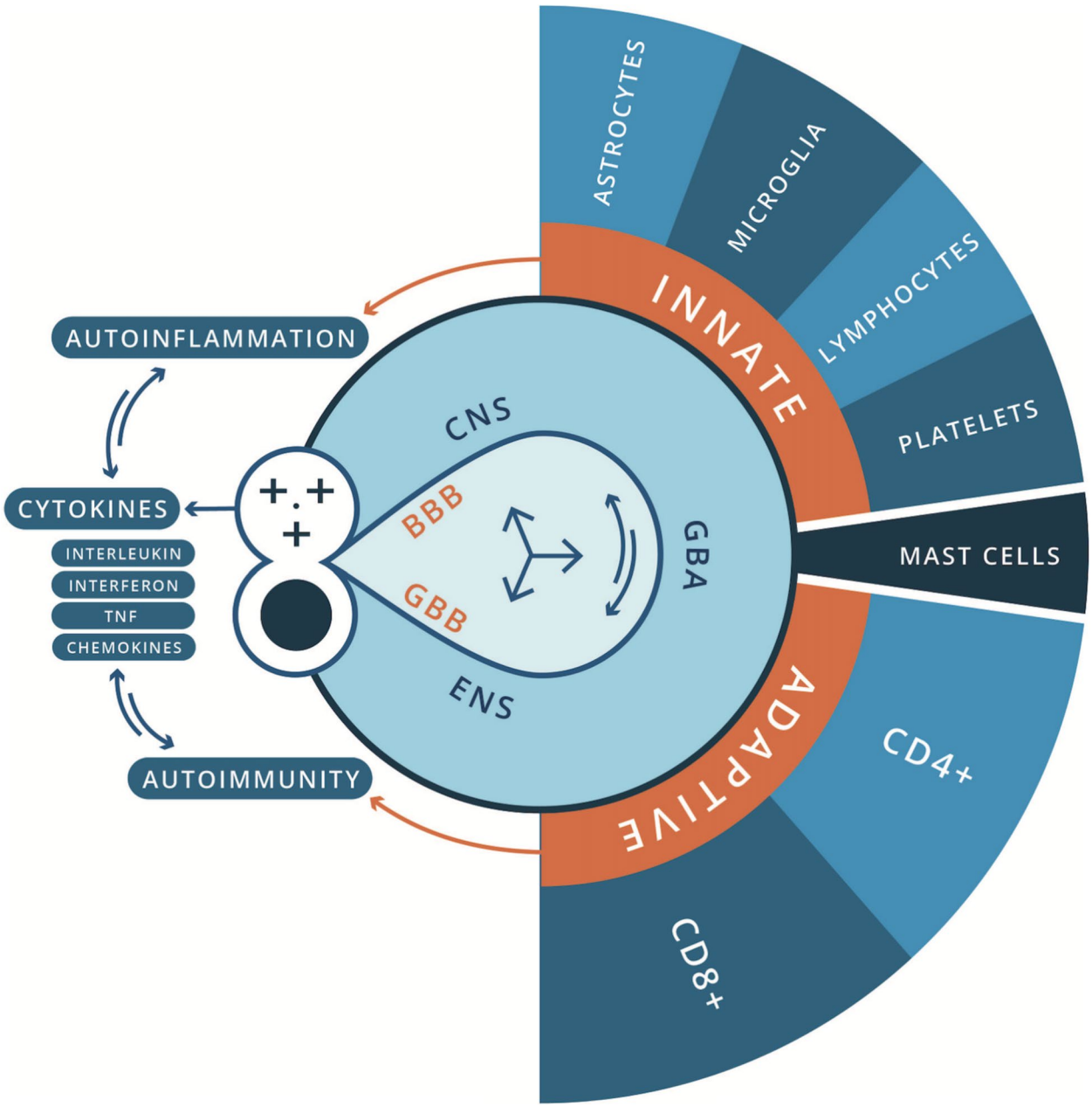

Fig. 1 Disorders of the neuroimmune system and ASD

In the context of disorders of the CNS, immune cell abnormalities have been reported in brain-resident innate and adaptive immune cells in children and adults diagnosed with ASD. This includes glial cells (i.e., microglia, astrocytes, and oligodendrocytes), monocytes, natural killer (NK) cells, thrombocytes, mast cells, and dendritic cells [24, 29, 410, 411]; and T cells (e.g., CD4 + T-helper cells (Th) (major lineages including Th1, Th2, Th17, Treg) [233] and CD8 + lymphocytes (Tc) (major lineages include Tc1, Tc2, Tc9, Tc17, Tc22) [293, 521]), and regulatory B cell lymphocytes [382]. Of note, immune memory was long thought to be restricted to the adaptive immune system; however, increasing evidence suggests that concepts of a trained immune system also apply to the innate immune system. Netea et al. [387] review the mounting evidence that cells of the innate immune system, which lack the antigen specificity, clonality, and longevity of T cells and B cells, do have some capacity to remember. This property would allow monocytes, macrophages, and NK cells to maintain homeostasis/allostasis by enhanced responsiveness when they reencounter xenobiotic insult. Many researchers have also investigated myriad chemical messengers and signaling

cascades that regulate pro- and anti-inflammatory processes for their role in the etiology of ASD and as biomarkers of CNS pathology. They include, for example, cytokines (such as interleukin (Il), interferon, tumor necrosis factor (TNF), and chemokines [596]), neurotrophic factors (e.g., nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)) [319] and insulin-like growth factor-1 (IGF-1) [209]. In parallel, current research also highlights the role of neurotransmitters (e.g., serotonin, dopamine, norepinephrine, acetylcholine, oxytocin, endogenous opioids, cortisol, histamine, glutamate, and GABA) [302, 341] in the pathophysiology of ASD. All these molecules are not restricted to modulating only static neurons; they also modulate mobile immune cells. Their role from a neuroimmunological perspective would be important, and evidence is provided for their involvement in the pathophysiology of ASD. This would indicate an overall departure from brain biochemical homeostasis. Also pertinent is sex bias and the role of sex hormones in the pathogenesis of ASD (male bias) and autoimmune disorders (female bias) have been well documented and also further explored as a possible nexus between these disorders. With all of this said, it is noteworthy that no universal or robust biological signature or biomarker for ASD has been found. This would suggest that there is no single specific "*chemical or immune imbalance*" in the CNS of all autistic individuals.

ASD, Inflammation & Oxidative Stress

Oxidative stress can be defined as an imbalance between pro-oxidants and antioxidants, resulting in a damaging action toward the cell caused by reactive oxygen species (ROS) and reactive free radicals [490]. All these molecules are produced during the activity of peroxisomes, endoplasmic reticulum, proteasome, and mitochondria *(PERM)* [91]. Chirumbolo and Bjørklund [91] introduce the "*PERM hypothesis*" to describe the complex dynamical system as a single master tuner of cellular decision-making. The authors highlighted that the ability of this system to adapt to stressors, insults, and stimuli may lie in its chaotic behavior, mainly formed by synchronized oscillatory mechanisms, involving calcium signaling, ROS, and mitochondria polarization.

Recent evidence indicates that mitochondria lie at the heart of immunity and play a key role in innate and adaptive immune responses [25, 364, 570]. That is, mitochondrial signaling dictates macrophage polarization and function and is necessary for responses to activators of innate immune signaling. Mitochondrial ROS regulates Th (T helper) cell activation, differential metabolic pathways regulate CD4 + cell differentiation, and mitochondrial metabolism regulates CD8 + memory formation [570]. Hanaford and Johnson [199] review preclinical and clinical evidence for the immune system's role in the pathogenesis of mitochondrial dysfunction and disease. Current knowledge highlights a disturbed mitochondrial function in immune cells for various immunological diseases [570]. Other psychiatric diseases associated with mitochondrial disorders include bipolar disorder, anxiety disorders, schizophrenia, and ASD [339].

Several studies have suggested that redox imbalance and oxidative stress are integral parts of ASD pathophysiology [24, 59, 457, 458, 546] and inflammatory responses [487]. Substantial percentages of ASD patients display peripheral markers of mitochondrial energy metabolism dysfunction [430], such as elevated lactate, pyruvate, and alanine levels in blood, urine, and cerebrospinal fluid [157]; serum carnitine deficiency [147, 157]; and enhanced oxidative stress [157, 407]. Recent evidence from post-mortem studies of autistic brains points toward abnormalities in mitochondrial function as possible downstream consequences of immune dysregulation and altered calcium signaling [407]. Children with ASD are considered more vulnerable to oxidative stress because of their imbalance in intracellular and extracellular glutathione levels and decreased glutathione reserve capacity. Ghanizadeh et al. [173] discuss the role of glutathione in the context of ASD, including its involvement in neuroprotection against oxidative stress and neuroinflammation.

Innate Immune Dysregulation Encephalitis & ASD

Current research indicates that innate neuroimmune reactions play a major pathogenic role in an undefined proportion of autistic patients [548]. Glial cells (including astrocytes, microglia [443], and oligodendrocytes [483]), natural killer (NK) cells [135], mast cells [90], dendritic cells [95], and platelets [110] play pivotal yet distinct roles at various developmental stages of the fetal and neonatal nervous system. Accordingly, the immune system would have explicit and important roles in the pathogenesis of any neurodevelopmental disease, especially those whose etiology is rooted in environmental xenobiotic insult. Moreover, in the developing brain, it is important to note that the energy requirement during the rapid postnatal growth period is due to a swift developmental progression, predominantly driven by the intricate maturation and refinement of existing neurons, as neurogenesis primarily occurs before birth. Cantando et al. [82] elaborate on the interplay between astrocytes, microglia, and metabolic dysregulation in the context of ASDs, revealing a complex landscape for their potential contribution to the pathogenesis of these neurodevelopmental conditions.

The Pathophysiology of Glial Cells in ASD

Microglia are the major brain-resident macrophages that act as the first line of defense against injury and infection in the

CNS [348]. In addition, microglia are reported to be the nervous system's "*electricians"* [186] and have an important function in forming a network of immune components within the CNS and ENS [185, 210, 465]. New controversies have also emerged, such as the question of whether microglia are active or reactive players in neurodegenerative disease conditions, or whether they may be "*victims*" themselves [185]. The current consensus indicates that microglia both play a prominent role in neurodevelopmental processes like synaptic pruning and neuronal network maturation [376] and are involved in neurodegenerative diseases [185]. Microglia induce the formation of both inhibitory (I) and excitatory (E) synapses in the hippocampus as regulators of physiological homeostasis [456]. Moreover, using *in-vivo* imaging in rodent models, Haruwaka et al. [204] demonstrate that microglia play a dual role in maintaining BBB integrity. Deng et al. [116] further elaborate on how gut metabolites can directly regulate the functional states of microglia, or indirectly regulate them via the GBA, and their role in the pathogenesis of neurodegenerative diseases and NDDs. Microglial dysfunction in ASD is reported to be attenuated or excessive synaptic pruning, disturbance of the brain's excitation *vs.* inhibition (E *vs*. I or E/I) balance [141, 284, 296, 305, 325, 426, 587]. Microglial abnormalities have been identified in ASD, including in density, function, and morphology in the brain [141, 296], deficient microglia autophagy [284], and pathological mechanisms involving other brain resident glial cells (i.e., astrocytes and oligodendrocytes) [325, 425, 587].

Astrocytes compose at least one-half of human brain tissue volume, and up to a few decades ago, were assumed to be primarily giving structural, metabolic, and functional support for neurons [419]. More recent discoveries have identified multiple functionalities of astrocytes beyond primary supportive roles, including homeostatic (molecular, cellular and network, systemic, organ, metabolic) and defensive processes of the CNS [550, 559]. In the brain, astrocytes are involved in the control of synapse formation, neurogenesis, and brain vascular tone [245]. They may have not only harmful effects of aggravating neuro-inflammation and hindering synaptic sprouting or axon growth, but also beneficial effects of anti-inflammation and neuroprotection [127]. Brain physiology and pharmacology research further indicate that wakefulness and sleep depend on astroglia calcium signaling [66, 418]. Astrocytes are also deemed essential to the maturation, maintenance, and regulation of the BBB in the healthy brain [127]. However, as discussed by Pociūtė et al. [429], little is known about the effects of astrocyte-secreted factors on the integrity of the BBB under physiological conditions. Alterations in the neuron–astrocyte partnership have emerged in the literature and have been shown to underlie brain lesions in pathologies as varied as brain tumors, Alzheimer's disease, and amyotrophic lateral sclerosis [413]. Astrocytic excitation is chemically encoded and is revealed not through electrophysiology, as for neurons, but by assays of intracellular calcium concentration transients and oscillations [493]. Astrocytes are seen as local communication elements within the CNS that can generate various signals, for example, through the regulated release of '*gliotransmitters*' including glutamate [559]. Alterations in astrocytic processing (neurogenesis, synaptogenesis, inflammation, myelination, glutamate) and number have been deemed significant contributors to ASD pathophysiology [16, 82, 192, 547].

Oligodendrocytes myelinate the brain and spinal cord to insulate axons electrically and provide neurons with trophic and metabolic factors [47]. Emerging evidence supports the notion that oligodendrogenesis and neural myelination may play a pivotal role in the pathophysiology of ASD and its clinical presentation [164]. Steinman and Mankuta [500] provide evidence of the putative role of IGF-1 in the genesis of ASD. IGF-1 directly affects the rate at which oligodendrocytes promote myelination in the CNS [499]. IGF-1 signaling pathways are crucial for adequate axonal myelination and oligodendrocyte differentiation, but, when disrupted, can lead to white matter alterations, learning challenges, ASD-like behaviors, and neurodevelopmental and neuropsychiatric disorders [446, 450].

The Pathophysiology of NK Cells in ASD

NK cells were originally defined as effector lymphocytes of the innate immune system [555] that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage [215]. Recent research highlights that NK cells are also regulatory cells engaged in reciprocal interactions with dendritic cells, macrophages, T cells, and endothelial cells [556]. NK cells are potent effectors of immune homeostasis, with receptors allowing them to sense the "*non–self*" or "*missing-self*" status of target cells. There is increasing evidence that NK cells link innate and adaptive immunity and play an important role in the pathogenesis of autoimmune conditions [176, 318]. NK cells have been implicated in the pathology of neurological and behavioral disorders, including Tourette syndrome, schizophrenia, multiple sclerosis, neuromyelitis optica spectrum disorders, autoimmune encephalitis, Guillain-Barré Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, and idiopathic inflammatory myopathy [135].

Over 30 years ago, Warren, Foster, and Margerten [567] reported altered NK activity in adults and children with ASD. Recently, Ebrahimi, Rostam-Abadia, and Rezaei [131] reviewed and highlighted a growing body of research detailing NK cell dysfunction in children with ASD as well as their parents. The authors discuss changes in the frequency, gene expressions, cytotoxicity features, and receptors of NK

cells in children and adults with ASD. Highlighted studies include those of López-Cacho et al. [322]. Their investigation indicated an increase in the percentages of CD8 + Tc cells and B-cells, a decrease in NK cells, and a trend toward increased apoptosis in monocytes in patients with ASD. Vojdani et al. [557] further explored NK cell activity in 1027 blood samples from autistic children obtained from 10 clinics in the USA and compared the results to 113 healthy controls. 45% of a subgroup of children with ASD suffered from low NK cell activity. The authors discuss the role of low intracellular levels of glutathione [542], as also underscored by Ghanizadeh et al. [173].

The Pathophysiology of Mast Cells & Dendritic Cells in ASD

Mast cells are critical for allergic reactions but are also important in immune response and inflammation cascades in the nervous system [295]. Together with dendritic cells, they are the first line of defense in the immune system against invading pathogens [384]. Mast cells are present in the brain and its meninges, including the area postrema, choroid plexus, and thalamic-hypothalamic region [212]. Mast cell–neuron interactions can involve the ENS and regulation of the GBB permeability and GI pathophysiology [526]. For example, mast cell activation by allergic, infectious, environmental, and stress-related triggers, especially perinatally, can release pro-inflammatory and neurotoxic molecules and disrupt the GBB and BBB, contributing to ASD pathogenesis and phenotype [26, 447].

The role of mast cells in the pathophysiology of ASD has been extensively explored and discussed by Theoharides and coworkers [524, 525, 527, 528]. Researchers speculate that stress and environmental stimuli trigger cascades involving mast cells and microglia, leading to abnormal synaptic pruning and dysfunctional neuronal connectivity [528] in brain pathology. For example, processes at a cellular level in these systems could alter the "*fear threshold*" in the amygdala and lead to an exaggerated "*fight-or-flight*" response. As a further example, corticotropin-releasing factor is secreted from the hypothalamus under stress and, together with neurotensin, can stimulate brain mast cells to release inflammatory and neurotoxic mediators that disrupt the BBB, stimulate microglia, and cause focal inflammation [527, 528]. Also noteworthy, in allergy/immunology practice, it is not unusual to find food allergies in children with ASD [588]. Angelidou et al. [26] further speculate that subjects with hypersensitive mast cells may represent a unique subgroup of patients who are more likely to respond to environmental and stress triggers, precipitating or worsening ASD. Jyonouchi highlights studies that indicate a high prevalence of non-IgE-mediated food allergies in young children with ASD and further speculates that food allergies may account for some but not all GI symptoms observed in children with ASD [258]. These findings also suggest that non-allergic autoimmune mechanisms involving mast cell activation, probably in response to environmental and stress triggers, could contribute to inflammation and the pathogenesis of autism.

Alongside mast cells, dendritic cells have important functions in the modulation of the immune system and the phagocytosis of pathogens or debris, antigen presentation, activation of naïve T cells, induction of tolerance, and cytokine/chemokine production [106]. Dendritic integration plays a fundamental role in sensory processing, cognition, and conscious perception processes [196] and is hypothesized to be impaired in individuals with ASD and NDDs. Impairments include problems with dendrite morphogenesis [95], integration [385], and frequency [345]. Breece et al. [69] conducted a study of the frequencies of dendritic cells and their association with behavioral assessment and MRI measurements of amygdala volume. 57 patients with ASD were enrolled and compared to 29 typically developing controls. Researchers reported a significant increase in the frequency of myeloid dendritic cells, which was also correlated with abnormal right and left amygdala enlargement, severity of GI symptoms, and increased repetitive behaviors. Alterations in dendritic cell frequency were corroborated in a study by Saad et al. [462] of 32 children with ASD *vs*. 30 healthy children. Researchers enumerated data from flow cytometry of peripheral blood samples and indicated higher percentages of myeloid dendritic cells and plasmacytoid dendritic cells in the ASD group. Basheer et al. [44] also reported elevated myeloid dendritic cells in a comprehensive evaluation of various peripheral immune cell subsets and associated serum cytokine levels in 30 children with ASD, compared to 30 typically developing children.

The Pathophysiology of Platelets In ASD

The classical role attributed to platelets is the maintenance of hemostasis; however, more recent evidence has highlighted a central role for platelets in the host inflammatory and immune responses [253], by virtue of their high prevalence and ability to rapidly release a broad spectrum of immunomodulatory cytokines, chemokines, and other mediators, as circulating sentinels [253]. Moreover, platelets share common biological and molecular characteristics with neurons (calcium-dependent activation and secretion mechanism, cell surface receptor, and secretory vesicles with neurotransmitters such as serotonin, dopamine, glutamine, and GABA transporters) [75]. They also contribute to brain homeostasis [308], mediate protective neuroinflammation, and promote neuronal plasticity at the site of neuronal injury [129]. In general, dysfunction, abnormal activation, and morphological alteration of platelets have been implicated in many complex neurological disorders such as schizophrenia, migraine,

Parkinson's disease, Alzheimer's disease, and ASD [184]. Clinical research by Farmer et al. [142] suggests that elevation in BDNF may be partially explained by higher platelet counts in children with ASD. Although many studies reveal associations between platelet biomarkers and ASD, there is an important knowledge gap in linking these markers with ASD and explaining the altered platelet phenotypes detected in ASD patients [406].

Adaptive Immune Dysfunction, Autoimmune Conditions, & the Pathophysiology of ASD

Alongside a decline in the incidence of most infectious diseases since the 1900 s, there has been a steady rise in the incidence in industrialized countries of chronic inflammatory disorders and autoimmune diseases [32]. Autoimmune diseases are caused by an inappropriate immune response against "*self*" antigens, resulting in local tissue-specific and systemic chronic cascades of inflammation and tissue damage. Autoimmune conditions are hypothesized to occur through exacerbation of the immunoregulatory deficiency. This deficiency is speculated to be due to the loss of microorganisms (dubbed the "*hygiene hypothesis*" or "*Old Friends hypothesis*") from modern urban environments, with which humans have coevolved and tolerated and relied on for the development of immunoregulatory circuits [454]. Like other chronic diseases, autoimmune diseases exhibit shared alterations in the gut microbiota. Wang et al. [564] report microbial alterations among autoimmune diseases that were substantially more consistent compared with those of other diseases (cancer, metabolic disease, and neurological disease), with microbial signatures exhibiting notable discriminative power for disease prediction. Akdis [11] further discussed an epithelial (e.g., skin and gut) barrier hypothesis, which proposes that the increase in epithelial barrier-damaging agents linked to industrialization, urbanization, and modern life underlies the rise in allergic, autoimmune, and other chronic conditions, including ASD. One alternative hypothesis that ties infection with autoimmune disease is molecular mimicry [14]. Mechanisms of molecular mimicry essentially involve infectious agents containing an antigen cross-reactive to a host antigen in the body; a less specific activation of the innate immune response can also promote autoimmune disease [13, 14]. No convincing or rigorous proof exists for the theory of molecular mimicry by pathogenic agents [13, 14]. However, as reviewed by Segal and Shoenfeld [474], a growing body of research implicates mechanisms involving xenobiotics, including prophylactics, in the development of autoimmune conditions. As with ASD, autoimmune diseases are heterogeneous in prevalence, manifestations, and pathogenesis. The CDC estimates that as many as 50 million people in the USA have an autoimmune disease, making it the third most prevalent disease category, surpassed only by cancer and heart disease [393]. There are more than 80 known autoimmune diseases, including about 30 autoimmune disorders of the nervous system [56, 523].

Oxidative stress plays an important role in the pathogenesis of autoimmune diseases, and many environmental agents can participate in and amplify the cascade mechanisms involved [277]. Autoimmune diseases are typically defined by the autoantibodies that are produced by autoreactive B cells and autoantigen-reactive Th cells against their host [321]. Natural autoantibodies provide immediate protection against infection and prevent inflammation by facilitating the clearance of oxidized lipids, oxidized proteins, and apoptotic cells [320]. The role of autoantibodies in the development of autoimmunity is still unclear [321] and the initial trigger for autoantibody production in patients with CNS autoimmunity is still widely unknown. However, autoantibody detection to neuronal or glial targets has resulted in a better understanding of CNS autoimmunity and reclassification of some diseases previously thought to result from infectious, '*idiopathic,*' or psychogenic causes [434]. Pathogens and commensals stimulate pattern recognition receptors, including toll-like receptors (TLRs), to protect against autoimmunity [32]. Pathogenic mechanisms of autoantibodies in autoimmune diseases include interaction with cell surface receptors, cell surface binding and lysis, immune complex-mediated damage, binding to extracellular molecules, and autoantibody transfer across the placenta [321]. One theory speculates that faults of the CD4 + T cell line [600] and reduced microbial stimulation of the TLRs in early life could lead to a weaker Th1 response and a stronger Th2 response to allergens. Th1 cells mainly develop following infections by intracellular bacteria and some viruses, whereas Th2 cells predominate in response to infestations by GI nematodes and are associated with allergies [453]. Emerging evidence suggests Th2 responses also play a crucial role in CNS homeostasis and disease pathogenesis [337]. Th17 cells have also developed a reputation as a destructive element in several chronic diseases [346] and auto-inflammatory neurological disorders such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and schizophrenia [515]. Regulatory T (Treg) cells are a population of T cells that can functionally suppress an immune response and are fundamental in maintaining T cell tolerance to self-antigens and immune homeostasis in healthy individuals [268]. Mitochondrial-regulated Tregs are also hypothesized to be involved in the occurrence and progression of autoimmune diseases of the CNS [198].

Antibodies against self-antigens are also found in cancer and during massive tissue damage [49]. Cancer involves uncontrolled cell proliferation, whereas NDDs are connected to anomalies in the development of the nervous system. Wen and Herbert [573] discuss the overlap between ASD and cancer and speculate on possible common mechanisms regarding signaling pathways related to metabolic alterations. Wen

et al. [572] also conducted pathway network analyses for ASD, revealing multisystem involvement, major overlaps with other diseases, and convergence upon MAPK and calcium signaling pathways. In 2023, Yavyz et al. [589] published a large-scale study of de novo mutations in approximately 8000 samples with NDDs and approximately 10,000 tumor samples from The Cancer Genome Atlas. Mutations in NDDs tend to have a weaker functional impact and are more likely to influence differentiation compared to those in cancer.

A myriad of publications implicate MIA in schizophrenia and ASD [137, 238, 290]. This would support a link between cellular immune dysregulation and ASD-related behaviors. For example, Braunschweig et al. report an association between the transfer of IgG autoantibodies during early neurodevelopment and the risk of developing autism in some children [68]. Informed by these studies, an alternative and novel hypothesis for the etiology of ASD implicates autoimmune pathology involving a maladaptation of the immune system in the CNS [133]. Money, Bobrow, and Clarke [372] provide the first reports that autoimmunity of the CNS may be etiologically important in ASD. In a case report in 1971 the authors describe a child with multiple diagnoses and a strong family history of autoimmune disorders. Thirty-five years later, Edmiston, Ashwood, and Van de Water provided the first review of investigations, implicating autoimmunity and autoantibodies in individuals with ASD [133]. Moreover, epidemiological studies document a significant association between ASD and autoimmune disorders such as celiac disease, type 1 diabetes, asthma, multiple sclerosis [143], epilepsy, and atopic disease [126, 524].

In 2017, Ahmad et al. [8] reported that children with ASD have imbalances between the anti- and pro-inflammatory milieu in blood leukocytes. Based on an analysis of peripheral blood mononuclear cells of children comparing ASD with a typically developing control group, researchers reported increased pro-inflammatory cytokine production and decreased anti-inflammatory molecules. In a sequel paper, Ahmad et al. [9] indicated dysregulation of Th1, Th2, Th17, and Treg cell-related transcription factor signaling in children with ASD. In the final study published in 2019, Ahmad et al. [7] used RT-PCR and western blotting to report elevated expression and significant mRNA and protein induction of IL-16 in children with ASD compared with typically developing controls. IL-16 is a chemoattractant for various CD4 + cell lines associated with proinflammatory processes and activation of glial cells. It is also reported to be closely involved in the pathology of multiple sclerosis and other inflammatory diseases in the CNS [237]. Nie et al. [392] also investigated CD4 + T cell subsets in 82 children with ASD and 50 healthy typically developing children from the Medical University of Yunnan Province. Overall, their data suggested an imbalance in inflammatory and regulatory immune responses in ASD. A higher effective T cell (Teff) to Treg ratio was associated with more severe problematic behavioral symptoms. Researchers also report that proinflammatory cytokine levels were higher in the plasma of children with ASD compared to typical controls. Molloy et al. [369] report that children with ASD had increased activation of both Th2 and Th1 arms of the adaptive immune response, with a Th2 predominance. Li et al. [313] reported elevated immune responses in the brains of autistic patients with elevated proinflammatory cytokines. However, in disagreement with reports by Molloy et al., the Th1/Th2 ratio was significantly increased in ASD patients enrolled in this study. Basheer et al. [44] report activated Th17 cells on analysis of blood serum from children with ASD. The role of Th17 cells in auto-inflammatory neurological disorders has been highlighted [237]. Moreover, Th17 cells increase the migration of other immune cells, such as neutrophils, into the inflamed CNS through the BBB and trigger inflammatory reactions that occasionally lead to irreversible neuronal damage [432]. B cells play multiple roles, including the capacity to produce antibodies and cytokine milieu, and play fundamental roles in autoimmune diseases [349]. Nadeem et al. [382] report an imbalance in pro-inflammatory and anti-inflammatory cytokines in B cells of children with ASD. This study indicated that in ASD subjects, pro-inflammatory cytokines such as IL-6 and TNF-α were elevated in B cells while anti-inflammatory cytokine IL-10 was lowered. The elevation of TNF in individuals with ASD would indicate neuropathology involving neuronal signaling and homeostasis [374, 412]. Cruz-Machado et al. [488] report higher nocturnal saliva levels of TNF and IL-6 in 20 individuals with ASD compared to 20 normally developing individuals. Cruz- Machado et al.[488] also speculate that the involvement of immune-pineal axis activation, with elevated TNF but not IL-6 level, is associated with disrupted pineal melatonin release and sleep dysfunction in ASD. Further discussion of the brain-immune crosstalk in sleep is provided in a review by Marshall and Born [343]. The limbic system, amygdala, and related structures have been extensively researched in the context of the pathophysiology of ASD [514]. Limbic encephalitis is characterized by adaptive autoimmune inflammation of the limbic system. It has recently been identified as a major cause of temporal lobe epilepsy accompanied by progressive memory disturbance and emotional and behavioral changes [58].

This is noteworthy as it is now established and widely recognized that children with ASD are at high risk for developing epilepsy [539, 558]. Several researchers [539] provide further reflection on the autism-epilepsy phenotype and a growing body of evidence for shared neuronal networks that can account for both ASD and epilepsy. Epilepsy is a paroxysmal disorder characterized by abnormal electrical brain activity associated with a variety of

behavioral manifestations. Autoimmune encephalitis and epilepsy have been linked to neural-specific autoantibodies targeting both intracellular and plasma membrane antigens [532]. The autism-epilepsy phenotype has also recently been shown to be associated with macrocephaly, a pathologic condition due to accelerated brain growth in early development, leading to ASD. Cerebellar alterations are often observed with epilepsy, including structural changes and modulation during seizures [508].

The role of cerebellar circuitry alterations in the pathology of sensorimotor and other ASD-related behaviors has been extensively highlighted [48, 124, 380, 510]. Numerous studies have focused on the cell pathology of the cerebella involving Purkinje cells for ASD [144]. Purkinje neurons project into deep cerebellar nuclei and are the only output cells of the cerebellar cortex; they play an important role in motor coordination, sensory processes, and cognition [109]. They contain the inhibitory neurotransmitter GABA and the calcium-binding protein calbindin, and their output from the cerebellar cortex is wholly inhibitory [86]. Reports have indicated 35–95% fewer cerebellar Purkinje cells [48] and a reduction of cell size in ASD brains compared to controls [144]. The cerebellum can be a frequent target of autoimmune attacks. The underlying cause for this vulnerability is unclear. Hampe and Mitoma [197] speculate that region-specific differences in BBB permeability, the high concentration of neurons in the cerebellum, and the presence of autoantigens on Purkinje cells are potential explanations. Wills et al. [582] examined plasma from children with ASD for antibodies directed against human cerebellar protein. Western blot analysis revealed that 13 of 63 subjects with ASD possessed autoantibodies that demonstrated specific reactivity to a cerebellar protein. Intense immunoreactivity to what was determined morphologically to be the Golgi cell of the cerebellum was noted for 7 of 34 subjects with ASD.

GBS is an autoimmune disease of the peripheral nervous system. Its annual incidence in children under 15 years old ranges from 0.34 to 1.34 per 100,000 [581]. TLR and cytokines have been reported to have a critical role in the pathogenesis of the disease [397]. Despite having great clinical value, the interconnection between GBS and ASD has not been established and remains a mystery. Hasib et al. [205] evaluated the differential expression pattern of genes from two RNA-seq datasets to discover potential common biomarkers for GBS and ASD. Seventeen common differentially expressed genes were identified for these two disorders. Common genes identified the protein–protein interaction (PPI) network and pathways associated with both disorders. PPI networks are distributed in complex diseases, including cancer and autoimmune disorders [463].

Taken together, the findings of autoimmunity in families and the plethora of anti-brain antibodies reported for individuals with ASD suggest that in some patients, autoimmune encephalitis and autoantibodies that target the CNS and ENS may be a pathological or exacerbating factor in neuronal and ASD development.

Autoimmune Encephalitis, N-Methyl-D-Aspartate (NMDAR) Encephalitis & ASD

Autoimmune encephalitis comprises a group of CNS inflammatory disorders. The presentation of autoimmune encephalitis can be like encephalitis secondary to an environmental insult. A study by the California Encephalitis Project, a center focused on the epidemiology and etiology of encephalitis, found that 63% of the patients remained without infectious etiology based on a battery of tests for 16 potential infectious agents. Of these patients, the most common etiology was immune-mediated [161]. Encephalitis is indicated by acute or subacute symptoms of decreased or altered level of consciousness, lethargy, short-term memory loss, and personality changes such as apathy, irritability, agitation, and, commonly, seizures [477]. In children, neurological manifestations such as seizures, movement disorders, and focal neurological deficits are more prominent at initial presentation than psychiatric or behavioral symptoms [201]. When psychiatric symptoms do occur, they often manifest as temper tantrums, aggression, agitation, and rarely psychosis. Speech disorders are also a common complication of encephalitis in children (estimated 15–38% [396]).

NMDAR (N-methyl-D-aspartate (NMDA) receptor) encephalitis is the most common form of antibody-mediated limbic encephalitis in children and adults [165]. NMDARs are voltage-dependent ionotropic glutamate receptors [409] and glutamate is a major excitatory neurotransmitter of the CNS. It is implicated in many basic neuronal functions and CNS processes, including learning, memory, and synaptic plasticity [391]. The anti-NMDAR autoantibody is a typical synaptic protein that can bind to synaptic NMDA glutamate receptors, leading to dysfunctional glutamate neurotransmission in the brain that manifests as psychiatric symptoms (psychosis, hallucinations, and personality changes) [267]. A growing body of case reports documents NMDAR antibodies in the serum and cerebrospinal fluid of children with developmental regression, particularly of social communication skills, mimicking an autistic regression [193, 282]. Kern et al. [275] review the evidence for encephalitis and microglial and astrocytic activation, a unique and elevated proinflammatory profile of cytokines, and aberrant maladaptation of B cells. The authors speculate that at least 69% of individuals with an ASD diagnosis have encephalitis. Tzang et al. [540] correlated ASD with dysfunctional autoimmunity and anti-NMDAR encephalitis. The authors also

report autoantibodies, cytokines, decreased lymphocytes, serum immunoglobulin level imbalance, and T cell lineage to mediate immune responses as important biomarkers for autoimmune pathologies in ASD. Tarabeux et al. [517] explored rare or de novo mutations in NDDs. Researchers sequenced the seven genes encoding for NMDARs in a large cohort of individuals affected with schizophrenia ($n=429$) or ASD ($n=428$) *vs.* typical controls ($n=568$). Sequencing identified two de novo mutations in patients with sporadic schizophrenia and one de novo mutation in a patient with ASD. Data here further support the hypothesis that rare de novo mutations could account for some cases of sporadic ASD. This study also further supports the importance of NMDARs in psychiatric disorders with neurodevelopmental origins. In NMDAR encephalitis, unique electroencephalogram (EEG) patterns of 20–30 Hz beta activity riding on rhythmic 1–3 Hz delta waves, called extreme delta brush, have been described [56].

It remains to be seen if the relation between encephalitis and ASD is uni- or bidirectional; that is, whether children with ASD have an epigenetic diathesis to developing encephalitis (such as those mediated by the NMDAR), or conversely, if deranged or inflamed neuroreceptor processes are implicated in its development, or on occasion, both.

GI Pathology, the Immune System & Pathophysiology of ASD

There is substantial evidence that provides not only a correlational but also a causal relationship between intestinal pathology and autoimmune [151, 280] and neurodevelopmental diseases [4]. Notably, the largest component of the body's immune system is gut-associated lymphoid tissue (GALT), comprising secretory lymphoid aggregates known as Peyer's and caecal patches. GALT plays a central role in maintaining GI homeostasis, including baseline levels of inflammation, prevention of microbial overgrowth, and neuroimmune interactions. Microfold (M) cells found in Peyer's patches actively transport luminal antigens to the underlying lymphoid follicles to initiate an immune response, leading to autoimmune diseases [292], and play a role at the interface between innate and adaptive immunity [257]. M cells can engulf molecules in the intestinal mucosa and pass on information to the antigen-presenting cells, such as macrophages and dendritic cells, with further crosstalk with B cells for antibody production [363].

Because of their ability to transport luminal antigens and bacteria, Peyer's patches can be considered immune sensors in the intestine [257]. The essential role of Peyer's patches includes their influence on gut microbiome composition, communication in the ENS, and influence on behavior as part of the GBA [4, 160]. A high comorbidity of celiac disease, an immune-mediated, autoimmune reaction to gluten, and ASD has also been reported and extensively discussed in the context of ASD pathophysiology [94, 120]. Of note, the pathophysiology of celiac disease has been speculated to be neurological, involving loss of Purkinje cells and atrophy and gliosis of the cerebellum [381]. A commonly used restrictive dietary intervention for ASD is the gluten-free casein-free diet (GFCF) [93], which is based on the opioid excess theory [518]. Panksepp first proposed this theory to explain the pathogenesis of ASD and hypothesized that opioid peptides released from gluten and casein could pass through the mucosa and cross the blood–brain barrier, reaching the CNS and affecting brain function [408].

With opioids, the neurotransmitter serotonin has also been extensively investigated for its role in the pathophysiology of ASD in the CNS [272, 569] and its ability to modulate neural plasticity and networks [311]. Serotonin is detected in the first trimester and regulates neuronal growth, differentiation, migration, and survival [107]. Serotonin also shares a strong relationship with the pathological cases of tumors (migration, metastatic dissemination, and angiogenesis), inflammation, as well as pathogen infection, and is speculated to participate in the pathogenesis of autoimmune disease [481, 563]. In a systematic review and meta-analysis, Gabriele, Sacco, and Persico [162] report that approximately 30% of children with ASD show higher levels of serotonin in the blood in comparison to typically developing control groups. Serotonin signaling is also ubiquitous in the GI tract, as a neurotransmitter in the ENS, and is involved in epithelial proliferation and decreased injury from intestinal inflammation [478]. Outside the CNS, serotonin is produced in the ENS and released predominantly by enterochromaffin cells (estimated to be up to 90% of the body's serotonin production [169]) of the gut mucosa and immune cells, with influence not only on the ENS but also on the CNS via the GBA [283]. In addition, not only does the gut secrete serotonin, but it also expresses a kaleidoscopic abundance of serotonin receptors and serotonin transporters [172]. The impressive multi-functional nature of enteric serotonin has made the identification of physiological roles difficult and sometimes controversial. A novel hypothesis for documented GI pathology for ASD could be that immune-mediated insult damages the enteric innervation (enteric ganglionitis) with increased mucosal serotonin produced, predominantly by enterochromaffin cells of the GI tract [112].

Sex Hormones, the Pathogenesis of ASD & the Immune System

While sex hormones have long been recognized for their roles in reproductive functions, within the past two decades, scientists have found that sex hormones are integral

signaling modulators of the human immune system. Sex hormones are implicated in the immune response, with estrogens as enhancers at least of the humoral immunity and androgens and progesterone (and glucocorticoids) as natural immune suppressors [102]. The sex hormonal status is also known to modulate the hypothalamic–pituitary–adrenal axis (HPA), with accumulating evidence indicating that estrogen has excitatory effects, while androgens have inhibitory effects on HPA function [353]. There is also compelling evidence to suggest that sex hormones are important in the maturation of the immune system during fetal life [355]. The inherent differences in sex-dependent neuroimmune development are predominantly orchestrated by a surge of gonadal hormones unique to males, specifically occurring within a critical perinatal window that significantly impacts brain development [28].

Fetal testosterone exposure is one of several hypotheses that attempt to explain the male preponderance of NDDs, especially in ASD [145]. Fetal testosterone is involved in many aspects of development and may interact with neurotransmitters, neuropeptides, or immune pathways to contribute to male vulnerability. Gonadal hormones may also impart male-biased behavioral vulnerabilities to immune activation via microglial mitochondrial function and directly influence neurons, as well as oligodendrocytes, endothelial cells, and astrocyte functioning. McCarthy and Wright [352] review the role of microglia and astrocytes in directing brain masculinization. These authors further speculate that the natural process of brain masculinization puts males at risk of ASD by moving them closer to a vulnerability threshold, breached by refractory inflammation during critical periods of brain development [574]. Alternative hypotheses are provided by El-Ansary, Bhat, and Zayad [134], who speculate that higher ASD phenotypes in males compared with females could be attributed to the protective effect of estrogen, the higher diversity and predominance of probiotics in females, and the lower liability of females to develop leaky gut, neuroinflammation, and excitotoxicity. Kushak and Winter [298] discuss the bidirectional relationship between sex hormones and intestinal microbiota and speculate that sex bias in males may be associated with more significant changes in the intestinal microbiome than in affected girls. The sexually dimorphic prevalence of autoimmune disease for females [5, 102, 117, 289, 379, 390, 594] and ASD for males [145, 352, 574] remains one of the most intriguing clinical observations among both groups of these disorders. This raises the question of whether sex hormones could provide a bridge to understanding common etiologies of these conditions, in some neonates, occurring through differing gender-dependent mechanisms of pathogenesis.

ASD: From Biochemical, Immune, and Electrophysiological Correlates of Cognition, Sentience and Consciousness to the Biology of the Self

Moving on from the underlying biology of ASD, consideration can be given to linking across the levels at which ASD can be distinguished from neurotypicality, including pathophysiology (e.g., genomic vulnerability, toxicant-induced metabolic and microbiome dysfunction, and immune dysregulation) to conditions such as brain disease (e.g., encephalopathy), to higher levels of coordination that generate neuromotor, perceptual, emotional, cognitive, and social consciousness capacities. High-level processes of consciousness, including self-consciousness and processing of emotion in autistic individuals, have been researched from standpoints and in the context of a "*brain-centered*" neurocentric psychiatric disorder. From this hierarchical perspective, the fundamental perturbations of human consciousness associated with the ASD syndrome that we perceive directly with our perceptual capacities (and which are heterogeneous across the ASD spectrum) need to be linked more clearly to sets of alterations in underlying biology. However, partly due to a reductionist structuring of most "*brain disorder*" research, the process of identifying these linkages is essentially in its infancy.

We briefly review central and current neuroanatomical, neurofunctional, and neurocognitive theories of ASD as an integrated complement to neuroimmunological standpoints provided thus far. Moreover, based on the mounting evidence of the role of the immune system in the pathophysiology of ASD, we would endorse an expansion from primarily psychiatric and neurocentric perspectives to a broader framework that also includes (neuro)immunocentric, microbiome, and environmental underpinnings. This is not only to understand the pathophysiology of ASD, but also to incorporate components of higher-level cognition and sentience for individuals on the spectrum into comprehensive multiscale/multisystem perspectives. Such perspectives should not only consider the interactions of the nervous and immune systems with the host microbiome, but also their collective role as "*systems of relations*" with all other physiological systems of the body, at all biological scales (or different hierarchical levels of resolution) (Fig. 2), for a holistic explanation of the system functioning, regulation, or maladaptation. This would, in addition, potentially provide a framework for understanding and potentially approving existing as well as novel therapeutic modalities able to address the core symptoms of ASD. Such perspectives would also provide useful future directions to establish a comprehensive basis to achieve partial to full recovery of at least some individuals, especially children, on the spectrum.

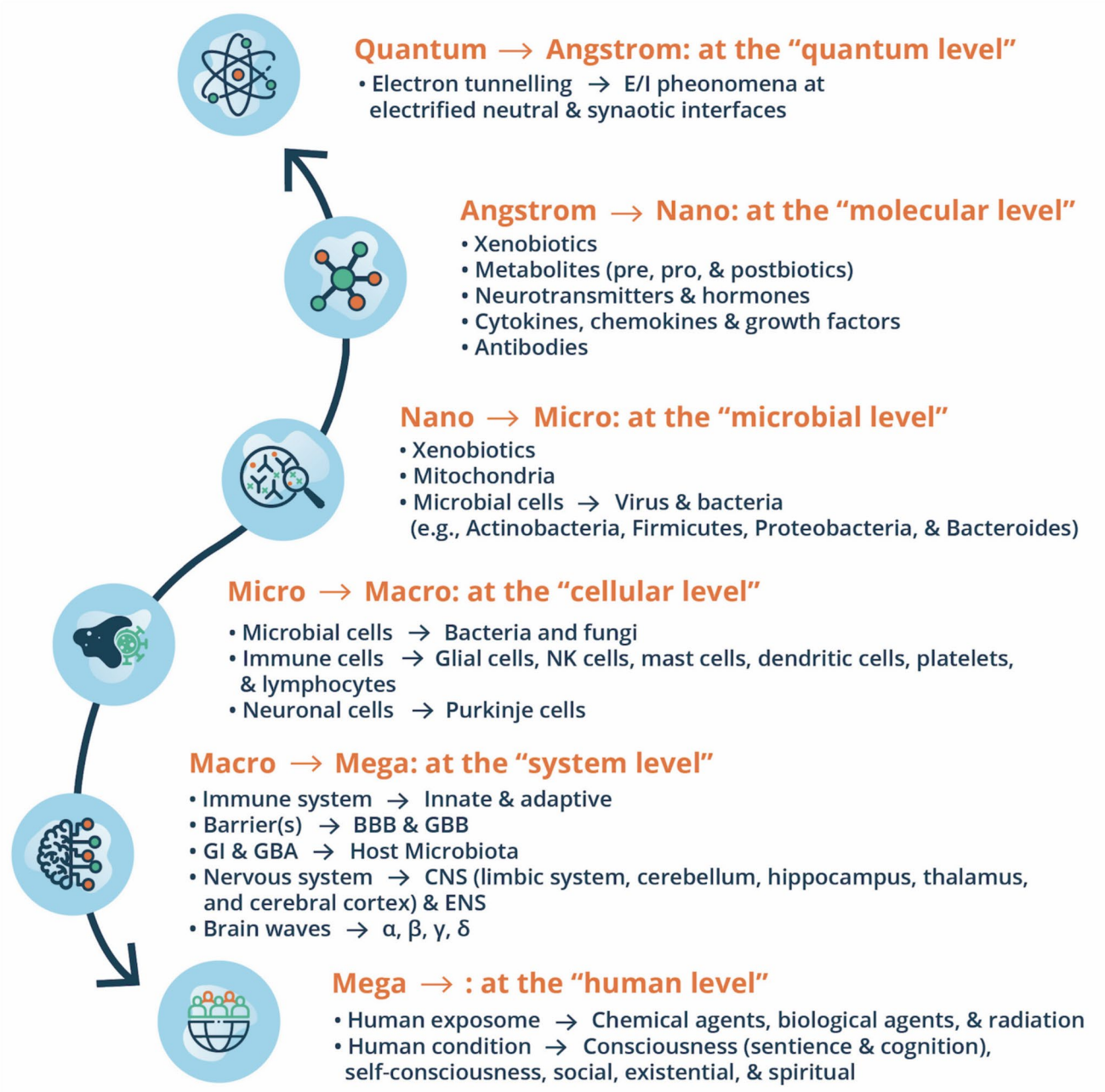

Fig. 2 ASD from different hierarchical levels of biological resolution

ASD From Underpinnings of Homeostasis/Allostasis & Sentience

The fundamental interplay between the nervous and the immune systems with the host microbiome to dynamically control physiological and psychological processes of homeostasis and allostasis cannot be overstated. Physically, every immune organ is innervated, and bi-directional communication between neural and immune systems at a cellular level is established in numerous physiological systems [332]. In addition, as highlighted by this study, the gut microbiome is in a persistent state of dysbiosis for some individuals on the spectrum. As elucidated in this review, the GBA and ENS are fundamental drivers of CNS homeostasis and brain plasticity and are therefore fundamental inputs to the development and maintenance of higher-level processes of consciousness, not only for healthy individuals but especially for those on the spectrum or with other neurological challenges.

The capacity for–and qualities of–feeling (or sentience) can be perceived as closely related to the capacity to

dynamically control the physiological processes of homeostasis and allostasis [441]. Pereira distinguishes between sentience and cognitive consciousness, with a specific emphasis and application to the medical sciences [421]. As part of this paradigm, sentience refers to feeling or sensation as distinguished from perception and thought or cognition. The physiological correlates of sentience are proposed to be the system underpinning the dynamic control of biochemical homeostasis and allostasis, interrelating with functions of emotions and the capacity to feel that are higher in the overall hierarchy of functions. In contrast, the correlates of cognitive consciousness are referred to as patterns of bioelectrical activity in networks manifesting in cognition and the capacity to think. Cognition, as part of this paradigm, is proposed to be principally correlated to E/I balance of the brain in the context of homeostatic synaptic plasticity [89] and "*metaplasticity*" [242]. Based on the paradigm presented by Pereira, cognitive consciousness depends on sentience, but not vice versa. Pereira's dynamic of sentience is adaptive, not restricted to the central nervous system (CNS) but composed of "*whole-body*" [422] interoceptive cycles that involve elaborate innervation of vital organs (e.g., the heart) [31] with their inputs from and outputs to the CNS and active striated motor with kinesthetic sensors. Pereira's main hypothesis is that cognitive consciousness depends on sentience, implying that more attention should be given to the neural correlates of sentience in therapy.

From Neuroanatomical to Neurofunctional Underpinnings of ASD

Through the examination of postmortem brain tissue specimens and in vivo analysis with advanced imaging techniques such as structural nuclear magnetic resonance imaging (MRI) [113], in the vast majority of cases, an immature autistic brain will display global and regional structural differences when compared to comparably aged non-autistic controls. Brain regions investigated in the context of ASD include the brainstem, cerebellum, hippocampus, limbic system, prefrontal cerebral cortex, thalamus, and white matter volume [46, 128, 217, 222–224, 494]. For high-level processes of consciousness, sentience, and cognition, there is a common distinction in neuropsychology between the limbic system as an emotional center and the associative prefrontal cortex as the seat of reason and self-consciousness. Khetrapal highlights the role of the amygdala in ASD and further explores the implication of the interaction of emotion with consciousness, and provides a framework for disturbed affective consciousness in ASD [281]. Baron-Cohen also proposes an "*amygdala theory of autism"* and presents plausible abnormalities of the amygdala as a cause of ASD based on a review of MRI studies [43].

Many of these early studies assumed a priori that brain anatomy was fixed, as per early assumptions that ASD was a congenital disease that irreversibly determined the state of the mind. However, with the emergence of a body of data documenting differences in autistic brains that were most likely of physiological origin–particularly neuropathological identification of neural and glial inflammation associated with enlargement of the areas of the brain, including cerebrum, that continue to grow and mature postnatally–the assumption of congenital origin came under question, since the processes of generating such changes are often associated with environmental etiologies including oxidative stress and neuroinflammation generated by noxious environmental exposures, including activation of glial cells [46, 271, 315, 377, 411, 522, 548]. Due to its neurodevelopmental character and the large phenotypic heterogeneity among individuals on the autism spectrum, the neurobiology of ASD is inherently difficult to describe, and much is still to be learned about specific neurobiological mechanisms driving atypical brain development. However, as elucidated by Ecker [132], it is important to note that the neuroanatomical differences are neither unique to nor necessarily causal for ASD. Instead, there is considerable overlap between the set of brain regions that mediate symptoms and, as also highlighted in this study, the neural systems underlying similar symptoms in other psychiatric and neurological conditions. We would endorse, as do Donovan and Basson [128], the performance of large-scale, longitudinal studies to determine the scale and incidence of anatomical differences, particularly during the development of the cerebellum, amygdala, and cerebrum (including both grey and white matter). Moreover, based on the mounting evidence of an immune component in some individuals with ASD and the putative role of the GBA in its pathophysiology, anatomical (volume, weight, and uniformity), network, and functional alterations should be considered neither the principal cause nor necessarily fixed in ASD but rather a correlate of disease in the context of a multifactorial and multidimensional/multiscale aetiology and pathogenesis [113] along with multifactorial environmental insult in the setting of genetic and genomic vulnerability. These types of influences may have the potential to evolve or even be deliberately influenced over time via interventions that modify the multifactorial contributors.

State-of-the-art functional and molecular imaging includes magnetic resonance spectroscopy imaging (MRS) and using nuclear radiotracers in positron emission (PET) and single-photon emission computed (SPECT) tomography to further provide insight into dynamic cellular processes in the brain of autistic individuals and offer higher resolution to decipher the role of atypical pathophysiology and environmental insult in its etiology and pathogenesis. This includes mitochondrial dysfunction and metabolic and oxidative stress. Cagnin, Gerhard, and Banati [79] briefly

outline the rationale for employing PET for imaging of activated microglia to detect in vivo inflammatory changes occurring in a variety of brain diseases and at different disease stages, and to monitor the progression of neuroinflammation as an in vivo marker of disease activity. Researchers note that while imaging of activated microglia with PET does not serve to override an a priori clinical classification, it does provide a generic measurement of disease location and progression in the clinical presentation of patients with neurodegenerative disorders. Giron and Mazzi [177] and Tillisch et al. [530] discuss PET imaging and agents that could be applied to study the dynamic interactions of the GBA. Researchers conclude that by combining the evaluation of symptoms, behavior, and brain responses to relevant stimuli, the use of neuroimaging provides a basis to move the focus of the study of brain–gut disorders to an emphasis on underlying neural and physiological networks, with more subjective outcomes playing, if anything, a secondary role.

Thomson et al. [529] review the literature of MRS studies measuring brain metabolites, including those involved in neural and glial integrity (e.g., N-acetyl aspartate (NAA), choline, myo-inositol), and oxidative stress (e.g., glutathione) in autism cohorts. The authors report significantly lower concentrations of GABA and NAA in ASD and speculate that lower concentrations of NAA in the limbic and prefrontal regions may be indicative of mitochondrial dysfunction. Zürcher et al. [603] and Li et al. [314] provide a systematic review of molecular PET and SPECT for adults and children with ASD. A clear single indicator of a specific "*chemical imbalance*" is unapparent since serotonergic, dopaminergic, glutamatergic, and GABAergic systems are all deemed critical in shaping the disturbed neural circuitry of ASD, with few studies providing neuroinflammatory perspectives.

A notable study is provided by Suzuki et al. [511] using PET. In this study, researchers investigated microglial activation and distribution in high-functioning autistic adults. Study results indicated increased binding in brain regions such as the fusiform gyrus, the orbitofrontal cortex, the cingulate cortex, the midbrain, and the cerebellum. Suzuki et al. [511] also endorse the need for multi-center and multimodal investigations to individualize and elucidate unique signatures and biomarkers of neurophysiological underpinnings and delineate biologically and clinically meaningful subgroups of ASD. On the other hand, there are also risks and health effects associated with the use of nuclear magnetic resonance diagnostic devices and radiotracers. For example, current safety standards do not account for synergistic effects of ionizing radiation and magnetic and electromagnetic fields [72]. In addition, to avoid motion artifacts, the sedation of some young participants is necessary. A careful risk/benefit evaluation must therefore be performed when planning the enrollment of children, especially before widespread clinical application [314].

ASD at the Level of Brainwaves & Synchronized Neural Activity

Thus far, after the historical introduction about early conceptions of autism, this paper has discussed a wide range of biological processes found to be different from "*normal*" in at least some subclasses of ASD. The question then becomes: how do we bridge the gap between these atypical underlying immune, host microbiota, metabolic, and other processes and the features of the higher-level phenomenology of ASD? One model suggests that such underlying processes alter or compromise brain oscillatory activity or "*brainwaves*" and their syntax, which can arguably be considered a fulcrum between the underlying tissue physiology and the manifest phenomena and alterations in outputs at higher levels of integration, including neuroanatomy, neurofunctional coordination, and consciousness.

Neuronal networks in several anatomical locations support oscillatory E/I activities and related synchronization phenomena in association with a wide range of cognitive and executive processes, with oscillatory bands that span from approximately 0.05 Hz or even lower to 500 Hz [78, 163] and categorized as delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–200 Hz) [486]. John [255] highlights the modulation and neuronal synchronization created by gamma oscillation, principally correlated to neural oscillations in cortical structures, the hippocampus, and the basal ganglia. Gamma band oscillations are deemed a necessary condition for awareness of stimuli and large-scale integration, or '*binding'* of local field potentials, which is crucial for perception, movement, memory, and emotion [190, 255]. Gallotto et al. [163] review intensifying evidence that cortical oscillatory signatures, for example, activity in the alpha-band, may index or even causally support conscious perception. Ward [566] reviews the thalamic dynamic core theory of conscious experience and the central importance of synchronized neural activity in corticothalamic circuits.

Neurodegenerative diseases, including Alzheimer's and Parkinson's, are associated with abnormal neural synchronization [543], and numerous publications report impaired gamma oscillations in schizophrenic patients in a variety of behavioral tasks [542, 544]. Guan et al. [190] highlight the susceptibility of gamma-band wave oscillations to disrupt CNS homeostasis. Buskila, Bellot-Saez, and Morley [77] and Oliveira and Araque [401] review and elaborate on mechanisms by which astrocytic Ca^{2+} signaling and glutamate clearance play an essential role in the regulation of the network activity and K + homeostasis, which ultimately would affect the neuronal excitability underlying network

oscillations, including cortical oscillations [50, 242]. These studies have provided a basis to further mine EEG data for inference of the progression of any neuroinflammatory pathologies early into the diagnosis of ASD, especially in neonates.

In comparison to studies of schizophrenia, the data on brainwave activity in autism are scarce and controversial [470, 542]. Uhlhaas et al. [542] review EEG studies detailing the potential role of neural synchrony in ASD and the relationship between neural synchrony and aberrant brain development in ASDs. Researchers highlight dysfunctional gamma- (e.g., [404]) and alpha- (e.g., [426]) band activity. In a recent study published in 2023, Santarone et al. [470] retrospectively reviewed 292 routine polysomnographic EEG tracings of preschool children (age < 6 years) with ASD. In 78.0% of cases, the EEG recordings were found to be abnormal, particularly during sleep. During wakefulness, most of the children (96.0%) did not display EEG alterations, while a minor percentage (4.0%) showed paroxysmal slowing and interictal epileptiform discharges or abnormal slow waves. Using magnetoencephalography, Kenet and coworkers [278, 279] report increased long-range feedforward connectivity and reduced long-range feedback as characteristic of functional connectivity abnormalities in ASD.

Alterations in abnormal neural synchronization, brain E/I homeostasis, and synaptic plasticity are vital for network stability and sophisticated processing of patterned inputs and cognitive functions [89]. In 2003, Rubenstein and Merzenich hypothesized that some forms of ASD might be caused by a reduction in signal-to-noise in key neural circuits (sensory, mnemonic, social, and emotional) [459]. However, the precise nature of such abnormalities is inconsistent across studies, and there is no consensus in peer-reviewed literature regarding how altered cortical structure relates to E/I balance or how altered neural oscillations relate to underlying pathophysiology [115]. Contributors to such phenomena could include altered brain homeostasis, oxidative stress, and neuroinflammatory cascades, which have been correlated by EEG data for NMDAR encephalitis [56] and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [307].

Routine EEGs are not recommended as a screen for epileptic discharges in current practice guidelines for children with ASD [512]. However, not only is there significant comorbidity between epilepsy and ASD [539, 558], but it is also the case that there are non-epileptic electroencephalographic correlates of ASD [415]. Screening EEGs for children not only with ASD but also normally developing children [512] could provide a safe, high-resolution, low-cost, and non-invasive diagnostic tool for wide-scale clinical application. In addition, it can provide a reference and benchmark if faced with clinical changes or when the patient develops into adulthood [260]. That said, the use of EEG to detect non-epileptiform abnormalities requires a level of sophistication that is not common, and in addition, most EEG studies are performed in non-shielded environments, where the pervasive presence of Wi-Fi and other sources of electromagnetic fields adds noise to EEG data that complicates interpretation, which has unfortunately discouraged EEG's use.

Further electrophysiological correlates of ASD are also provided by the auditory brainstem response (ABR) of developing neonates. ABRs are "*far-field*" (i.e., recorded from the scalp) reflections of neural potentials evoked by a brief auditory stimulus and represent the neuroelectric events in the cochlear end organ and brainstem pathways set in motion by the auditory response. Evidence from ABR studies suggests that prenatal maturation in the central auditory system far precedes other aspects of sensory-motor maturation [494, 497, 538], which in turn form the foundation of social interactions and communication. In a landmark study, Torres et al. [538] provide the basis for a digital screening biomarker to flag neurodevelopmental derailment in neonates, capturing the nonstationary and nonlinear nature of the neonatal data using ABR. In this pilot study, babies were followed over time, and researchers report that babies who go on to receive an ASD diagnosis show profound delays perinatally in the latencies of the ABR across all seven regions of the brainstem. A caution here is that we cannot assume the prenatal origins of all cases of autism, since exposures driving the autism onset may be postnatal, and the latency alterations may emerge later.

Neurocognitive Theories of ASD

Hill and Frith outline the three main neurocognitive theories of ASD as: (a) theory of mind (ToM) deficit, (b) weak central coherence, and (c) weak executive dysfunction [154]. ToM refers to the ability to understand the mental states and behavior of oneself and others [41]. Ploog discusses unresolved and critical issues surrounding ToM [427] and highlights the scientific "*conundrum*" of the "*unobservable*", the logical fallacy of circular reasoning and reification, the lack of neuroscientific correlates of ToM, and the role of language as a prerequisite for ToM. Indeed, speech and language have historically been conflated, and loss of speech in ASD doesn't always mean lack of language. For example, in a retrospective study of 31 adolescents and adults with ASD, with limited or no speech, Jaswal et al. [250] objectively developed and assessed literacy with an iPad game. As earlier discussed, researchers report that many autistic individuals who do not talk could learn how to spell or have already learned orthographic English conventions. Jaswal et al. further speculated that if they were given appropriate opportunities, individuals with ASD who lack verbal

communication would be able to learn to communicate by typing.

A characteristic of neurotypical information processing is the ability to draw together diverse information to construct higher-level meaning in context, or "c*entral coherence*" [200]. Individuals with ASD have been reported not to show the normal bias towards processing certain types of information at a global level, i.e., inefficiencies in global processing in combination with a greater propensity for detail-focused processing [155, 249]. Frith and Happe suggest that weak central coherence in autism may be most appropriately viewed as a preference for a particular cognitive style, rather than a form of deficit or impairment. "*Executive function*" is an umbrella term used to describe cognitive tasks such as planning, working memory, impulse control, inhibition, and shifting set, as well as the initiation and monitoring of action [229, 439, 591]. In an extensive review, Hill [230] acknowledges the complexity of investigating executive function in ASD. This would include the possible influence of IQ on executive performance in these groups, and the possibility of overlap between performance on tests of executive function in other NDDs that are likely to involve differences in the frontal lobes. Additionally, there are considerably contradictory findings of people with ASD and diminished executive function by laboratory measures, operational tasks, and ratings-based measures, especially in preschoolers with ASD [291].

As highlighted in this study, the leading causes of any cognitive impairment in ASD could involve neurological, immune, and gastrointestinal processes, which should account for environmental and nutritional influences both pre- and perinatal and perhaps even later. Given the critical importance of food to both basic survival and cultural interaction, Allen [15] introduced a ''*theory of food*'' (ToF) (analogous to ToM) to represent another complex network essential for normal cognition and in the context of neurocognitive adaptation. As part of this theory, Allen speculates that the evolved internal cognitive representation of our diets in our minds, like other complex cognitive abilities, relies on complex and overlapping dedicated neural networks that develop in childhood under familial and cultural influences. Implications of ToF, as highlighted by Allen, would be that cognitive activities related to food may be cognitive enhancers for maintaining healthy brain function in aging, with implications for neurodevelopmental disorders and ASD.

ASD & the Biology of the Self

From psychiatric perspectives, the ASD syndrome can be integrally understood to involve fundamental perturbations of human consciousness and self-consciousness. The first perceptual awareness of the human organism is evident in the neural integration and prospective, primary sensorimotor intentions of the second-trimester fetus [114], with self-consciousness emerging around the third year of life. Self-consciousness is a multidimensional concept that involves as much the awareness of one's own body and image as the recognition of oneself with awareness of one's own identity. Disorders of self-consciousness have been extensively researched in devastating neuropsychiatric disorders such as schizophrenia [549]. Like ASD, schizophrenia is a heterogeneous condition with no known or single specific etiology and is characterized by delusions, hallucinations, passivity phenomena, disordered thought processes, disorganized behavior, and cognitive deficit. Tordjman et al. [535] discuss self-consciousness disorders in schizophrenia and ASD, and how impairments of body-self can lead to impairments of self-other differentiation and its consequences on social communication, emotion, cognition, and empathy. Body-self impairments, for example, can be expressed through abnormal recognition of self-image in its physical dimension, and alterations of body experience are characterized by an experience of embodiment default. Authors highlight how ASD provides a model for exploring the nature of self-consciousness, requiring the ability to reflect on mental states and the awareness of one's own body and image as the recognition of oneself with awareness of one's identity. Frith and Happé highlight experimental studies of normal and abnormal development, suggesting that the abilities to attribute mental states to self and others are closely related [156].

From a philosophical standpoint, the characteristics of self/oneself recognition, specificity, and memory are shared only by the immune and nervous systems [246]. Although the mechanisms by which peripheral immunity may influence neuronal function are largely unknown, recent findings implicate its influence on cognitive capabilities, such as spatial learning and memory [601]. Filiano et al. [146] implicate adaptive immune dysfunction in social dysfunction and suggest a co-evolutionary link between social behaviour and an anti-pathogen immune response driven by interferon signalling. In 2002, Robertson elucidated an "*astrocentric hypothesis*" describing the essential role of astrocytes in consciousness and memory formation [451]. Pereira further elaborates on the potential connection between the immune system and conscience using a neuro-astroglia interaction model of mental activity [420]. Pereira also speculates on transitioning from a neurocentric to an astrocentric perspective for cognitive and sensory processing [419].

Costantini [96] provides perspectives on the biological link between bodily self-consciousness and the immune system [108], and Sánchez-Ramón and Faure [469] present a brain self-theory from an evolutionary biological perspective by analogy with the "*immune self.*" Researchers hypothesize that the distinction of self/non-self (internal/external) inputs

by the brain has a cellular basis similar to the immune self. With further expansion of the analogy to outline the postulates for archetypical autophrenic diseases involving the "*rupture of the self,*" such as schizophrenia and some forms of epilepsy, by extrapolating from the postulates that define autoimmune diseases. Bhat et al. [57] question if false inference at an immunological level alters the message passing at a psychological level (or vice versa) through a principled exchange between the two systems. Researchers also introduce the novel concept of "*neuroimmunological diaschisis*" and the possibility that a diaschisis of threat-avoidance may contribute to the overlap between psychiatric disorders, immunological hypersensitivities, and environmental influences and etiologies.

ASD and Biological Influences: A Two-Way Street

Placing the underlying physiological mechanisms and contributory environmental exposures that have been identified alongside the soaring rates over time, it is hard to avoid the conclusion that, from the biochemical/pathophysiological standpoint, ASD lies, at least for the most part, on the other side of various kinds of "*tipping points*", some perhaps yet biophysiologically uncharacterized, in the development of function that would represent a departure from the usual modes of brain homeostasis, which has been assumed to be, for the most part, permanent. From the perspective of ASD, the concept of "*tipping point*" refers to a critical threshold at which perturbations can shift a system into a new and different type of self-organization [489]. In most of this discussion, "*new and different self-organization*" has been tacitly assumed to be "*worse*." However, such an assumption paints an incomplete picture. First, many people with autism cherish their differences and have unusual or unique talents; there is no intrinsic reason to exclude either the possibility or the value of such eventualities. Secondly, environmental trauma can have both constructive and destructive roles. Nonetheless, there are many cases of partial to full recoveries from ASD, often achieved through extensive and independent effort on the part of the parents of autistic children, and they constitute a shift into a new and different type of organization in a different direction [211]. Comparable to ecological restoration, these efforts involve increasing healthy inputs, aggressively reducing the total load of destructive inputs, and seeking multiple levels of such interventions at which these hopefully constructive changes produce higher levels of integration across systems that potentiate the optimization of physiological and psychological processes of homeostasis.

Future Directions and Therapeutic Modalities for ASD

In the 1940 s, Leo Kanner attributed the etiology of ASD to the emotional unavailability of an affected child's mother [203]. While erroneous, this misconception originally and lastingly branded autism as a "*brain-centered*" psychiatric disorder, requiring psychiatric therapy and medications [98]. In addition, there have been nearly eight decades of a common scientific consensus on a "*static*" genetic etiology. Only in the last decades have researchers taken "*whole-body*" pathologies for neonates and children diagnosed with ASD [216]. Moreover, much like the issue of regressive autism, the evidence that ASD for some is not a lifelong condition is a relatively recent addition to the knowledge of ASD [211]. Isolated reports talking about children "*growing out of autism*" peppered the research literature in the 1980 s and 1990 s following some earlier initial interest in this topic [579].

A further limitation to our understanding of the ASD phenotype includes the reductionist paradigm, which views the human organism as a compilation of single targets for intervention and symptom alleviation without investigating its networks of interconnection. This paradigm has been central to modern healthcare models for over 150 years [531]. Although it can offer a useful first step in understanding complex systems, this paradigm also tends to oversimplify non-communicable diseases and neglect the heterogeneity of their contributing factors. This makes it not only an ineffective tool for sufficiently understanding and treating the complex nature of heterogeneous disorders such as ASD, but also an obstacle to the aspiration for the restoration of normal psychological and physiological well-being, which requires a non-linear dynamical systems approach. It is also clear that the non-linear, dynamic nature of the developing mind and the nervous and immune systems implies that potential deviations from typical development cannot be meaningfully captured with static, discrete, and linear parametric scales imposed a priori [537].

The debate continues as to the role of the immune system in ASD and whether the immune abnormality in ASD children is hyperactive or hypoactive [73] or whether that varies across the spectrum. In addition, the heterogeneous nature of ASD is reflected not only on a cellular level but also in whole-brain anatomy [411, 433] and disorders of the peripheral nervous systems [70]. The need to empower and accelerate precision medicine [206] and personalized medicine approaches has become apparent and essential for the efficacious treatment of ASD [433]. Moreover, modern therapeutic modalities usually take a reductionist

approach and often use medication under the guise of a "*magic bullet*" that can purportedly eliminate a disease's cause or symptom. This single-target perspective tends to neglect consideration of how these medications unintentionally impact the overall regulatory ability of the human organism from *"whole-body"* perspectives. A systems approach would instead suggest that medications should be designed to mimic, modulate, or promote the body's natural resolution mechanisms instead of interfering with them. Given the current healthcare and medical challenges, it is evident that the single-molecule, single-target paradigm does not provide the specificity and sophistication that a multitargeting model has the potential to offer [182].

ASD: Viewpoints from Environmental Exposomes, Omics Technologies & BrSYS Medicine

Critical windows of vulnerability include the period of maternal preconception exposures and of early pregnancy through childhood, where the establishment of the immune system, host microbiome, nervous system, and endocrine system can proceed in either a healthy or unhealthy direction depending on the exposome [336]. The window of vulnerability to fetal and neonatal neurodevelopment brings further specificity to the ASD phenotype. Recent research in various health disciplines demonstrates that deficiency and toxicity are common etiological determinants of ill health in the contemporary era [170]. The totality of this often-combined exposure and deficiency can be described as the "*human exposome*" and refers to the variety of external and internal sources, including chemical agents, biological agents, or radiation, from conception onward, over a complete lifetime [554]. The chemical exposome further captures the diversity and range of exposures to synthetic chemicals, dietary constituents, psychosocial stressors, physical factors, and their corresponding biological responses [551]. The exposome chemical space remains largely uncharted due to the sheer number of possible chemical structures, estimated at over 10^{60} unique forms [466]. Individual responses to current exposures and disease susceptibility are influenced by multiple factors, including genetics, genomic variants, epigenetics, physiology, and health status, which all involve changes in biological pathways; these factors may devolve from present or past exposures (i.e., from a legacy of prior exposures or even ancestral exposures) [297]. Krausová et al. [297] review the potential early-life impact of multi-factorial exposures that can influence the exposome during gestation or after birth and highlight the lack of large-scale studies covering a broad range of xenobiotics. Hertz-Picciotto et al. [226] also report that exposure levels in pregnant women and infants are largely unknown for most contaminants and that exposome-scale studies of large cohorts with broader chemical space coverage are scarce. Recently, Tartaglione et al. [24, 519] conducted a systematic review of 24 case–control studies and indicated several pollutants within the first three years of life to be significantly associated with the risk of NDDs. However, the authors acknowledge that further studies are also needed to more accurately characterize the risk of NDDs by applying an "*exposome approach.*"

The exposome can be seen as a complement to the genome [580] and encompasses all external and internal factors that influence functional proteins, metabolites, and gene expression [35, 445]. It would be vital to consider individual exposomes as a basis for precision medicine [265]. Our understanding of the role of chemical exposomes in chronic non-communicable diseases has advanced considerably with high-throughput molecular-omics techniques (metagenomics, proteomics, metabolomics) [228], which provide tools for a new emphasis on interdisciplinary research and personalized medicine for ASD. Maitre et al. [333] developed a blueprint of how multi-omics technologies can capture individual exposomes and establish signatures of disease. In a multi-center cohort of 1301 mother–child pairs, researchers associated individual exposomes of > 100 chemical, outdoor, social, and lifestyle exposures during pregnancy and childhood. Of note, pregnancy exposures were predominantly associated with child DNA methylation changes. In contrast, childhood exposures are associated with features across all omics layers. A review by Higdon et al. [228] elaborates on how distinct disease subtypes can be identified in ASD through the integration and analysis of clinical and multi-omics data.

The science of omics technologies and the immune system in particular can be described as immunomics [76]. Immunomics represents a bridge to elucidating the complex interactions between genes, environment, disease pathology, and the immune system. It also provides a new dimension to understanding immunopharmacology and immunotoxicology, with huge potential to impact disease etiology and pathogenesis, and for the development of novel and personalized therapeutics. Inflammasomes are multimeric regulatory proteins that form in the process of cytosis, in response to danger signals that perturb cellular homeostasis and are involved in inflammatory responses, including the production of proinflammatory cytokines and programmed pyroptosis and autophagy [472]. Inflammasome activity is closely associated with numerous human disorders, including autoinflammation, cardiovascular diseases, neurodegeneration, and cancer [158]. Saresella et al. [471] report that multiple inflammasome complexes are activated in ASD and suggest that therapeutic strategies targeting inflammasome activation could be useful in ASD. Considering the role of environmental insults in the etiology and pathogenesis of ASD, these early investigations provide a basis for a broad and multifactorial analysis of potential individual root causes of

ASD, and strategies for precision and personalized therapy. Further direction to benchmark individual exposomes on a diagnosis of ASD in children would provide high-resolution inference and be essential to diminish any further escalation of disease states in the first instance.

Complex systems are now recognized as demonstrating "*emergent*" behavior, with functions arising from the totality of system interactions, which are often nonlinear and stochastic. With the application of omics technologies, a systems biology approach [219] further provides a dynamic, multi-scaled, and "*whole-body*" approach to understanding ASD and the development of personalized therapeutics. This approach defines the human body as a complex biological network of interconnected components (molecules, cells, tissues, organs) [442]. This includes not only the immune system and the nervous system but also integrated systems of structure and maintenance. Goldman et al. [182] further extend the systems biology paradigm by merging it with regulatory and relevant empirical and treatment models, which they designate as "*bioregulatory systems medicine.*" BrSM is rooted in the idea that robust and effective solutions for complex diseases should optimize an individual's homeostatic and allostatic systems and their interactions across all biological systems and emerges in part as a response to the limitations of the reductionist perspective model [531]. A goal of BrSM would be to eventually develop biomarkers tailored to individual pathophysiological disease states that predict the health-disease continuum and allow for therapeutic interventions at the specific stage of a patient's disease. A BrSM approach also incorporates a multi-scale approach and would also emphasize the simultaneous and complex dynamic interactions of activities across all biological scales [188].

ASD Therapeutic Modalities: Standard of Care & State-of-the-Art

The common phrase "*children are not little adults*" is even more true in drug development, with infants, toddlers, and children placed in the special "*vulnerable population*" category [187]. Clinical development of therapeutics for ASD poses challenges regarding the identification of suitable endpoints, lack of biomarkers for progression, and regulatory considerations [175, 354]. Moreover, in nonverbal children or children with communication difficulties, side effects can be challenging to recognize, since children may exhibit different behaviors as side effects of the same therapeutic intervention [577]. Adverse events may also be camouflaged by comorbidities in individuals with ASD. On this basis, one must acknowledge the explicit need for an authentic human connection between practitioner and patient with ASD.

Doctors often use psychiatric drugs to address symptoms associated with ASDs. Risperidone and aripiprazole are both antipsychotics and are the only medications currently approved by the US FDA for the management of irritability in children with ASD [92]. Other classes of pharmaceuticals commonly prescribed off-label include stimulants (e.g., amphetamines and methylphenidates), selective serotonin reuptake inhibitors (SSRIs), α2-adrenergic agonist inhibitors (e.g., clonidine and guanfacine), and selective norepinephrine reuptake inhibitors [191, 299, 431]. West et al. [577] found that current pharmacological interventions used for ASD are only moderately useful in treating symptoms associated with ASD, such as attention, aggression, or repetitive movements, and they are only minimally effective in addressing the core deficits of ASD. All these classes of pharmaceuticals carry specific side effects and require professional long-term monitoring and management of adverse effects [18, 344, 541, 576]. As an example, King et al. [285] conducted a randomized clinical trial of 149 individuals with ASD who received either citalopram ($n=76$) or placebo ($n=76$) over the 12-week therapeutic period. Clinical results indicated no significant difference in the rate of positive response. Moreover, citalopram use was significantly more likely to be associated with adverse events, particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus. Additionally, the vast majority of psychiatric drugs display a high potential for physiological dependence [370, 371] which would make testing and use in pediatric populations challenging and potentially risky, if not redundant.

Biologics and immunosuppressive drugs are the primary treatment tools for autoimmune disorders, along with nonsteroidal anti-inflammatory drugs and SSRIs [180, 378]. Immunomodulating agents are designed to resemble antibodies, receptors, and other immunological factors. Emerging immunomodulating agents, including biologics, many of which were developed only recently, may provide additional treatment options for ASD subjects. However, published data on clinical trials in ASD subjects are scant [259]. The use of anti-inflammatory drugs in ASD has been reviewed by Hafizi, Tabatabaei, and Lai [194]. This included amantadine, an antiviral and anti-Parkinson drug; celecoxib, a nonsteroidal anti-inflammatory drug; the corticosteroid, galantamine, an acetylcholinesterase inhibitor; intravenous immunoglobulin; lenalidomide, a derivative of thalidomide; memantine, an NMDA receptor blocker; minocycline, a tetracycline-class antibiotic with anti-inflammatory effect; the antioxidant N-acetylcysteine; pioglitazone, an antidiabetic medication; riluzole, an inhibitor of presynaptic release of glutamate; palmitoylethanolamide, a fatty acid amide with neuroprotective, anti-inflammatory, and anti-nociceptive properties; pentoxifylline, a xanthine derivative that has an inhibitory effect on inflammatory responses; spironolactone, an antagonist for the aldosterone receptor; and topiramate,

an anti-epilepsy medication. The authors concluded that for all pharmaceuticals reviewed, there was a lack of rigorous clinical trials and very few successful replications that did address the core characteristics or associated symptoms of ASD. Moreover, all therapeutic agents exhibited low safety profiles, including serious systemic side effects.

First-line treatments for autoimmune encephalitis include aggressive pharmaceuticals, including intravenous steroids and immunoglobulin, plasma exchange, and immunoadsorption [485]. Efficacy studies with these drugs have yielded contradictory results, and each of these treatments can result in an immune-compromised state, putting the affected population at risk for serious infections or immune-related illnesses, malignancy, and cardiovascular conditions [329]. Clinical investigations using stem cell products are currently being applied for a wide spectrum of conditions using a variety of stem cell types [122]. Siniscalco, Bradstreet, and Antonucci [492] reviewed the therapeutic potential of hematopoietic stem cells (HSC) in ASD-related inflammation. Researchers conclude that although HSCs are attractive candidates for the potential restoration of ASD-related immune-mediated pathologies, concerns about several life-threatening risks were raised. These include abnormal trafficking of stem cells by the BBB into the CNS, resultant unintended consequences, the bidirectional nature of stem cells and the potential contribution to the inflammatory state, and the risk of graft-versus-host disease [312].

Other novel interventions for ASD include microbial transplant therapy (MTT). Indeed, in 2019, the FDA recognized microbial transplant therapy with a "*fast-track*" designation for ASD treatment [6]. MTT is a novel method to modify the microbial ecosystem in the GI tract of the hosts. MTT has indicated success in clinical trials with significant improvements in GI symptoms, autism-related symptoms, and gut microbiota ecology. Kang et al. [261] report important changes in gut microbiota at the end of treatment that remained at follow-up, including significant increases in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella*. However, such interventions are intrusive, can have adverse effects, and come with several limitations regarding the source and uniformity of donor feces. In addition, the use of adult fecal donors may correlate with the development of aging physiological function and unwanted immune reactions [88]. Besides, there is a lack of clinical data in children regarding many facets of MTT, such as the uniformity of transplant protocols used and the route of administration (oral, endoscopy, or enema).

ASD Therapeutics: Personalized & Precision Nutrition and Mind–Body Modalities

The maxims of "*let thy food be thy medicine"* attributed to Hippocrates (*circa* 400 BC) and '*you are what you eat'* by Jean Anthelme Brillat-Savarin (in 1826) remain as pertinent today as they were then. In the contemporary era, research into these bioactive natural products originating from medicinal plants, fungi, and microorganisms is also based on ancient ethnopharmacological (including entheogenic) human practices [367, 590]. Real-world evidence has provided ample verification from parents of children with ASD and clinicians of the utility of food and diet for the treatment of symptoms and sporadic reversal of the core symptoms of ASD [85]. These approaches principally involve an adjustment in dieting habits that begins with the removal of all ultra-processed foods and the encouragement of organic and whole-food diets. Indeed, the essential role of nutrition in optimizing, promoting, and recovering mental health is only now becoming recognized within medical practice and the scope of practice in psychiatry [460]. Peper and Shufor [416] coined the term "*grandmother therapy assessment*", in a recommendation that diet and nutritional deficiency be the first line of assessment of ASD and ADHD. GI disorders in ASD and their treatment through nutritional therapy may also provide paths for modulating the expression of social and behavioral symptoms through the GBA. This includes not only the application of foods rich in probiotics [480], but also direct administration of prebiotics, as well as postbiotics [597]. The latter provides strategies to support natural gut healing and a shift in GI homeostasis from potentially pathogenic to beneficial and congenital microbial ecologies or, at least, to restore gut eubiosis. Indeed, GI microbiome restoration would be a prerequisite to the successful amendment of inflammation processes identified in any chronic disease [323, 326]. van den Brink et al. [71] further elaborate on strategies to (re)gain inflammatory flexibility by regular mild metabolic triggers through perspectives of trained immunity, hormesis, and pro-resolution.

Modulating the neuro-immune-microbiome axis with "*full-spectrum*" functional foods and botanical plant-based medicines further provides a multitargeting paradigm and allows for a synergistic or "*entourage effect.*" The "*entourage effect"* essentially refers to the interaction of not only primary and secondary therapeutic agents (e.g., alkaloids, pre- and postbiotics, antioxidants, and microbial communities living in fermented foods) shown to have therapeutic potential, but also myriad secondary metabolites in the "*nutritional dark matter"* in the "*foodome*" [448, 479, 590]. Animals generally avoid these potentially toxic molecules, but our hominid ancestors elected to selectively consume foods rich in secondary metabolites [310] (i.e., polyphenols, flavonoids, carotenoids, phytosterols, polysaccharides, triterpenoids, tannins, saponins, and ash) as a means of complementing their nutrition and which later formed the basis of natural and omnipresent archaic medicine practices and folklore. Wellness and therapeutic metabolites found in food and botanicals when taken in their natural matrix are

generally safe even for chronic consumption, with extremely low toxicity, presenting ease in uptake or breakdown by the body, having low retention, and presenting low potential for physiological dependency [583].

Despite considerable interest and real-world evidence for the utility of dietary interventions for ASD, no consensus exists regarding optimal nutritional therapy, while there is much controversy regarding its effectiveness [125, 153, 263, 269, 303, 373]. As for pharmaceutical interventions, the lack of consensus is unsurprising, considering the heterogeneous nature of ASD. This further emphasizes that there is no "*one-size-fits-all*" and that the need for a precision and personalized medicine paradigm that goes beyond the modern reductionist approach, through the application of multi-dimensional, multi-disciplinary nutritional therapy, is strong. One paradigm to address current pitfalls for successful nutritional intervention in ASD could be through the convergence of nutrition science with omics technology, or "*nutrigenomics*" [402] (Fig. 3). The integration of nutritional systems with gene and protein expression profiles and metabolic fingerprints allows a more extensive analysis of the individual response to any nutritional intervention [33]. *"Nutrigenomics"* provides a more global, comprehensive understanding of how food components influence health status [33] and new opportunities oriented toward personalized interventions [33]. A few studies of transcriptomic, proteomic, and metabolomic studies have demonstrated the ability of functional foods and their bioactive components to fight against oxidative damage [375] and to modulate the underlying dynamics of low-grade chronic, systemic inflammation, impaired metabolic flexibility, and dysregulation

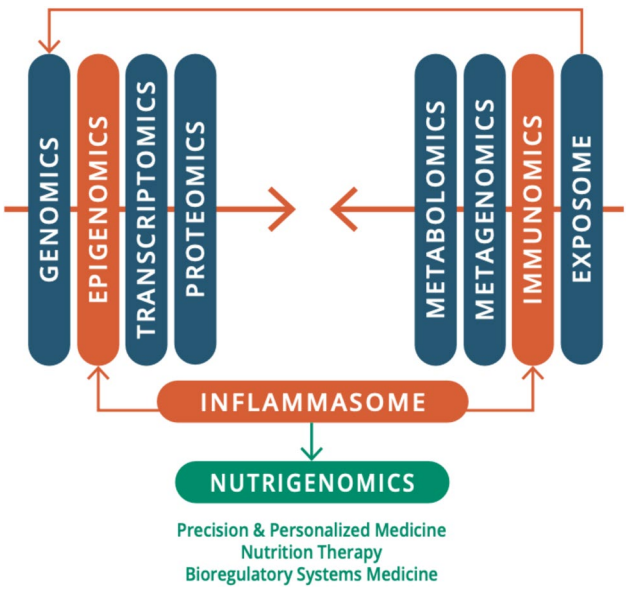

Fig. 3 Omics; nutrigenomics and bioregulatory systems medicine for ASD

[81]. Indeed, although the concept of combined "*omics*" (Fig. 3) is an interesting conceptually, it remains theoretical, and much work will be needed to develop such a platform as a standard of care in the clinic.

Moving along from "*body-mind*" modalities, "*mind–body*" modalities have also been endorsed by health practitioners active in the field, and there is modest clinical evidence supporting their efficacy for outcomes such as social communication, cognitive functions, and anxiety [12, 239]. Non-pharmacological interventions that are standard of care include cognitive and behavioral therapies (CBT) to address issues of anxiety for children with ASD [505, 585] and to promote autonomy and emotional well-being [365]. CBT helps strengthen cognitive skills, such as mental flexibility and problem-solving, which are essential for an independent and fulfilling life [365]. Also of note, it has been speculated that approximately 90% of vagal fibers between the gut and brain are afferent, suggesting that the brain is more of a receiver than a transmitter concerning brain-gut communication [54]. Nonetheless, this still establishes the role of non-pharmacological "*mind–body*" interventions for the restoration of normal neuro-immuno-microbiota functioning for individuals with ASD. At the very state-of-the-art, Baniel et al. [36] provide a theoretical foundation for the application of the Feldenkrais method and Baniel Method® NeuroMovement® intervention modalities with children and adults experiencing diverse motoric, cognitive, and social challenges. These methods leverage neuroplasticity through the utilization of movement, through a dance-like dyadic process of self-discovery that mimics the spontaneous, organic way typically developing children play, learn, and grow. This therapeutic modality would also exemplify the application of sentience [422] to influence and remedy higher-level processes of self-consciousness and cognition, and to improve social interactions for individuals with ASD.

Other cutting-edge non-pharmacological technologies include breathwork training [10, 366]. The use of conscious breathing practices for physical, psychological, emotional, and spiritual healing has a long and varied history [148]. However, there has been little work to bring these practices into a coherent and unified form that contributes to the field of body psychotherapy [553]. Overall, research findings indicate that breathwork may be efficacious for treating anxiety, depression, and PTSD [10]. Physical benefits of breathwork can be summarized as improving immune function; regulating arousal; decreasing sinus problems; balancing hormones, enzymes, neurotransmitters, and brainwaves; stabilizing blood gasses; promoting digestion, circulation, and proper organ function; facilitating waste metabolism, aligning posture, decreasing muscle tension; and increasing motility, mobility, and movement efficiency [17, 34, 87, 553]. Despite preliminary evidence for breathwork's efficacy in treating common psychological distress, more research is

needed to evaluate its utility for treating symptoms and core deficits of ASD [17, 34, 87, 553].

Concluding Remarks

The explicit role of environmental (xenobiotic) insult in the etiology and pathogenesis of ASD has been speculated upon for over half a century and highlighted here. Chronic or acute xenobiotic activation of the immune system would trigger self-reinforcing disease processes through failed shut-off of stress-responsiveness. ASD, therefore, is an example of a situation that emerges as things "*go beyond the tipping point*" at various vulnerable states of neurological and immunological development. As highlighted by this review, the complex pathophysiology and heterogeneous ASD phenotype are hypothesized, for some individuals with ASD, to be related to the deregulation of the immune system. This raises the question for some individuals diagnosed with ASD of whether the manifestation of immune cell pathology and immune system dysregulation is truly involved in the pathogenesis, or whether they are epiphenomena of the disorder; and whether their brain is truly and intrinsically electrochemically "*defective*" or instead biochemically "*obstructed*"? In support of the latter model, recently D´Adamo et al. [104] provided a case report of the reversal of autism symptoms in one of two dizygotic twins, each living with a different parent, where reversal occurred only in the child who received a personalized lifestyle and environmental modification approach. These findings and other published cases of ASD reversal are encouraging. We would endorse more dialogue between parents, clinicians, and academics, with further documentation of regression and recovery. In addition, we would also endorse more research to take a "*bottom-up/middle-out/top-down*" approach to address the problem of how to explain the transmission of immune/biochemical/metabolic/bioenergetic perturbations (bottom) into neuro-immuno-biochemical-metabolic-bioenergetic synchronization and coherence (middle) and thence into neurocognition/behavior/social functioning (top) for individuals with ASD. A crossover of ASD pathophysiology with autoinflammatory and autoimmune conditions further provides a novel hypothesis for understanding the pathogenesis of ASD. Moreover, omics and immunomics could provide game-changing platforms to elucidate the complex interactions between genes, environment, disease pathology, and the immune system, leading to ASD phenotypes and the development of safe and effective personalized therapeutic solutions that address the core symptoms of ASD. Indeed, a key takeaway of this study would be to highlight the primary need for a multiscale, multisystem, individualized intervention approach to helping people with ASD. In addition, as such a program begins to mature, we would also endorse the design and implementation of collaborative research infrastructures to capture cognitive/emotional/social/consciousness outcomes and account for the full range of hierarchical levels of biological resolution in the people receiving these integrated treatments.

In 2009, Plotkin, Gerber, and Offit made the bold statement that: "Autism is not an immune-mediated disease. Unlike autoimmune diseases such as multiple sclerosis, there is no evidence of immune activation or inflammatory lesions in the CNS of people with autism" [428]. Perspectives, theories, and scientific and clinical research provided in this study are in stark contradiction to the statement expressed above. In addition, after reviewing the incredibly complex neuro-immuno-microbiota interactions implicated in clinical research, we believe that only once we understand that ASD is not genetically inevitable or a genetic tragedy but an environmental and physiological catastrophe, will we truly be able to grasp and address the root causes of the dramatic rise in its prevalence. Indeed, scientific evidence presented here would suggest that people with ASD are the "canaries in the coal mine" – that is, they are the most susceptible among us who are affected first by problems that might eventually reach us all [383]. Moreover, it is quite plausible that this catastrophe goes beyond ASD. The rise of ASD may well to a significant extent evolve, or emerge, from overlapping vulnerability pathways associated with systemic problems of other chronic diseases [572]. The point henceforward becomes not just to support and seek full recovery for those diagnosed with ASD, but also to forthrightly address how we as individuals, families, communities, and society in the contemporary era can most effectively protect future generations.

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Declarations

Competing interests The authors declare no competing interests.

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