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REVIEW

Perinatal Hypoxia and Immune System Activation in Schizophrenia Pathogenesis: Critical Considerations During COVID-19 Pandemic

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Summary

Schizophrenia, a severe psychiatric, neurodevelopmental disorder affecting about 0.29-1 % of the global population, is characterized by hallucinations, delusions, cognitive impairments, disorganized thoughts and speech, leading to significant social withdrawal and emotional blunting. During the 1980s, considerations about diseases that result from complex interactions of genetic background and environmental factors started to appear. One of the critical times of vulnerability is the perinatal period. Concerning schizophrenia, obstetric complications that are associated with hypoxia of the fetus or neonate were identified as a risk. Also, maternal infections during pregnancy were linked to schizophrenia by epidemiological, serologic and genetic studies. Research efforts then led to the development of experimental models testing the impact of perinatal hypoxia or maternal immune activation on neurodevelopmental disorders. These perinatal factors are usually studied separately, but given that the models are now validated, it is feasible to investigate both factors together. Inclusion of additional factors, such as metabolic disturbances or chronic stress, may need to be considered also. Understanding the interplay of perinatal factors in schizophrenia's etiology is crucial for developing targeted prevention and therapeutic strategies.

Keywords

Schizophrenia • Perinatal hypoxia • Perinatal infection • Microbiota, SARS-CoV-2

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Introductory remarks on Professor Jan Herget's contribution to understanding developmental disorders

In this Special issue of Physiological Research, we celebrate the legacy of Professor Jan Herget (1945-2019) of the Second Faculty of Medicine, Charles University in Prague, Czech Republic. Although this review focuses on perinatal factors in schizophrenia, it is pertinent to remember Jan's unique contributions to uncovering the long-term effects of perinatal hypoxemia on responses to decreased oxygen in adulthood [1].

In the pioneering experiments, pregnant rats were placed into the hypoxic chambers and were kept there until their offspring were a week old. After placing the animals into the normoxic air, they recovered from hypoxia and had comparable pressure in pulmonary circulation as control mice unexposed to perinatal hypoxia. However, when these animals were re-exposed to acute hypoxia in adulthood, their responses were more severe than in animals born in normal air [1]. The perinatal exposure to hypoxia also blunted humoral immune responses in adult rats [2]. The mechanisms of these intriguing, lifelong-lasting effects are not yet fully understood. [3]

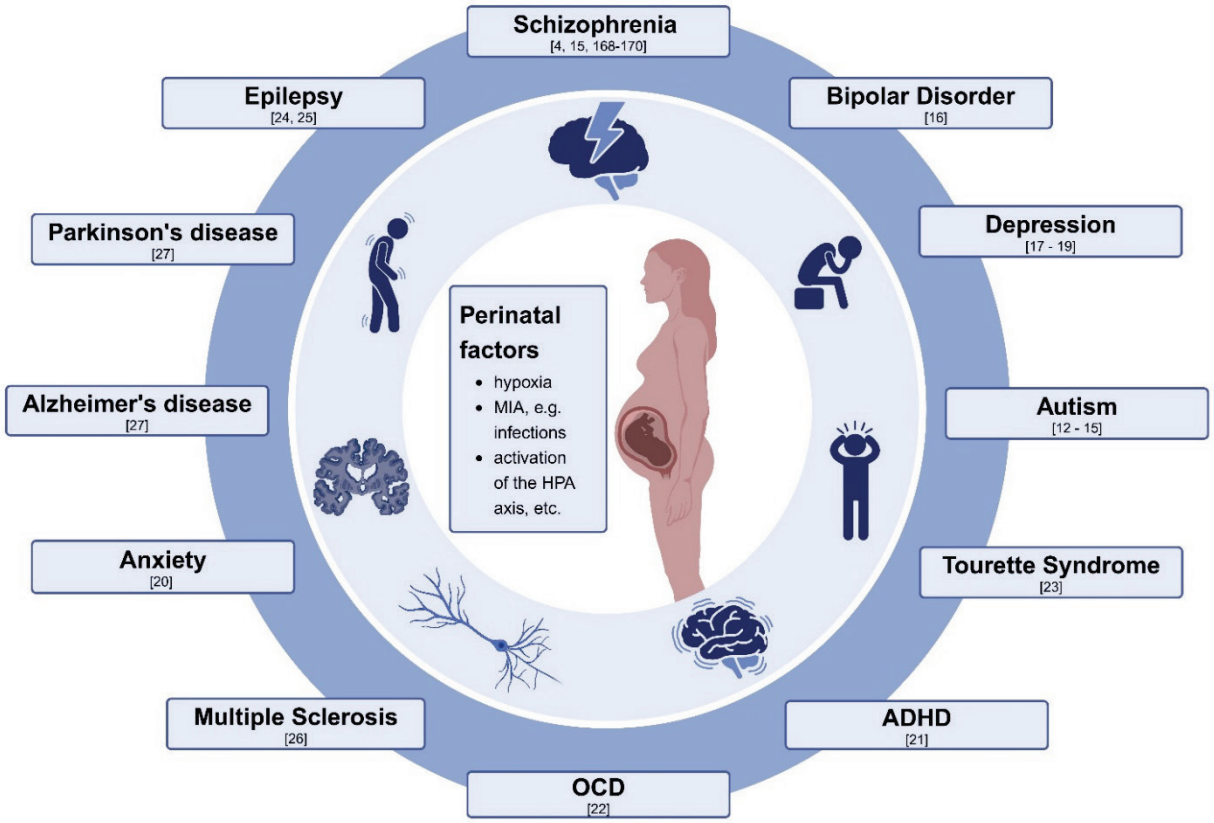

Fig. 1. Multiple factors acting perinatally can increase a risk for neurodevelopmental conditions that may manifest during childhood and adulthood. The picture was made with using a Biorender template.

Jan received the Robert F. Grower Prize from the American Thoracic Society for his research work. He was also an astounding teacher and mentor who profoundly impacted his students and research trainees. His vision that the course of a disease processes needs to be studied from a very early time in life took another dimension with models where perinatal hypoxia and maternal immune activation were identified as critical players in neurodevelopmental conditions.

Perinatal exposures and risk for neurodevelopmental conditions

Many perinatal factors influence the fetus during the perinatal period and affect the inherently complex and highly active brain tissue. For example, perinatal exposures that are related to increased risk of schizophrenia include conditions that cause hypoxemia, infections (especially influenza, rubella and toxoplasmosis) [4,5], maternal and offspring psycho-social stress [6], genetic factors [7], advanced paternal age [8], nutritional deficiencies [9], urbanicity [10] and migration status [11].

Vice versa, if we look at one group factors, e.g., maternal immune activation (MIA) initiated by viruses, bacteria, fungi, autoimmune conditions, they can play a role in a variety of childhood- or adulthood-onset of disorders, as depicted in Figure 1. They include autism [12-15], schizophrenia [4,15,168-170], bipolar disorder [16], depression [17-19], anxiety disorder [20], attention deficit-hyperreactivity disorder [21], obsessive-compulsive disorder [22], Tourette's syndrome [23], epilepsy [24,25], multiple sclerosis [26], Parkinson's disease and Alzheimer disease [27].

The precise mechanisms by which individual perinatal factors increase susceptibility to various neuropsychiatric conditions remain incompletely understood. The interplay of genetic predisposition, the timing of exposure, and the intensity of these factors collectively determine the outcomes. Elucidating these intricate details presents a formidable intellectual challenge. Resolving this complexity is crucial for identifying diagnostic biomarkers that enable clinicians to detect individuals at elevated risk for these conditions and to provide care strategies that may mitigate the likelihood of disease development.

In clinical psychiatry, diagnoses are based on symptoms and co-morbidities are a very common finding. In turn, making accurate diagnoses is arduous. Significant efforts are ongoing to define objective biomarkers that reflect distinct pathological processes, though they present by mixed behavioral symptoms. Understanding the pathophysiology is a prerequisite for diagnostic precision and enhancing effectiveness of treatment of schizophrenic patients [28].

We will focus here on hypoxia and perinatal immune activation as risk factors for schizophrenia. These two conditions have a high prevalence globally and often coincide, and the recent SARS-CoV-2 pandemic, or Severe Acute Respiratory Syndrome Coronavirus 2, very likely enhanced MIA in pregnant women during the pandemic.

Introduction to schizophrenia

In this selective review, we will focus on one of the neurodevelopmental disorders: schizophrenia, a severe psychiatric illness affecting about 0.29 % to 1 % of people worldwide. In the age group of 15-24 year-old individuals, it is the third most frequent mental disease, after anxiety and depression [29,30]. Patients experience symptoms such as hallucinations, delusions, cognitive impairment, disorganized speech and thought processes, which are categorized as “positive symptoms” of the disease. Their altered perception of reality often provokes severe anxiety and leaves them in profound loneliness. Patients have reduced expressions of emotions and typically withdraw from social contact. These symptoms are labeled as “negative symptoms”, and are more difficult to control by pharmacological treatment. Besides the impact of the disease on affected individuals, there is also a collateral toll on patient’s caregivers, families, friends, and colleagues [31-35]. In addition, the annual societal cost is high [36].

The pathogenic disturbances leading to schizophrenia syndrome result from interactions of multiple genetic and environmental factors [37] that start affecting brain circuitries during brain development [38], though the symptoms manifest in late adolescence to early adulthood. Most patients are affected between 15-25 years of age, with males having an earlier onset than females. In about 20 % of patients, the onset of schizophrenia occurs after forty and before 60 years, and rarely also, the disorder begins in childhood or adults above 60 years of age [29]. The differences in age of onset may reflect distinct pathogenic pathways or accumulation of causative factors, as suggested by the multiple-hit hypothesis [39].

Diagnosis of schizophrenia is still based on clinical symptoms because no objective, validated biomarkers exist for clinical use. As a result, diagnosis is not based on mechanistic principles; existing treatments are non-curative, and 30 % of patients remain resistant to existing therapeutics [40]. A better understanding of pathogenesis will help us subtyping patients into groups according to distinct pathological processes in individual patients and treat patients with high precision, as it has already been developed for cancer patients [41]. To this end, we focus here on the early events that increase the chance of schizophrenia development. Extensive research suggests that schizophrenia is a neurodevelopmental disorder, with the pathological processes potentially commencing as early as the in-utero stage [42,43], and progressing to a neurodegenerative condition [44].

Pathophysiology of schizohrenia

Reasons for poor understanding of schizophrenia include the high heterogeneity of patients, the inaccessibility of human brain tissue for biopsy sampling, and the involvement of animal models that do not fully capture the polygenic nature and multitude of environmental factors [45-48]. Our understanding of schizophrenia’s pathophysiology has been to a large degree based on postmortem brain studies, imaging studies, effects of pharmacotherapy and genetic studies.

Morphological considerations

Postmortem brain studies

Studies on brain pathology in schizophrenia initially focused on post-mortem brain specimens of individuals with schizophrenia. One major challenge with postmortem studies is the variability in findings due to factors such as the stage of the disease, medication status, and comorbid conditions at the time of death. Additionally, postmortem changes and tissue preservation issues can complicate interpretations. Despite these challenges, a consistent pattern has been identified in patients with chronic schizophrenia. Macroscopic findings include an enlargement of lateral and third ventricles, reduced brain volume, reduced gray matter involving the cortex, especially the prefrontal cortex, as

well as changes in subcortical gray matter (decreased volumes of hippocampus and thalamus, and increased basal ganglia volume) [49,50].

At the microscopic level, the altered density of neuronal and glial cells was reported in the *prefrontal cortex,* as well as reduced size of pyramidal neurons, reduced number of parvalbumin interneurons, decreased dendritic spine density and reduced neuropil (regions in the gray matter with dense, interwoven network of axons, dendrites, and glial cells), which contribute to disruptions in synaptic connectivity and plasticity [51-56]. In the *hippocampus,* findings in brains of patients with schizophrenia included neuronal disarray, reduced numbers of neurons and interneurons and decreased gene and protein expression of somatostatin-positive and parvalbumin-positive interneurons [57]. *In the thalamus*, numbers of neurons and parvalbumin positive interneurons were reduced [58]. *Basal ganglia* in individuals with schizophrenia are characterized by changes in the density of neurons and cholinergic interneurons [59]. *In the corpus callosum*, reduced myelin, axon density, and gliosis were noted [60].

Brain imaging

The macroscopic structural findings in schizophrenia were later confirmed in *in vivo* brain imaging studies [61]. Structural changes in the gray matter include reduced volume of frontal, prefrontal and temporal cortices with progressive loss over the course of the disease [62]. With regard to the white matter, a smaller total volume at a later stage of the disease [63] and hypoactive connectivity in major networks were reported [64].

Brain imaging also enabled the study of patients at different stages of the disease. Comparing individuals at prodromal state, first-episode of psychosis (FEP) or chronic schizophrenia revealed the progressive nature of brain pathology.

Ultra-high risk (UHR) individuals at prodromal state are people with personal features (e.g., subthreshold psychotic symptoms or a history of self-limiting brief intermittent psychotic symptoms) or a family history (e.g. first degree relative with a psychotic disorder) that puts them into a risk of developing a full-blown psychotic disorder. UHR individuals show early signs of anatomical and neuropathological abnormalities, e.g., reduction in frontal, prefrontal, and temporal cortices, often subtler than in FEP, affecting cortical and subcortical gray matter [65]. In FEP, prefrontal hypoactivity and hippocampal and subcortical hyperreactivity were described [66]. Gray matter changes are most robust within thalamocortical networks and brain activity is most altered in fronto-parietal circuitries [66]. In chronic schizophrenia, reduced gray matter involving the cortex (frontal, prefrontal, temporal), decreased volumes of hippocampus and thalamus, and increased basal ganglia volume were described [62].

Neurochemical considerations

Understanding of biochemical disturbances in schizophrenia has been evolving since 1950s when it was discovered that chlorpromazine has neuroleptic effects during anesthesia (Laborit *et al.*), and later shown to improve symptoms of schizophrenia [67]. Chlorpromazine effects include dopamine receptor inhibition [68]. Studies of postmortem brain showed dysregulation of dopamine synthesis, receptor expression or intracellular signaling in prefrontal and cingulate corte [69,70], hippocampus [69], thalamus [71] and basal ganglia [72,73]. Later it became clear that mono-amine theory of schizophrenia is over-simplified and pathophysiology involves also alterations in glutamatergic and GABAergic systems [74]. In addition, the effectiveness of several medications provided further clinical insight into the roles of neurotransmitters in the pathogenesis of schizophrenia, e.g., blockade of dopamine D2 receptors by a typical antipsychotic (e.g. haloperidol), serotonin 5-hydroxytryptamine (5-HT)-2A receptor inhibition, and 5-HT-21A receptor activation by atypical antipsychotics (e.g. risperidone) and partial glutamatergic agents, such as N-methyl D-aspartate (NMDA) receptor modulators [75,76]. Also, adjunctive treatment of schizophrenia has involved medications affecting GABAergic system, including benzodiazepines, though their use may need to be honed [77].

Genetic factors

Genome-wide association studies revealed over three hundred genes that represent risk factors for schizophrenia [78]. Twin and family studies showed that heritable risk for schizophrenia is about 67 %, which may be inflated due to common environmental conditions of the participants in the study, and thus environmental factors play significant role in development of the disease [79]. Concerning the perinatal factors discussed in this review, risk genes in pathways relevant to hypoxia [80,81] immune [82,83] and gut microbioma [84] responses are significantly enriched.

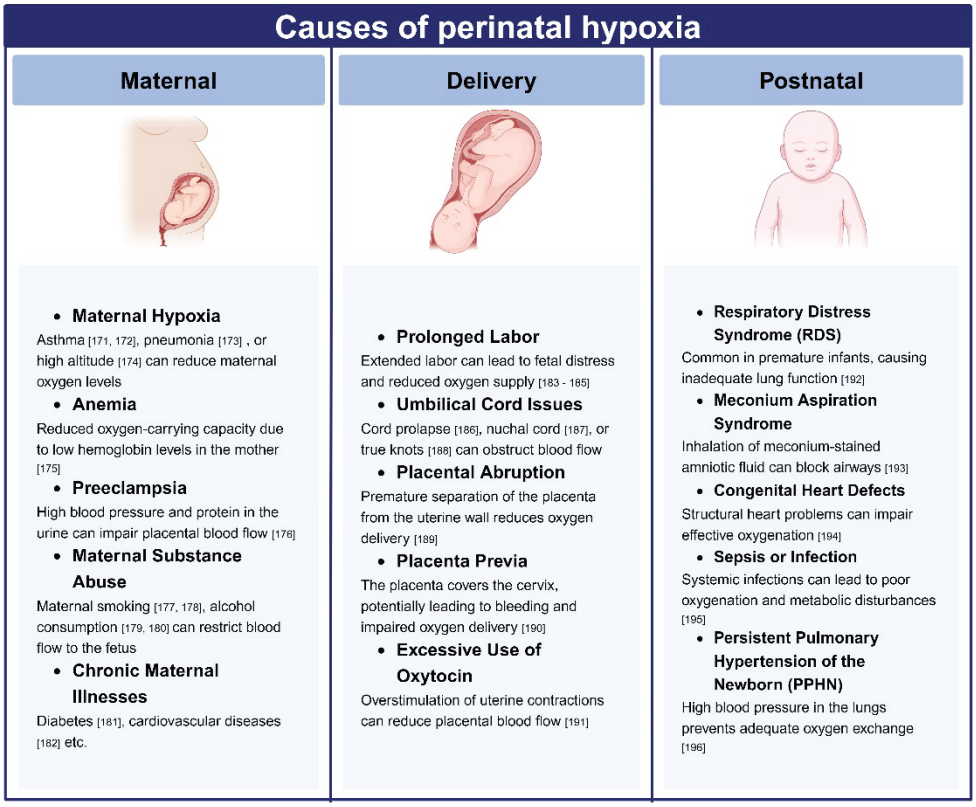

Fig. 2. Maternal, fetal and neonatal causes of decreased oxygen content in the blood supplying offspring's brain. The picture was made with using a Biorender template.

The relation of perinatal hypoxia to schizophrenia

Many conditions are associated with various degrees of maternal and fetal hypoxemia (Fig. 2). Perinatal hypoxia exerts extensive effects on the brain's histopathology, neurophysiology, and long-term health outcomes. The impact of hypoxemia on brain cells is modulated by the degree and duration of hypoxia. Mild hypoxia may induce reversible cellular changes, leading to adaptations and possibly alterations in transcription programs to cope with reduced ATP synthesis. In contrast, severe or prolonged hypoxia can result in irreversible damage and cell death. Additionally, the effects of hypoxia are influenced by the activity at a specific brain site and time, which is complex in healthy infants and in premature babies.

Clinical findings relating perinatal hypoxia to schizophrenia

The hypothesis that the development of psychotic conditions may be associated with brain hypoxia in the perinatal period was formulated in 1975 by a child psychiatrist, H. Allen Handford, based on the clinical history of patients seen in his practice, highlighting at that time that additional factors than genetics are at play [85].

Epidemiological studies then showed that hypoxia-associated obstetric complications significantly increase the risk for schizophrenia with early onset, before the age of 22 years (odds ratio, OR, 2.16) [86], and the degree of hypoxia-associated obstetric complications correlates with risk for developing schizophrenia [87]. After adjusting for other obstetric complications (e.g. maternal history of psychotic illness and social class), the association between signs of asphyxia at birth and schizophrenia reached odds ratio (OR) 4.4 [88].

Concerning the impact of perinatal hypoxia on the brain tissue of newborn, brain imaging studies revealed that the most susceptible areas include injuries within watershed areas, hippocampus, basal ganglia, thalamus, hippocampus and white matter. The impact depends on maturation stages of the brain [89]. Prefrontal cortex that is consistently linked to schizophrenia, is supplied by both anterior and middle cerebral arteries and includes the watershed area between them, making it sensitive to hypoxemia. Prefrontal cortex is also

connected to the subcortical nuclei, e.g. thalamus, hippocampus, striatum, and hypoxia-induced white matter injury may affect the connectivity. Also, post-mortem brain analysis of the posterior hippocampus in patients with schizophrenia revealed a negative correlation between events associated with hypoxia and the numbers of pyramidal cells in CA4, a deep polymorphic layer of dentate gyrus [90]. Correspondingly, brain imaging studies in patients with psychotic disorder uncovered a decreased hippocampal volume in individuals with schizophrenia as compared to healthy controls, and those volumes were further decreased in patients with hypoxia events in their early life [91]. In summary, hypoxic insults, though highly variable in their strength and timing, appear to impact many areas shown to be affected also in schizophrenia.

It was suggested that the level of susceptibility to hypoxia may depend on genetic background. To this end, Nicodemus *et al.* tested thirteen hypoxia-regulated genes related to neurovascular functions. Changes in single nucleotide polymorphisms (SNP) in four genes were identified: AKT1 (AKT serine/threonine kinase 1; three SNPs), BDNF (brain-derived neurotrophic factor; two SNPs), DNTBP1 (dystrobrevin-binding protein 1; one SNP) and GRM3 (S-adenosyl-L-methionine-dependent methyltransferases superfamily protein; one SNP). These findings support the gene-environment interactions in schizophrenia [92]. Concerning functional responses to fetal hypoxia, a protein product of one of the factors – BDNF- was increased in cord blood in control subjects without schizophrenia, while in cases with schizophrenia, BDNF levels were decreased by hypoxia [93]. HMGA1 (High mobility group A protein 1a) was found to be a hypoxia-inducible RNA-binding trans-acting factor for aberrant splicing of presenilin-2 pre-mRNA. Morikawa *et al.* found increased HMGA1a mRNA and protein in patients with schizophrenia [94]. Recently it was also shown that hypoxia-inducible factor induces MIF expression (macrophage migration inhibitory factor, a neuroprotective cytokine at the cross-road of inflammatory and stress responses) by binding to hypoxia-response element at the MIF promoter and that SNP at this site represents a risk factor for schizophrenia by reducing production of MIF in response to hypoxia [95]. Hypoxia also affects the extensively studied pathway of DISC1 (Disrupted in schizophrenia 1, a scaffold protein that interacts with many other proteins and is required for synaptogenesis, neurite outgrowth, and neuronal migration) by reducing the half-life of DISC1 protein [96].

Experimental studies in animal models

Experimental models of schizophrenia induced by perinatal hypoxia typically involve oxygen deprivation during critical developmental periods. For example, a rodent brain at postnatal days 7-8 corresponds to the late gestational period in humans. It represents a critical period for dendritic outgrowth, formation of synapses, and maturation of neuronal tissue [97], neuronal networks with alterations in the glutamatergic receptors (switch subunits of NMDA receptors from GluN2B to GluN2A subtypes) [98] and transformation of GABAergic system from excitatory to inhibitory effects [97]. All the parameters studied during developmental stage can now be linked using 3D eMouse atlas [99] that builds on morphological staging developed by Karl Theiler [100].

The immature brain in this sensitive age is quite vulnerable and depends on the timing and duration of hypoxic insult as it affects dynamic functions, such as neuronal proliferation, migration, and maturation. The models mimic obstetric complications, e.g., C-section, perinatal/postnatal hypoxia, or placental insufficiency [101]. Experimental hypoxia includes several protocols that employ acute or chronic oxygen reduction at sea level barometric pressure or hypobaric conditions where the percentage of oxygen remains the same, but decreased barometric pressure leads to less oxygen delivered to the lungs' alveolo-capillary membrane.

In relation to schizophrenia, neuregulin-1 (a key factor seen elevated in patients with schizophrenia) was 32 % higher in the frontal cortex of adult rats exposed to 7-day neonatal hypoxemia [102]. In a recent study, perinatal hypoxia was shown to dysregulate spontaneous activity patterns critical for forming functional templates for generating cortical architecture and guidance for establishing thalamocortical and intracortical circuits. These circuits are affected in patients with schizophrenia [103].

Hypoxia-induced behavioral changes resembling schizophrenia

C-section results in greater amphetamine-induced locomotion in adult rats, both in animals born in normoxia or hypoxia as compared to vaginal delivery. Amphetamine increases dopamine levels, and increased locomotion in response to amphetamines indicates heightened sensitivity to dopamine, which models the dopamine dysregulation seen in schizophrenia. The rats

also spent more time sniffing than grooming, and hypoxia during C-section was linked to prolonged rearing in adult rats [104]. In animal models, spending more time sniffing the environment and less time grooming can be indicative of increased anxiety or hyperactivity, both of which are observed in individuals with schizophrenia. Prolonged rearing indicates increased exploratory behavior and hyperactivity. In schizophrenia models, this behavior can reflect the hyperdopaminergic state associated with positive symptoms of schizophrenia, such as agitation and hyperactivity.

Adult guinea pigs had also increased amphetamine-induced locomotion and disrupted pre-pulse inhibition (PPI) of acoustic startle, but hypoxia during C-section reduced amphetamine-induced locomotion [105]. PPI is a neurological phenomenon used to measure sensory gating, the brain's ability to filter out unnecessary information. The test consists of the startle reflex, a rapid, involuntary response to a sudden loud noise or other sensory solid stimulus. When a weak pre-stimulus (pre-pulse) is presented shortly before a strong startling stimulus, PPI occurs, and the startle response to the subsequent more substantial stimulus is reduced. Disrupted PPI in animals indicates impaired sensory gating, a key feature of schizophrenia. In another study, postnatal hypoxia induced by bilateral, continuous occlusion of the common carotid artery in 12-day-old male rats resulted in schizophrenia-like behavior, including locomotor activity in pubertal rats (postnatal day 35) and impaired PPI in post-pubertal males (postnatal day 50) [106].

Hypoxia-induced impact on neurotransmitters and/or their receptors related to schizophrenia.

All three central neurotransmitter systems are affected by hypoxia:

1) *Dopamine.* Animal models of C-section hypoxia resulted in altered levels of dopamine or dopamine receptors, the key neurotransmitter associated with schizophrenia. Decreased levels of dopamine were found in the prefrontal cortex [107,108], while dopamine release was increased in the nucleus accumbens [108] and amygdala [109];

2) *Glutamatergic system*. NMDA receptor binding decreased, and transcription of NR1 subunit increased in frontal and temporal regions, nucleus accumbens, and hippocampus. NR2A subunit expression was downregulated in hippocampal sub-regions. On day 120 postnatally, gene expression of NR1 was still increased in hippocampal, frontal, and temporal sub-regions, as well as nucleus accumbens - a pre-pulse inhibition deficit points to schizophrenia-like behavior in 4-month-old rats. Compensatory upregulation of NR1 expression may occur due to NMDA receptor hypofunction. A subset of glutamate receptors, kainite receptors, increased after exposure to hypoxia [104]. Neuregulin -1, a protein that interacts with glutamate receptors, was elevated after hypoxia in 7-day rats [102];

3) *GABA* in the hippocampus increased in 7-day old rats after 1hr ligation of the left carotid artery and exposure to air where the content of oxygen was reduced from 21 to 8 % [110].

In summary, perinatal hypoxia has been linked to many neuropsychiatric conditions. Concerning schizophrenia, the link was established by epidemiological and genetic studies, in vitro experiments on human cells, and *in vivo* experimental studies in several animal species.

Perinatal immune system activation and the brain

Perinatal infections encompass a range of infectious diseases transmitted from mother to fetus in-utero or during birth or occur shortly after delivery. Any infectious microorganisms, including bacteria, viruses, fungi, or parasites, can cause these infections. Immune responses to invading microorganisms are associated with local and systemic activation of immune cells and the production of soluble molecules, including interleukins, cytokines, complement peptides, and antibodies. The presence of these molecules alters the brain development.

Clinical studies in patients with schizophrenia

Epidemiological evidence.

The link between perinatal infection and schizophrenia started to be considered more than three decades ago. In a Finish birth cohort study, Mednick *et al.* showed that mothers in the second trimester of their pregnancy during the 1957 influenza endemic had children who were much more likely to be admitted by 26 years in an inpatient facility with the diagnosis of schizophrenia [5]. Subsequent birth cohort study employed an improved design by involving pregnant women whose respiratory infection was recorded by a physician and whose offspring had continued follow-up with a diagnosis of schizophrenia established by face-to-face interview [111]. Second-trimester infection represented an increased risk for schizophrenia with

a relative rate of 2.13 [111]. Going beyond the in-utero period, a two-fold risk for schizophrenia was found in adults who experienced childhood infections, especially influenza, as a meta-analysis revealed. These findings highlight that the critical developmental period continues in the postnatal period [112]. A recent population-based nationwide cohort study addressed the hazard ratio for neuropsychiatric conditions in children of mothers with autoimmune diseases. The hazard risk with regards to schizophrenia was 1.35, demonstrating increased risk in offspring of women with conditions such as autoimmune diabetes or rheumatoid arthritis [113].

Serologic findings

Other efforts focused on finding infectious microorganisms responsible for these observations. In a nested case-control study, blood samples of mothers of children who turned out to be schizophrenic patients in adulthood were measured. The samples were collected at the end of their pregnancy and were found to have elevated total immunoglobulin (Ig)G and IgM and elevated IgG specific against herpes virus type 2 glycoprotein gG2 [114]. In another nested case-control study, archived blood samples of mothers pregnant between 1959 and 1966 were tested, and offspring were followed for psychiatric disorders for 30-38 years. Influenza infection during the first trimester increased the risk for schizophrenia 7-fold and 3-fold after broadening gestational periods to early to mid-pregnancy [115].

The studies on viral pathogens also expanded to protozoan parasites, toxoplasmosis gondii, and bacterial infections. Xiao *et al.* developed new antibodies for enzyme-linked immunosorbent assay to distinguish three distinct clonal lineages of toxoplasma and then tested the sera of pregnant mothers whose children developed schizophrenia and schizoaffective disorder with sera of mothers of unaffected children. Serological positivity for Toxoplasma type I, Ukrainian infection, increased risk for the development of psychoses with an odds ratio of 1.94. For affective psychoses, the odds ratio was 5.24 [116]. Bacterial infections during pregnancy also represent a significant risk for the development of schizophrenia (adjusted odds ratio 1.8, primarily when the infection affects multiple systems, which raises the adjusted odds ratio to 2.9 [117].

Neuroanatomic considerations

In patients with schizophrenia, postmortem analyses and brain imaging studies done by the early 1990s established that pathology occurs within fronto-striatal-temporal regions [118]. As further details were learned, more details were identified, and the frontal cortex, hippocampus ([119], cerebellar vermis [120], substantia nigra [121] were added to the neuroanatomical areas related to schizophrenia. A recent review of meta-analyses concluded that schizophrenia is characterized by lower grey matter volumes and cortical thickness, accelerated grey matter loss over time, abnormal gyrification patterns, and lower regional SV2A levels (Synaptic Vesicle Glycoprotein 2A is a protein that plays a crucial role in the regulation of neurotransmitter release at synapses) and metabolic markers in comparison to controls (effect sizes from ~ -0.11 to -1.0), and that critical regions affected include frontal, anterior cingulate and temporal cortices and the hippocampi [42].

Concerning the association between immune system activation and schizophrenia, metanalysis revealed a significant increase in the density of microglia, especially in the temporal cortex, while densities of macroglia (astrocytes and oligodendrocytes) did not differ significantly. On the molecular level, increased expression of proinflammatory genes on transcript and protein levels was seen in schizophrenia, while anti-inflammatory gene expression levels did not differ between schizophrenia and controls [122].

Complex developmental trajectories were detected in the brains of patients with autism and schizophrenia spectrum disorders, which are distinct disorders where autism starts in early childhood and schizophrenia in young adulthood. However, patients with autism are three times more likely to develop schizophrenia later in their life [123]. This association may result from interactions between genetically-defined abnormalities and many environmental factors to which each individual is likely exposed at different times. For a better understanding of the mechanisms of this complex phenomenon, animal models of maternal immune activation (MIA) were developed.

Experimental studies in MIA model

Robert Sidwell's group established foundations for the MIA by involving C57/BL6 pregnant mice infected with human influenza virus on gestational day 9 and assessing offspring on day 0 after the birth and at 14 weeks. They were the first to report short- and long-lasting impacts both on adult offspring's behavior and brain neuropathology, including macrocephaly and pyramidal cell atrophy [124]. Paul Patterson and his team

then employed the synthetic double-stranded RNA polyinosinic-polycytidylic acid (Poly (I:C)) instead of the influenza virus and demonstrated a similar impact on brain structures and functions [125]. The deficits in pre-pulse inhibition in the acoustic startle response linked the model to autism and schizophrenia spectrum disorders [126]. Using synthetic mimetics of the influenza virus significantly simplified the methodology of this model and facilitated subsequent studies that involved different Toll-Like Receptor (TLR) ligands administered to pregnant dams at different stages of pregnancy [127].

Paul Patterson's group was pivotal in developing the model's neuropathology and identifying behavioral abnormalities (e.g., deficits in social interaction, increased anxiety, and cognitive impairments), which helped to draw parallels between the animal model findings and symptoms of patients with autism and schizophrenia [15,128]. They also established essential roles of cytokines, particularly interleukin (IL)-6, in mediating the effects of MIA on neurological abnormalities in exposed offspring [126]. Another critical cytokine, IL-17, is required for elicitation of abnormal cortical and altered behavior in offspring, as discovered by Gloria Choi [13]. Her group further refined the MIA model by establishing neuronal circuitry that is affected by IL-17 [129,130].

Urs Meyer's group demonstrated the relevance of the model to schizophrenia and the multi-hit hypothesis. In their experiments, MIA-exposed animals received stressful stimuli in the peripubertal period, which resulted in synergistic effects on brain pathology and behavior in adulthood. The MIA exposure significantly increased the vulnerability of the pubescent offspring [131]. Given that the onset of schizophrenia occurs in young adults, this model involving a combination of perinatal and peripubertal challenges likely reflects real-world scenarios.

In summary both preclinical and clinical studies have linked inflammation and maternal immune activation to pathogenesis of schizophrenia. The critical questions that need to be resolved are when the inflammatory processes within the brain are beneficial and when they are detrimental, and how can the injurious events be therapeutically inhibited without impacting the whole immune system and rendering treated individuals more susceptible to infections.

The complexity of interactions in the MIA model is evident from this outline. However, another layer of complexity was added when Sarkis Maznamian's group reported that MIA alters the gut microbiome, significantly affecting exposed offspring's neurodevelopment [132].

Gut microbiome and the brain

The gut microbiota comprises over 100 trillion bacteria, viruses, and fungi, which form an essential physiological system. The interactions between the large mass of microorganisms and the gastrointestinal wall are highly regulated by the gut-associated lymphoid tissue, which represents the immune tolerance's cardinal site. The gut microbiota interacts with other organs through a multidirectional communication network, via which it also influences brain development and functions [133].

The microbiota communicates with the brain *via* nerves and in an endocrine fashion. Regarding nerves, autonomic parasympathetic, vagal, and splanchnic plexus fibers are directly wired to the central nervous system. The endocrine role of gut microbiota is reflected in the release of many substances that then travel through interstitial fluid or blood to local or distant targets [134].

The most relevant molecules produced or metabolized by the microbiota are short-chain fatty acids (produced by bacteria), bile acids (from the liver and metabolized by the microbiota), and tryptophan (an essential amino acid originating mainly in a diet and then metabolized by the microbiota) [135].

The microbiota can transform tryptophan into indole and other aryl hydrocarbon receptor ligands, critical for maintaining epithelial cell renewal and integrity and controlling intraepithelial leukocyte interactions [135]. Tryptophan is also metabolized by indoleamine-2,3-deoxygenase in epithelial and immune cells to kynurenine and downstream products, which regulate inflammation, adaptive immune responses, and neurotransmission [135]. Another critical role of tryptophan is being a precursor for serotonin. It is produced by two enzymes, tryptophan-hydroxylase 1 and 2, located in the gut and brain. About 95 % of serotonin is found in the gut, produced by enterochromaffin cells [136]. Serotonin acts as a hormone and neurotransmitter in the peripheral and central nervous systems. In the gut, serotonin influences intestinal peristalsis and motility, secretion from gastrointestinal glands, and vasodilation. Serotonin is also a part of the content of platelet and mast cell granules and contributes significantly to inflammatory responses.

Clinical studies on microbiota in schizophrenia

Zheng and his team established the relationship between gut microflora and schizophrenia. They showed that schizophrenia patients exhibited reduced diversity in bacterial species, and revealed a correlation between discriminative microbial markers and the severity of schizophrenia symptoms [137]. A positive correlation was found for Lachnospiraceae OTU (Operational taxonomic unit) 477, Lachnospiraceae OTU629, Ruminococcaceae, Bacteroidaceae OTU 172, and streptococcaceae OTU834, and negative correlation was reported for veillonellaceae OTU191 and Rumino-coccaceae OTU725 [137]. The authors then went beyond establishing the clinically obtainable correlative relationships and addressed the pathogenic role of gut microflora in a translational experiment where fecal microbiota from schizophrenic patients versus healthy controls were transplanted into experimental mice. Animal behavior in group recipients of the stool from schizophrenic patients corresponded to behavior considered characteristic in experimental models of schizophrenia. These changes were accompanied by biochemical alterations in the cortex and hippocampus, which are consistently reported to be affected in schizophrenia [137].

In another study, Li *et al.* show that microbiota in patients with schizophrenia is related to structural changes in their brains. Structural magnetic resonance imaging revealed a reduction in gray matter volume and regional homogeneity in several brain regions in patients. Alpha diversity of the gut microbiota in patients showed a strong linear relationship with the values of both MRI parameters. These results further strengthened the argument that gut microbiome may play a role in the neuropathogenesis of schizophrenia [138].

Evidence for clinical MIA affecting brain development via the impact on microbiota

Whether maternal infection during pregnancy affects the child's brain development at least partially *via* gut microbiota has not been documented. However, fragmented clinical evidence suggests that such a pathway exists. First, even a minor infection affects the composition of gut microbiota, as shown by a longitudinal study on patients with mild, asymptomatic SARS-CoV-2 infection. Their stool was collected during the infection, and then after they turned seronegative for the SARS-CoV-2 virus. The microbiota showed more microbial evenness during infection, and Bacteroidetes species were depleted. When seronegativity for the SARS-CoV-2 virus was reached, the microbiota was comparable with healthy controls [139]. Second, maternal microbiota changes affect an infant's microbiota composition [140]. Third, antibiotics taken during pregnancy alter maternal microbiota and are associated with the development of metabolic and allergic disorders later in childhood, including obesity and asthma [141]. In the context of existing information, maternal microbiota alterations likely affect human offspring's brain development.

Experimental studies on the impact of MIA on gut microbiome

Mazmanian's team reported first that MIA-impacted gut flora influences the severity of behavioral and neuropathological phenotypes in offspring by breaking the immune tolerance in the gut and activating the microbiota-gut-brain axis [132]. Oral administration of common commensals, Bacteroides fragilis, corrected gut permeability and microbial composition, improving communicative, stereotypic, anxiety-like, and sensorimotor behaviors [132].

A meta-analysis was performed to assess MIA's effect on microbiota and neurodevelopmental conditions in rodents. Combining the results of thirteen studies revealed that maternal microbiome disturbances affect the brain, as reflected by a decrease in offspring's sociability and an increase in stereotypic behaviors [142], which supports the validity of the concept.

Since indigenous spore-forming bacteria from the mouse and human microbiota promote serotonin biosynthesis from colonic enterochromaffin cells [143], MIA's impact on the serotonin pathway was tested by MacDowell *et al.* [144]. MIA reduced serotonin content in brain tissue and promoted changes in the expression of serotonin transporter, 5-HT2A, and 5-HT2C receptors. Long-term paliperidone treatment (a dopamine D2 and serotonin 5HT receptor antagonist) counteracted the MIA-induced changes [144]. These findings provide insight into mechanisms by which MIA's impact on the microbiota can affect the brain.

Microbiota can be altered by antibiotic usage. Except for a few, antibiotics have been considered safe for pregnant women. As we learn more about antibiotics' effects on microbiota, their safety may need to be re-assessed, and the benefit ratio may need to be considered individually. One of the safest antibiotics is penicillin. Administration at a low dose during the third trimester of

mouse pregnancy resulted in behavior changes of adult offspring [145-147]. The behavioral changes were sex-dependent. Female adult mice showed decreased anxiety patterns, while they had abnormal social behavior. The immune system was affected, as evidenced by a decrease in splenic FOXP3+ regulatory T cells, major players in preventing the development of autoimmunity [145].

In similar experimental conditions, Lebovitz *et al.* reported decreased expression of Cx3cr1 (a chemokine receptor for neuron-derived fractalkine) in the microglia of the prefrontal cortex [148]. In another report, dysbiosis-induced microglial expression of CxC3cr1 was restored by treating mice with oral Lactobacillus species [146].

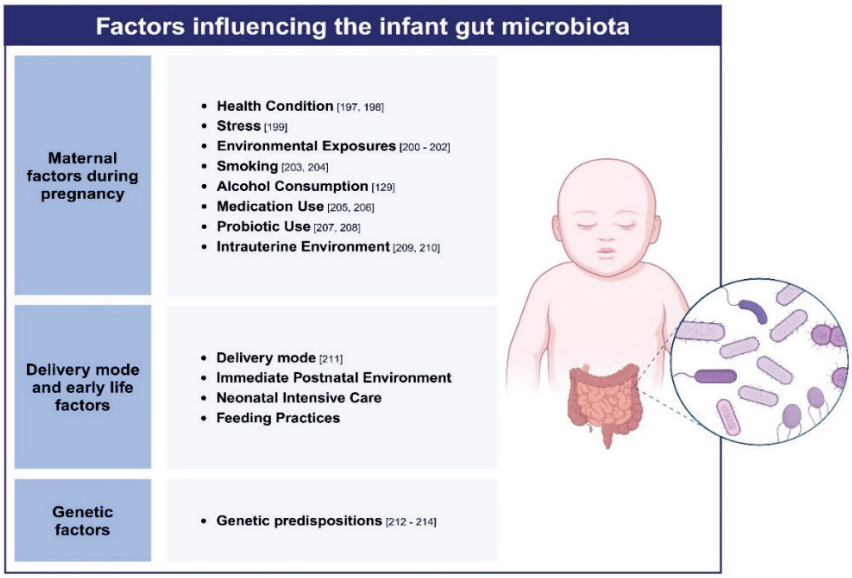

Fig. 3. Various factors that affect maternal and offspring microbiota, which may alter neurodevelopment in the child through gut-microbiota-brain axis. The picture was made with using a Biorender template.

Other causes of perinatal alterations of maternal or infant's microbiota

Both maternal and infant microbiota play crucial roles in shaping an infant's brain development, but their influences are intertwined and impact the infant at different stages. Maternal gut microbiota influences the immune environment and metabolic state during pregnancy, which can impact fetal brain development. During vaginal delivery, infants acquire microbiota from the mother's vaginal and intestinal flora, which is beneficial for early immune system development. After birth, the infant's microbiota continues to develop and is influenced by factors such as breastfeeding and environmental exposures. Breast milk contains beneficial bacteria and prebiotics that help shape the infant's gut microbiota. Figure 3 depicts conditions that can influence maternal or offspring microbiota.

MIA by SARS-CoV-2

World Health Organization declared global SARS-CoV-2 pandemic in March 2020 and announced its end in May 2023. Statistics vary about the number of women who were pregnant during the COVID-19 pandemic. It is, however, clear that SARS-CoV-2 infection worsened pregnancy outcomes. For example, a recent study reported outcomes of INTERCOVID study infections of the omicron variant of SARS-CoV-2 in pregnant women and their babies. Maternal, Neonatal, and Perinatal Morbidity and Mortality indices (MMI) relative risk were 1.16, 1.23, and 1.21, respectively. In unvaccinated women, Maternal MMI was 1.36; in women with severe COVID-19 symptoms, 2.51; and in unvaccinated women with severe COVID-19 symptoms, 2.88 [149].

Vertical transmission of the virus is believed to occur only rarely [150] and the human placenta has been considered a sound barrier that protects the fetus efficiently [151]. However, in a recent experimental study using mice that express human angiotensin-converting enzyme 2 that allows intracellular entry of SARS-CoV-2, the virus is found in the brain within 48 hours after the infection, indicating direct exposure of brain cells to the virus. All cell types within the brain (endothelium, neurons, glia, and astrocytes) can be infected [152]. Even if direct exposure

to human fetuses continues to be refuted, the placenta of infected women (including mild cases of SARS-CoV-2 infection) was reported to have vascular abnormalities (consistent with malperfusion) and villitis [153,154].

SARS-CoV-2 enters cells primarily via binding to Angiotensin Converting Enzyme-2 and Transmembrane Serine Protease 2. The virus also interacts with the host immune system through multiple TLRs, mainly TLR2, TLR4, TLR7, and TLR8, which were all shown before to play a role in MIA [23]. These interactions activate innate immune responses, including producing pro-inflammatory cytokines critical for controlling viral infection and contributing to MIA.

The abnormal fetus oxygenation, local inflammation, and the impact of SARS-CoV-2 on microbiota are all conditions, in which the neural development of the fetus may be affected. These mechanisms may be behind the findings in a recent retrospective study that examined one-year-old children exposed to SARS-CoV-2 in utero (confirmed by polymerase chain reaction test). The study revealed that exposure is associated with a higher rate of neurodevelopmental diagnoses, with an OR of 1.86. When the SARS-CoV-2 occurred in the third trimester, the OR was higher - 2.34 [155]. Another retrospective cohort examined electronic health records and uncovered that males but not females born to SARS-CoV-2 infected mothers were more likely to receive a neurodevelopmental diagnosis in the first 12 months after delivery [156].

While these findings will need additional validations, the existing data already warrant more experimental studies that can help explain histopathological mechanisms involved in the increased vulnerabilities to neurodevelopmental conditions and identify diagnostic markers applicable clinically. Meanwhile, professionals taking care of children exposed to SARS-CoV-2 in utero may closely monitor their development and support formulation of clinical practices where children with vulnerabilities receive more support, as it is the case with individuals at high risk for development of autism or schizophrenia where measures, such as diet, exercise [157,158] showed some positive outcomes.

Interactions between MIA and perinatal hypoxia

The impacts of perinatal hypoxia and MIA on the brain overlap in several key areas. Both conditions can lead to similar neurodevelopmental disruptions and are associated with increased risk for neuropsychiatric disorders, including schizophrenia. They both induce neuroinflammation, which involves microglia activation and release of pro-inflammatory cytokines in the developing brain [45,159]. Both conditions can lead to increased production of oxygen radical species and subsequent oxidative stress, which can cause cellular injury and impair neurodevelopmental processes, including synaptogenesis and myelinization [160,161]. Both perinatal hypoxia and MIA can cause epigenetic changes, such as DNA methylation and histone modification, which impact transcriptional programs involved in various developmental functions and adaptive responses [162-164] and may be dependent on severity of the stimulus [165]. Finally, both perinatal hypoxia and MIA alter the dopaminergic system, which is a crucial feature of schizophrenia [166]. To better understand pathways shared between perinatal hypoxia and MIA, we will need to await experimental evidence where MIA, due to the activation of different TLRs, is tested together with different degrees of perinatal hypoxia (including mild hypoxia). Such efforts can help develop biomarkers for new diagnostic panels, targeted interventions, and preventive strategies for at-risk populations.

Conclusions

This review underscores the roles of perinatal hypoxia, immune system activation, and microbiota in neurodevelopmental conditions, to which also belongs schizophrenia. Clinical and experimental studies demonstrate that these perinatal factors are associated with long-term changes in brain structure and function, as reflected in behavioral and neurotransmitter alterations observed also in schizophrenia. Sophisticated experimental models have been developed during the last two decades to address perinatal hypoxia and MIA but their cumulative effects are rarely studied together.

In light of the SARS-CoV-2 pandemic, these considerations may be needed for children exposed to SARS-CoV-2 in utero, particularly in situations where additional factors contributed to increased risk for asymptomatic brain tissue injury, including obstetric complications causing various degree of hypoxia, additional infection, maternal immune activation or psycho-social stress.

Limitations

One of the significant limitations of translational research on schizophrenia is the heterogeneity of the disease and the existence of subsets of patients that we are not yet able to distinguish objectively. Most existing studies approach schizophrenia as one condition that significantly limits the interpretation of data. The heterogeneity of schizophrenia stems from complex genetic backgrounds that make the susceptibility to environmental factors quite variable. In addition to the heterogeneous nature of schizophrenia, also ethical limitations exist that prevent access to the affected brain tissue.

Future directions

To enhance our understanding of schizophrenia development, using advanced animal models and testing more than one perinatal factor per experiment will be critical. The experimental studies linked to longitudinal clinical studies involving sufficient subjects and assessing patients multimodally will promote the translational value of such work. These efforts should identify objective biomarkers for subsets of patients and hopefully reveal objective biomarkers altered by perinatal factors that are sensitive enough to reveal even pathological processes not immediately evident clinically (e.g., sensory, motor or cognitive deficits) and that are possible to use in longitudinal monitoring during individual's development as they encounter further hits during their lives. That such goals are feasible is demonstrated by recent advances in other psychiatric conditions, namely Alzheimer disease, where a biomarker detectable in the blood was identified [167]. A better understanding of molecular mechanisms can lead to more effective individualized treatment. In addition, the focus of the research should not only be on the treatment of pathological status but on preventive measures that can limit the prevalence of neurodevelopmental conditions, including schizophrenia.

Conflict of Interest

There is no conflict of interest.

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