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TOPICAL REVIEW

Dysregulation of neural tube vascular development as an aetiological factor in autism spectrum disorder: Insights from valproic acid exposure

Jorge Manzo, María Elena Hernández-Aguilar, María Rebeca Toledo-Cárdenas, Deissy Herrera-Covarrubias and Genaro A. Coria-Avila

Instituto de Investigaciones Cerebrales, Universidad Veracruzana, Xalapa Ver, México

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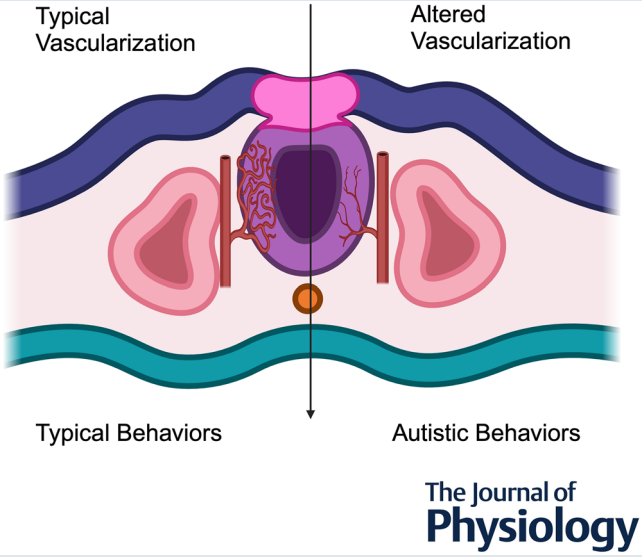

Abstract figure legend Relationship between neural tube vascularization and behavioural outcomes. This figure illustrates the proposed link between neural tube vascularization and behavioural development. The neural tube is divided by a central arrow, showing two pathways: typical vascularization on the left and altered vascularization on the right. On the left, typical vascularization is shown to result in typical behavioural outcomes, highlighting the importance of normal vascular development. On the right, reduced vascularization is associated with autistic traits, suggesting that compromising vascularization during neural tube development may contribute to atypical behavioural outcomes. Created in BioRender. Manzo, J. (2024) https://BioRender.com/l21m980.

Jorge Manzo is a leading professor and principal investigator in the Neurobiology of Autism Laboratory, where he focuses on uncovering mechanisms underlying neurodevelopmental disorders, particularly autism spectrum disorder. His primary research interest lies in designing and implementing strategies to stimulate brain plasticity through enriched environments. These interventions are aimed at enhancing cognitive and behavioural functions in affected individuals by promoting adaptive neural changes. Dr Manzo's work emphasizes the potential of non-invasive, environmental modifications to improve behavioural outcomes, with the goal of translating findings into practical approaches for therapeutic support in autism.

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Abstract Autism spectrum disorder (ASD) is a prevalent neurodevelopmental condition affecting a substantial number of children globally, characterized by diverse aetiologies, including genetic and environmental factors. Emerging research suggests that neurovascular dysregulation during development could significantly contribute to autism. This review synthesizes the potential role of vascular abnormalities in the pathogenesis of ASD and explores insights from studies on valproic acid (VPA) exposure during neural tube development. VPA, a widely used antiepileptic drug and mood stabilizer, crosses the placental barrier and impacts the developing fetal brain. Studies indicate that VPA disrupts normal angiogenesis by reducing the expression levels of vascular endothelial growth factor A (VEGFA) and its receptors, and purinergic signalling, which are crucial for both vascular and neural development. Such disruptions may lead to abnormalities in neuronal migration and pathfinding, potentially contributing to the neural and behavioural manifestations of ASD. Thus despite the relatively limited findings, improper vascularization of the neural tube appears to be a contributing factor in the pathogenesis of ASD, as also suggested by VPA studies. Integrating these insights, it is hypothesized that vascular factors should be considered in the aetiological analysis of idiopathic autism.

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Corresponding author J. Manzo, Instituto de Investigaciones Cerebrales, Universidad Veracruzana, Av. Luis Castelazo s/n, Col. Industrial Animas, Xalapa, Ver 91190, México. Email: jmanzo@uv.mx

Introduction

Autism spectrum disorder (ASD), commonly referred to as autism, is a complex neurodevelopmental condition characterized by atypical behavioural manifestations that emerge in early childhood. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (American Psychiatric Association, 2013), ASD is defined by two primary behavioural domains: deficits in social communication and interaction, and the presence of repetitive and restrictive behaviours. Each of these domains encompasses a range of specific behavioural patterns, highlighting the heterogeneity and complexity of ASD. Thus deficits in social communication and interaction can manifest as difficulties in making eye contact, challenges in understanding and using non-verbal communication and struggles with forming and maintaining relationships (Qin et al., 2024). Repetitive and restrictive behaviours include a preference for routines, repetitive movements such as hand-flapping and intense focus on specific interests (O´Loghlen et al., 2024).

Although considerable advancements have been made in delineating the neural underpinnings of ASD (Sato et al., 2023), a growing body of research suggests that abnormalities in the brain's vasculature may also contribute significantly to the disorder's pathophysiology (Ouellette et al., 2024). The brain's vasculature, integral to maintaining cerebral blood flow and supporting neural function, has been implicated in a variety of neurological and psychiatric conditions. In the context of ASD neurovascular dysregulation may influence neural development and connectivity, potentially contributing to the behavioural and cognitive symptoms observed in affected individuals.

Here, we propose that studies involving valproic acid (VPA) could enhance our understanding of neurovascular dysregulation as a potential trigger for ASD. It has been known for decades that fetal exposure to VPA in humans significantly increases the risk of developing autistic traits (Moore et al., 2000). Building on this foundation Patricia Rodier's research investigated the link between fetal VPA exposure and autism in rats (Rodier et al., 1996, 1997), establishing an animal model that has become pivotal for autism studies (Ingram et al., 2000; Reynolds et al., 2012). This model has since been extended to other species, including zebrafish, broadening our insights into the aetiology of autism (Camussi et al., 2024; Velázquez-Landa et al., 2023). The teratogenic effects of VPA are particularly related to the timing of neural tube closure, a critical period when vascularization is underway. A proposed mechanism underlying this involves an increase in purinergic receptors (Babiec et al., 2022), which compromises processes essential for both neural tube development and vascularization (Burnstock & Ulrich, 2011). These findings suggest that VPA-induced neurovascular disruptions during critical developmental windows may provide key insights into the mechanisms underlying ASD, highlighting the importance of vascular contributions to neurodevelopmental disorders.

Neurovascular development

The development of brain vasculature is an intricate process that involves the simultaneous growth and

interaction between the nervous and vascular systems. This complex process begins in the early stages of embryogenesis and continues throughout an individual's lifespan, underscoring its critical importance to overall brain health and function. During embryonic development the precise patterning of neurovascular structures is essential for the formation of functional neural circuits and the establishment of an extensive network of blood vessels that support the rapidly growing brain (Flamme et al., 1997; Risau, 1991). This process ensures that neurons receive the necessary oxygen and nutrients while also facilitating the removal of metabolic waste products. According to Ouellette and Lacoste (2021), the brain's development and function rely on several key vascular components: an appropriate vasculature, a functional blood–brain barrier (BBB) and the proper regulation of cerebral blood flow. The vasculature must be meticulously organized to meet the metabolic demands of the brain, whereas the BBB plays a critical role in maintaining the brain's microenvironment by selectively allowing substances to pass while protecting neural tissue from harmful agents (Patabendige & Janigro, 2023).

In the early twentieth century researchers began to investigate the development of neurovasculature in chick embryos and rodent models. Their pioneering studies revealed that the central nervous system (CNS) does not contain intrinsic vascular precursor cells. Instead blood vessels originate in the perineural vascular plexus and subsequently invade and ramify within the neural tissue over time (Bautch & James, 2009; Strong, 1964). The process of vascular invasion and branching within the CNS is meticulously orchestrated by various signalling mechanisms, including those emanating from radial glial cells. These glial cells play a crucial role in guiding the growth and ramification of blood vessels, ensuring that the developing brain receives an adequate blood supply. The interplay between blood vessels, glial cells and neural tissue forms a sophisticated structure known as the neurovascular unit (Fig. 1). The neurovascular unit not only supports neuronal function but also contributes to the formation of the functional BBB (Lok et al., 2007). The proper development and function of this unit are critical for brain homeostasis and function. Disruptions in the development or function of the neurovascular unit can have profound implications for neurodevelopment. For instance, aberrant signalling pathways or environmental insults during critical periods of development can result in faulty neurovascular interactions, potentially contributing to the pathogenesis of conditions such as ASD. Early impairments in these vascular networks lead to neurodevelopmental anomalies, as endothelial dysfunction has been linked to atypical behaviour and brain metabolism in ASD (Ouellette et al., 2024). Even genetic factors, such as microdeletions in the 16p11.2 region, can result in endothelial dysfunction, impairing angiogenesis. This is observed in approximately 2% of individuals with ASD and is associated with mitochondrial dysfunction in endothelial cells and alterations in glucose metabolism (Béland-Millar et al., 2023; Ouellette et al., 2020). Among these critical periods is the proper development of the neural tube and its vascularization, which is essential for normal CNS formation (Ouellette et al., 2024). This review synthesizes the potential role of vascular abnormalities in the pathogenesis of ASD and explores insights from studies on VPA exposure during neural tube development.

The neural tube

After fertilization the zygote undergoes a series of rapid mitotic divisions known as cleavage, resulting in the formation of multiple smaller cells called blastomeres. These blastomeres continue to divide and compact, eventually forming a structure known as the blastocyst (Pedersen & Burdsal, 1994). The blastocyst comprises an outer layer of cells called the trophoblast, which will contribute to the formation of the placenta, and an inner cell mass that will develop into the embryo. As the blastocyst implants into the uterine wall, significant surface changes occur, marking the beginning of the next critical phase of development. One of the first notable changes is the formation of the primitive streak, a structure that appears on the surface of the embryo and serves as a key organizer of embryonic development. The appearance of the primitive streak initiates the process of gastrulation, during which the single-layered blastula is reorganized into a three-layered structure known as the gastrula (Sadler, 2005). The three distinct germ layers

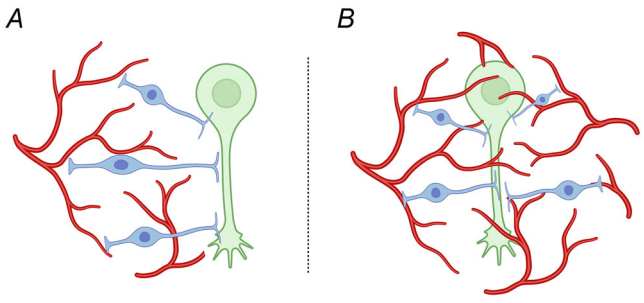

Figure 1. The neurovascular unit
A, This complex is composed of the perineural vascular plexus (blood vessels), radial glial cells (in blue) and nervous tissue (in green). Together these components form an intricate network essential for supporting neural development. *B*, Signals originating from the radial glial cells guide the growth and branching of blood vessels, initiating the vascularization process within the developing nervous system. These signalling mechanisms ensure that the neural tissue receives an adequate blood supply, which is crucial for providing oxygen and nutrients during early neural development. Created using BioRender. Manzo, J. (2024) https://BioRender.com/v76t810.

– ectoderm, mesoderm and endoderm – each give rise to specific tissues and organs in the developing embryo. The ectoderm, the outermost layer, differentiates into two primary structures: the neural plate and the surrounding cells that will become the epidermis. The focus of interest here is the development of the neural plate.

Time-lapse video recording techniques have been instrumental in documenting the developmental phases of the neural plate in *Xenopus* embryos (Keller et al., 1992). Initially the neural plate presents a broad and short configuration. This is followed by a dynamic process involving convergence, or mediolateral narrowing, along with antero-posterior lengthening, marking a significant phase of morphological transformation. These morphological changes are driven by a complex interplay of signals, such as Wnt proteins (Andre et al., 2015), and gene expressions originating from the endoderm, such as Hesx1 (Matsuda & Kondoh, 2014), which are crucial for the early stages of neural plate development (Esmaeli et al., 2024; Thomas & Beddington, 1996). The signalling mechanisms are so precise that they result in distinct developmental trajectories for the anterior and posterior sections of the neural plate. Each region responds to unique sets of transcription factors and enhancers that regulate gene expression, thus dictating the specialized functions that emerge across the neural plate (Kondoh et al., 2016). This differentiation of the neural plate into various regions underpins the formation of specialized neural structures and is fundamental to the subsequent development of the CNS.

Once the neural plate has formed, the next critical stage in embryonic development is its transformation into the neural tube, a process known as neurulation (Fig. 2). This fundamental morphological transition, which converts the flat neural plate into a tubular structure, is pivotal for the formation of the CNS (Greene & Copp, 2009; Sadler, 2005). Neurulation begins with the elevation of the neural plate's lateral borders, forming the neural folds. This initial shaping is facilitated by the proliferation of cells in the underlying mesoderm, which provides structural support and signalling cues essential for this upward folding (Stern, 2024). After the rise of the neural folds, the process proceeds through two distinct mechanical steps. The first step involves furrowing, which includes the formation of hinge points along the neural plate. These hinge points serve as areas around which the folds can bend inward. The second step, folding, occurs primarily at the mid-line hinge points and leads to the elevation and convergence of the neural folds towards the centre line. As the folds meet at the mid-line, they begin to fuse, initiating the closure of the neural tube. This fusion starts at specific points and progresses bidirectionally in a zipper-like fashion, both cranially and caudally. The completion of this closure results in the formation of the neural tube, which initially remains open at both ends, these openings known as the cranial and caudal neuropores. Typically the cranial neuropore closes first, followed by the closure of the caudal neuropore. The complete sealing of the caudal neuropore marks the culmination of primary neurulation (Frith et al., 2024). After primary neurulation secondary

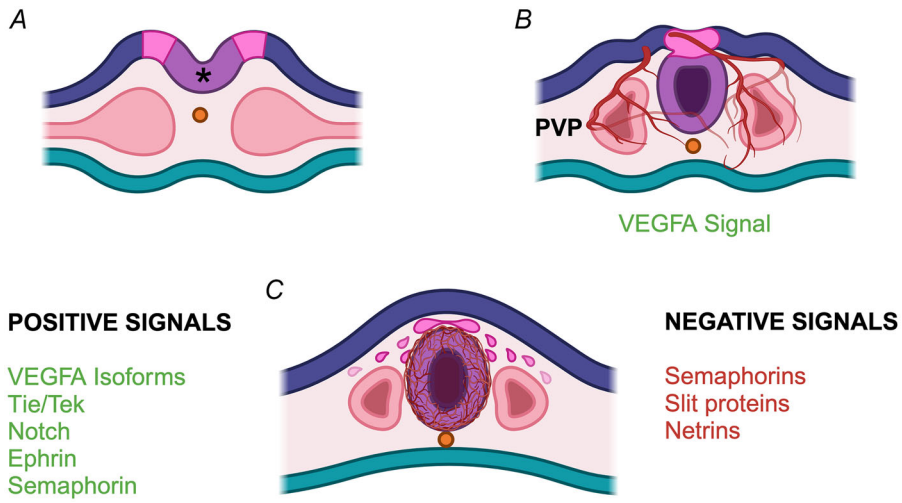

Figure 2. Vascularization of the neural tube
A, In the early stages of development, the neural tube remains avascular. *B*, A perineural vascular plexus forms around the neural tube, releasing vascular endothelial growth factor A (VEGFA) as the primary positive signal to stimulate further vascularization. *C*, A complex interplay between positive (in green) and negative signals (in red) regulates the ingression of blood vessels into the neural tube at specific locations, ensuring a balance between proper vessel formation and neural tube development. *, neural tube; PVP, perineural vascular plexus. Created using BioRender. Manzo, J. (2024) https://BioRender.com/c16o910.

neurulation begins, focusing on the development of the structures in the future spinal region. This phase involves the aggregation and transformation of a medullary cord into a tube through a process distinct from that seen in the cranial regions, highlighting the complexity and regional specificity of neural tube development (Choi et al., 2022).

Vascularization of the neural tube

Initially, the neural tube is avascular, lacking blood vessels until it reaches a certain thickness. The vascularization process then begins with the recruitment and assembly of a perineural vascular plexus around the neural tube. This plexus emits signals that attract angioblasts and organize the vascular network. It is suggested that vascular endothelial growth factor A (VEGFA) acts as a primary signalling molecule guiding the formation of these blood vessels (Hogan et al., 2004). Although VEGFA plays a critical role in neural tube development by regulating blood vessel ingression, this process involves a complex network of additional signalling pathways (Fig. 2). These include various VEGFA isoforms (VEGF121, VEGF165 and VEGF189), the Tie/Tek receptor complex, Notch proteins, Ephrin/Eph receptor interactions and the semaphorin/neuropilin/plexin pathway (Hogan & Bautch, 2004; James et al., 2009).

The presence of different VEGFA isoforms, such as VEGF121, VEGF165 and VEGF189, influences blood vessel formation, sprouts along the neural tube to promote blood vessel formation in specific areas and induction of vessel ingression points (James et al., 2009). The Tie/Tek receptor complex plays a crucial role in endothelial cell proliferation, survival, migration and their organization into functional blood vessels (Dumont et al., 1995). Notch signalling regulates angiogenesis and the maturation of vascular structures, ensuring adequate blood supply and maintaining vessel integrity (Tefft et al., 2022). Ephrins and their Eph receptors play a key role in early angiogenesis by differentiating endothelial cells into arterial and venous structures, facilitating their migration to organize the vascular network and regulating angiogenesis and haemodynamic functions to maintain vascular integrity (Hashimoto et al., 2016). Semaphorins, through interactions with neuropilin and plexin receptors, regulate the interplay between the vascular and neural systems during development by guiding axon growth and direction, ensuring they reach their appropriate targets and contribute to the establishment of a functional neurovascular unit (Lu et al., 2021). Besides the positive signals from molecules like VEGFA, there are negative cues that inhibit vessel ingression in certain areas (Fig. 2), essential for proper neural tube development (James et al., 2009). These negative cues include semaphorins, which inhibit endothelial cell migration in areas where new vessels are not needed and prevent sprouting to maintain blood vessel stability (Lu et al., 2021); slit proteins, which inhibit endothelial cell migration and induce repulsive signals for axon guidance (Yadav & Narayan, 2014); and netrins, which suppress angiogenesis and promote the repulsion of endothelial cells (Bouvrée et al., 2008).

The first functional circulation within the neural tube is established around the future motor column, where vascular sprouts from the perineural vascular plexus invade the neural tissue. This resulting vascular pattern forms a network that supports the developing neural tissue, ensuring adequate oxygen and nutrient supply as the CNS matures (Kurz, 2009). Concurrently, during the elevation and fusion of the neural folds to form the neural tube, cardiac neural crest cells (CNCs) arise from the dorsalmost tip of the neural tube. These CNC cells migrate to contribute to cardiovascular development, differentiating into various cell types, including smooth muscle cells and endothelial cells, crucial for heart development and the formation of the vascular system (Yamagishi, 2021).

The puzzle: Autism, VPA and neural tube vascularization

Autism is classified into two main types: idiopathic and secondary ASD. Idiopathic ASD accounts for approximately 85% of cases and refers to instances where no specific cause can be identified. Secondary ASD, comprising about 15% of cases, occurs when an identifiable underlying condition or pathology, such as genetic factors, teratologic agents, infections or inoculations, is present (Casanova et al., 2020; Persico & Napolioni, 2013; Rodier & Hyman, 1998). Among teratologic agents VPA has been extensively studied due to its strong association with autism. VPA is a short-chain fatty acid widely used in medical practice as an antiepileptic drug and mood stabilizer. It functions as a histone deacetylase inhibitor, impacting gene transcription by inhibiting histone deacetylation. This inhibition makes transcription sites more accessible, influencing a myriad of cellular processes, including cell differentiation, migration and survival (Chateauvieux et al., 2010). Despite its therapeutic benefits, VPA is linked with a range of side effects. Critically, prenatal exposure to VPA significantly increases the risk of the child developing autism (Arndt et al., 2005). The exact mechanisms by which VPA exposure leads to ASD are not fully understood, but it is thought to involve disruptions in early brain development, with evidence suggesting that this teratogen affects molecular pathways that impair vascularization and, consequently, neural tube development.

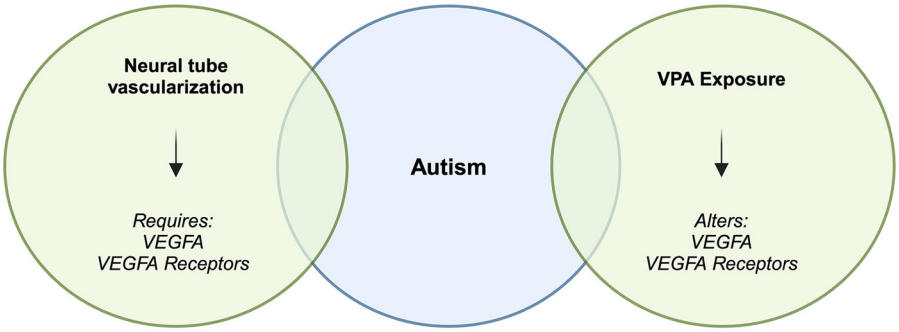

Figure 3. Solving the puzzle
This figure shows the interconnection between vascular endothelial growth factor A (VEGFA) and valproic acid (VPA) in neural tube vascularization and their potential link to autism. The left circle indicates that neural tube vascularization depends on VEGFA signalling and the activation of its receptors. The right circle shows that VPA exposure reduces the expression of VEGFA and its receptors. Together these insights, represented in the centre circle, suggest that disruptions in VEGFA signalling may impair neural tube vascularization, thereby contributing to the pathogenesis of autism. VEGFA serves as an example of these effects; however similar effects could also occur with other positive and negative signals involved in vascular development. Created using BioRender. Manzo, J. (2024) https://BioRender.com/n83y270.

In humans VPA is known to cross the placenta, reaching higher concentrations in the fetal circulation compared to maternal blood. Consequently about 8.9% of children exposed to VPA *in utero* are reported to develop autistic features, with the highest risk occurring when exposure happens during the first trimester of gestation (Elgamal et al., 2023). This risk escalates with higher doses of VPA, suggesting a clear dose–response relationship (Christensen et al., 2013), and the teratogenic effects of VPA are particularly critical around the time of neural tube closure (Arndt et al., 2005). Research in animal models has further elucidated the impact of VPA on development. Studies involving rats (Favre et al., 2013; Perez-Pouchoulen et al., 2016) and zebrafish (Chen et al., 2018; Velázquez-Landa et al., 2023) have shown that prenatal exposure to teratogenic doses of VPA can induce anatomical and behavioural abnormalities characteristic of autism. These models have proven invaluable in replicating the complex spectrum of autistic features, offering insights into the mechanisms by which VPA disrupts normal developmental processes.

Can VPA enlighten the connection between neural tube vascularization and autism? This article has outlined two critical observations: the neural tube plays a pivotal role in promoting its own vascularization, and VPA influences neural tube development, thereby triggering autism. Although existing studies corroborate these individual assertions, none have specifically explored VPA's impact on neural tube vascularization. In cases of ASD, there is evidence suggesting abnormal angiogenesis during development, which can reduce the formation of a proper vascular network. Such decrease can adversely affect neuronal migration and pathfinding, as indicated by recent findings (Wang et al., 2023). Furthermore, it is documented that VPA can reduce the expression levels of VEGFA and its receptor, subsequently affecting angiogenesis (Michaelis et al., 2004; Ruyani & Sumarsono, 2023). These alterations in vascular development could potentially contribute to the neural and behavioural manifestations observed in ASD (Fig. 3). The integration of these findings posits a compelling hypothesis: ASD might also be considered a vascular disorder. Therefore investigating vascular factors in idiopathic autism could be crucial for a comprehensive aetiological analysis.

Concluding remarks

Abnormalities in the vasculature of the neural tube represent a critical yet underexplored dimension of neurodevelopmental disorders. Such vascular anomalies may substantially influence the typical course of neurodevelopment, leading to the atypical patterns observed in individuals with ASD. This review aimed to address part of the puzzle by examining how modifications in early vascular development at the neural tube can lead to significant neurodevelopmental consequences. Vascular inhibition can impair the delivery of essential nutrients and oxygen to developing neural tissues, hinder the removal of metabolic waste and change the microenvironment necessary for proper neuronal growth and differentiation. These vascular deficiencies could result in the impaired formation of neural circuits and subsequent neurodevelopmental anomalies. Given the implications of these findings, it is crucial to consider vascular factors when investigating the aetiologies of ASD. This perspective not only broadens our understanding of ASD but also opens new avenues for potential therapeutic interventions that target the vascular aspects of neurodevelopmental disorders.

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Additional information

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