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Antonio L. Teixeira · Danielle Macedo
Bernhard T. Baune *Editors*

Perinatal Inflammation and Adult Psychopathology

From Preclinical Models to Humans

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Volume 84

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Danielle Macedo • Bernhard T. Baune
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Perinatal Inflammation and Adult Psychopathology

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Preface

Psychiatric disorders have been traditionally conceptualized as the result of an imbalance of neurotransmitters in the brain. Drugs that increase the levels of serotonin are used in the treatment of anxiety and mood disorders, while dopaminergic antagonists are the mainstay of the therapeutics for psychotic disorders. Other strategies aim at distinct neurotransmitters as glutamate and GABA. While the available pharmacological agents help many patients suffering from different psychiatric ailments, a significant percentage of subjects does not respond or tolerate them.

The need for alternative models that could act as targets for new drug development alongside the realization that the impact of psychiatric disorders goes beyond the brain and behavior brought the investigation of immune and inflammatory mechanisms to the forefront of biological psychiatry. Findings of immune changes in the periphery and the central nervous system have been described for almost all psychiatric disorders. A new term, immunopsychiatry, was even proposed in addition to the well-known concept of psychoneuroimmunology to describe this field of investigation (Pariante 2019).

In parallel with the "hype" around immunopsychiatry, perinatal psychiatry emerged as an area of research that investigates the role of perinatal events (e.g., pregnancy complications, pre- and postnatal infections) in the development of neuropsychiatric conditions, such as schizophrenia and mood disorders, later in life. Among the implicated pathophysiological mechanisms, perinatal-related immune and/or inflammatory processes have been proposed as major players, also being regarded as putative targets for therapeutic intervention. Therefore, the current volume provides a broad overview on the concepts and evidence implicating inflammation as a possible link between perinatal events and adult psychopathology.

The current volume brings 15 chapters that span from the theoretical foundations of the field to both experimental (maternal and neonatal infections, maternal immune activation models) and human studies, also addressing the role of epigenetics, neuroendocrine programming, and placenta physiology.

Reference

Pariante CM. From psychoneuroimmunology to immunopsychiatry: a brief history. In: Teixeira AL, Bauer ME, editors. Immunopsychiatry: a clinician's introduction to the immune basis of mental disorders. New York: Oxford University Press; 2019.

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About the Editors

Antonio L. Teixeira, MD, MSc, PhD, is Professor of Psychiatry and Neurology at the University of Texas Health Science Center at Houston, where he is the Director of the Neuropsychiatry Program. He also holds a professorial position at the Institute of Education and Research of Santa Casa, Belo Horizonte, Brazil.

After completing medical residency in internal medicine, neurology, and psychiatry, he had the opportunity to be trained in cellular biology and immunology. First at the Federal University of Minas Gerais and later at the University of Texas, he has developed basic and clinical/translational research aiming to understand the involvement of immune mechanisms in behavior and cognition. He was also involved in epidemiological studies assessing the burden of neuropsychiatric conditions.

He has published more than 700 peer-reviewed articles, reviews, and book chapters and edited several textbooks in neurology and psychiatry, most recently the book *Immunopsychiatry: A Clinician's Introduction to the Immune Basis of Mental Disorders* (Oxford University Press).

Bernhard T. Baune, PhD, MD, MPH, MBA, FRANZCP, is the Director of the Department of Psychiatry and Psychotherapy, University of Münster, Germany, and of the Laboratory Division of Molecular Neurobiology of Mental Health at the University of Münster. He has been the Cato Chair and Head of the Department of Psychiatry at the University of Melbourne, Australia, prior to being awarded the Director position at the University of Münster. He is a Fellow of the Royal Australian and New Zealand College of Psychiatrists (FRANZCP) and is a Professorial Fellow of the Department of Psychiatry, University of Melbourne, and also at the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia. He is known for his extensive research program into depression and cognitive dysfunction, personalized and molecular psychiatry, prediction and biomarker research and treatment response research as well as for his key research achievements in the field of immune-neurobiology of psychiatric disorders. His translational work at the University of Münster is designed to make real-world differences to the lives of people with mental illness by integrating neurobiological and clinical information, by personalizing treatments, and by targeting the mechanisms of functional recovery. His other related works include the leadership of an international consortium on the genomics of severe depression and response to ECT in affective disorders (GenECT-ic) as well as leading an international study on the genomics of cognitive function in depression and directing the ECNP TWG network on transdiagnostic pharmacogenomics and transcriptomics in psychiatric disorders. His research is nationally and internationally widely recognized. He has published more than 520 peer-reviewed articles, reviews, and book chapters and edited several textbooks in psychiatry, most recently the books *Personalized Psychiatry* (Elsevier), *Inflammation and Immunity in Depression: Basic Science and Clinical Applications* (Elsevier), and *Cognitive Dimensions of Major Depressive Disorder* (Oxford University Press).

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She has experience in neuroscience with an emphasis on animal models of psychiatric disorders such as schizophrenia and mood disorders and is devoted to the study of the long-term consequences of early-life adversities such as immune challenge and maternal separation. She has published more than 150 peer-reviewed articles, reviews, and book chapters.

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Perinatal Psychiatry: Ready for Prime Time?

Sudhakar Selvaraj, Haitham Salem, Cristian P. Zeni, and Antonio L. Teixeira

Abstract Perinatal psychiatry deals primarily with women's mental health before labor and up to the first year post-childbirth and the growth and development of their offspring. Early insults to the developing brain of the fetus are consistently linked to later neuropsychiatric disorders. Maternal stress and depression, for instance, can trigger inflammation in the fetal brain, and studies consistently show the link between these events and the development of psychiatric disorders in the offspring. Postnatal mental disorders increase maternal morbidity and interfere with maternal bonding, thus impacting the health and development of the offspring. The aim of this chapter was to provide a brief overview of the field of perinatal psychiatry.

Keywords Maternal mental health · Child psychiatry · Developmental neurology · Neuroinflammation

1 Introduction

The World Health Organization's study on the global burden of disease lists psychiatric disorders among the leading causes of disability worldwide [1–3]. Despite their personal and societal impacts, psychiatric disorders are plagued by stigma, preventing their proper recognition and management. The related stigma can be traced back to the history of theories about causation of mental illness as discussed later in this chapter.

Perinatal psychiatry is the area of psychiatry dedicated to the care of pregnant and parturient women. In 2011, the Centers for Disease Control and Prevention

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estimated the prevalence of perinatal depression as 9% among pregnant women and 10% among postpartum women who all meet the criteria for major depression disorder. Such numbers pose a significant cost to individuals, children, families, and the whole society as untreated perinatal psychiatric disorders can increase maternal morbidity and interfere with maternal bonding [3]. Due to the consequences of maternal symptoms in the emotional and physical health of the offspring, perinatal psychiatry has gotten significant attention lately. Indeed the need for early recognition and treatment to avoid or minimize negative outcomes for the mother, baby, and family cannot be overemphasized. Perinatal psychiatry requires knowledge from psychological constructs (e.g., attachment theory), neuroscience (specifically the neurodevelopment of the neonate and the infant), and an integrated effort with obstetrics and pediatrics [4].

Children and adolescents affected by psychiatric disorders have also been a growing focus of medical interest as these conditions prevent the individual to achieve his/her full potential in life [5–7]. Between 13% and 20% of children and adolescents worldwide are estimated to suffer from disabling mental illness [8]. The US Census Bureau estimated, in 2014, a population of approximately 1.8 billions youth (4–19 years old) around the world, among which approximately 241 million are affected by psychiatric disorders. One interesting fact is that the majority of the epidemiological research on the determinants of mental health has been conducted in high-income country populations, while the greatest burden and health disparities are observed in low- and middle-income countries. Multiple studies showed that children and adolescents coming from families with low socioeconomic status are more likely to develop mental health problems than their peers with higher socioeconomic status [9–11].

2 A Brief Historical Perspective on the Etiopathogenesis of Mental Illnesses

Documented human knowledge of mental illnesses dates back to ancient civilizations that attributed their causation to demons or wrath of angels, while exorcism techniques were employed to drive demons out of the afflicted person's body as treatments [12]. In the fifth century B.C., the Greek historian Herodotus wrote about a king who was driven mad by evil spirits [13]. The Greek physician Hippocrates, considered the Father of Medicine, proposed the humoral theory that viewed causation of mental illnesses due to an imbalance of the four body fluids called "humors." [5] Hippocrates reported four types of humors: yellow bile, black pile, phlegm, and blood; and he postulated that depression was caused by too much "black bile," hence the name "melancholia." [14]. Melancholia is derived from the Ancient Greek "melas" meaning black and "kholé" meaning bile. The therapeutic interventions targeted, therefore, the restoration of the body balance or equilibrium.

Current medical knowledge about mental illnesses evolved in the nineteenth century when psychiatric syndromes were beginning to be characterized, and brain anatomy was being detailed. Studies of the "general paralysis," later identified as neurosyphilis, showed the link between central nervous system infection and behavioral syndromes [15]. Over a few decades, the neuropathology of dementia and other neurodegenerative diseases was characterized by postmortem brain studies, while no consistent brain pathological changes were identified in "functional mental illnesses." To address the causation of these latter conditions, psychological theories were proposed [16] and psychoanalysis became highly influential, giving significant emphasis on early life events, such as the attachment of the mother to the baby [17, 18].

In parallel to diverse psychological theories, several physicians and researchers believed that disturbances in brain development could predispose for psychiatric disorders, but this concept remained largely underappreciated until the neurobiological research got back to the mainstream. The development of psychopharmacology after the 1950s and its strong impact in the treatment of mental illness were the underlying force for this paradigm shift. The dopaminergic hypothesis of schizophrenia [19] and the catecholamine hypothesis of affective disorders [20] were proposed. Advances in genetics confirmed the heredity of several psychiatric disorders but also suggested the role played by non-genetic, i.e., environmental, factors.

The current understanding of the etiopathogenesis of mental illnesses views that they are multifactorial, likely resulting from the interplay of genetics and environment factors, including prenatal events and life stress. Twin and adoption studies have demonstrated that heredity is a significant factor in the etiopathogenesis of schizophrenia [21, 22] and bipolar disorder [23]. As studies trying to identify specific genes predisposing to major psychiatric disorders were largely unsuccessful, the summation of multiple genes has been implicated in the etiopathogenesis of such complex conditions [23]. Currently, schizophrenia has been conceived as a neurodevelopmental disorder resulting from the interaction of genetic and environmental factors [24, 25], with impairments in cognitive, motor, and social functioning preceding the full manifestation of symptoms in early adulthood [26].

Several lines of research support the neurodevelopmental theory of schizophrenia [27]. First, brain imaging studies showed brain volume loss even before the onset of psychotic experience, i.e., hallucinations and delusions [26]. Second, despite its manifestation in early adulthood and its chronic course, neurodegenerative changes in postmortem human brains from patients with schizophrenia are not evident. Third, many patients exhibit early "soft" neurological signs at childhood before any psychotic symptoms. Fourth, there is a robust association between early brain trauma due to obstetric complications and later risk of schizophrenia. Maternal nutrition is another environmental risk factor that may play a crucial role in the causation of schizophrenia as epidemiological studies have shown a strong link between mothers' exposure to famine during the early pregnancy stages and later risk of schizophrenia in offsprings [28].

Emerging large-scale genetic studies suggest that other psychiatric disorders such as autism and bipolar disorder may share genetic and/or neurodevelopmental factors with schizophrenia [29]. Depressive disorders also run in families [30–32], though heritability estimates (37%) are substantially less than those for schizophrenia (83%) and bipolar disorder (85%) [33]. Actually, environmental factors seem to play a more relevant role in depression. Childhood adversity and trauma, particularly sexual abuse [34], has been linked to the later development of depression, personality features of neuroticism [35], and a more severe course of psychiatric disorders [36].

The neuropsychiatric disorders in the offspring do not necessarily replicate maternal psychopathology, reinforcing the role of mechanisms other than genetics. In the most important study of offspring of mothers with depression (STAR∗D), it was observed that nearly half of the offspring (45%) had a lifetime psychiatric disorder, including disruptive behavior (29%), anxiety (20%), and depressive (19%) disorders. The following characteristics of maternal depression were associated to specific offspring disorders: maternal comorbid panic disorder with agoraphobia and offspring depressive and anxiety disorders, maternal irritable depression and offspring disruptive behavior disorders and any disorder, and maternal substance use disorders and any disorder. Even though these associations are not specific for prenatal or postpartum depression, they emphasize the plurality of negative outcomes in the offspring. One interesting finding of this study is the concomitant improvement of mother and offspring when mothers received treatment, raising the issue of how interventions during pregnancy could impact the future generation [37, 38].

3 Inflammation: Connecting the Dots

A number of studies have investigated whether inflammatory mechanisms are involved in the pathogenesis of schizophrenia and other major psychiatric disorders [39]. In schizophrenia, for example, genome-wide association studies linked several inflammation-related genes to an increased risk of the condition [40, 41]. Postmortem prefrontal cortex samples from schizophrenic patients have shown upregulation of genes involved in inflammatory response [42]. Moreover, inflammation/neuroinflammation related to neuronal and synaptic plasticity presents a potential mechanistic role in the neurodevelopmental theory of schizophrenia [43]. A very important point is the timing of the insult to development of the neuropsychiatric disorder. One of the most accepted theories support the two-hit hypothesis. In this theory, besides the genetic background, problems that affect the mother will cause different consequences to the offspring (first hit) according to the moment of development, such as an earlier onset or a more severe disorder [44].

There are several stages of neurodevelopment from early conceptual stages to the birth of the baby and then postnatal brain development and cortical maturation that

continue for several years. Early fetal period, which extends to approximate midgestation, is critical in the development of the neocortex [45]. Differentiation of the neural progenitor cells and the formation of the neural tube are the first steps in the central nervous system development that start as early as the second week of gestation. Early fetal period is clinically important as many medications and other drugs that are taken by the pregnant woman during this period may affect brain development. For instance, sodium valproate, a widely used anti-epileptic and mood stabilizer, is not recommended in any women in childbearing age due to the risk of congenital malformations, especially neural tube defects [46]. After the formation of the neural tube, further maturation, neuronal and glial production, migration, and differentiation continue to shape the growing brain throughout the fetal gestation period until the second trimester. These are critical periods of vulnerability during brain development regulated by both genetic and environmental factors. Genetic factors provide the developing brain a template while environmental factors – through immune/inflammatory mechanisms, among others – shape and regulate the brain development and functioning. Disruption of these mechanisms (first hit) leads to the risk of development of neuropsychiatric disorders.

Most of the available studies on early mechanisms derive from experimental investigations with other species. Exposure to prenatal stress can lead to significant increase in microglial activity, the mainline of immune defense in the brain [47–49]. Maternal deprivation stress at early postnatal stage also increases inflammatory markers in the offspring brain [46]. Exacerbated immune responses were found in prenatally stressed animals that were subsequently given an immune challenge in adulthood [47–49]. These observations support the notion that early-life stress sensitizes microglial cells so that there is an exaggerated microglial response to stress in late adolescence or young adulthood, when the "second hit" usually happens, underlying the development of psychiatric disorders [47–53]. Once the condition is established, an inflammatory process might mediate progressive neuronal injury, resulting, for example, in the grey matter volume loss seen in schizophrenia and other major psychiatric disorders [49].

Maternal health, stress, and nutritional status have been long recognized to be among the most important factors in fetal neurodevelopment. Maternal depression during pregnancy is associated with decreased self-care, reduced rates of adherence to prenatal care, and increased recreational drug use [54]. These all culminate in poorer health outcomes for both mother and developing fetus. Maternal stress and depression can trigger inflammation in the brain, and studies consistently show the link between neuroinflammation and the development of psychiatric disorders in the offspring.

After childbirth, depressive symptoms can also severely impair the mother's ability to interact/attach and communicate with her child [55], exerting a detrimental effect on cognitive and emotional development of the child, leading to an elevated risk for behavioral and psychiatric disorders [49]. Actually, maternal mental illnesses create a stressful environment for infants at a vulnerable developmental stage in their life [56].

4 Conclusions and Future Perspectives

New research using animal models has been able to help psychiatry drift from previous nonempirical theories to a more mechanistic understanding of healthy development and mental disorders. Prenatal and early years of life are crucial for brain development. Minimizing the adverse impact of maternal psychopathology may lead to less brain insults and is very important to prevent long-term mental health problems. Despite the body of evidence supporting the link between prenatal/perinatal brain insults and later onset of psychiatric disorders in humans, there is a critical knowledge gap in the mechanisms involved and the strategies to improve early brain development. Current knowledge supports the participation of immune mechanisms in the onset of mental illness. Evidence-based strategies to personalize care of pregnant women and their offspring will be of great importance in the prevention of psychiatric disorders. In the meantime, early screening and intervention are pivotal in reducing the negative impact of mental health problems in the mother and the child. Embracing healthy lifestyle by cutting down smoking, drugs, and alcohol intake, managing stress, proper nutrition, and physical activity during pregnancy are attainable strategies that could have substantial impact in the prevention of neurodevelopmental and psychiatric disorders.

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Developmental Programming During Psychological Stress in Pregnancy: A Neurobiological Perspective

Natalie Aboustate and Bernhard T. Baune

Abstract This chapter reviews how psychosocial stress during pregnancy can program neuroimmunoendocrine regulation in the fetus and predict psychopathology across the life course. Perturbations to the stress response caused by maternal mental illness or social distress can be inherited by offspring through maladaptive changes to the fetal hypothalamic-pituitary-adrenal (HPA) axis, inflammatory response and neurodevelopment in general. We briefly review the physiology of maternal stress (including the role of glucocorticoids and inflammation), its 'programming effects' on the fetus and how these adaptations affect the stress response across the life course. We also discuss epidemiological findings and seminal mechanistic evidence underlying neuropsychiatric outcomes associated with *in utero* stress. Both the endocrine and immune systems play a significant role in modern theories on psychiatric disease; therefore, *in utero* development is important for understanding the long-term outcomes of antenatal maternal stress in her offspring.

Keywords Developmental psychiatry · Developmental programming · Psychological stress in pregnancy · Fetal programming · Transgenerational · Psychiatric disorder aetiology · Hypothalamic-pituitary-adrenal axis · Neuropsychiatric outcomes · Glucocorticoids · Immunoendocrine · Inflammation in psychiatry · Mental illness · Neurodevelopment

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1 Introduction

As a heterogeneous disease state, mental illness remains a complex challenge for medicine. Psychiatric disorders encompass heterogeneous phenotypes related to a combination of inherited, environmental and psychosocial factors. For example, an individual may be genetically predisposed to developing a specific disorder and when exposed to psychosocial distress, reinforced by social adversity, they may experience the onset of psychiatric illness. Fetal life is a critical period of development, involving genes and their interaction with environmental perturbations. Recent literature has demonstrated the importance of a mother's mental well-being on fetal biology. The *in utero* environment effectively 'programs' the fetus for its life *ex utero,* thereby adapting it to maternal physiology. Psychosocial stress affects maternal physiology by disrupting regulatory relationships between the immune and endocrine systems (e.g. chronic stress can cause hyposensitivity to cortisol [84] and is associated with pro-inflammatory cytokine dominance [54]). It can therefore increase fetal exposure to cortisol and inflammation, which not only increases the risk of pregnancy complications [117], but also affects fetal neurodevelopment [68]. These risk factors significantly affect neurobiology and therefore psychiatric outcomes, independently of, or in addition to the postnatal environment. While various mechanisms may program increased psychiatric risk during pregnancy (see [86]), this review focuses on the HPA-axis and its interaction with inflammation, as they both have well-established roles in the stress response.

2 Stress and the HPA-Axis

Animals and humans experience stress when exposed to a perceived threat. The stress response is then mediated by the limbic system, as initiated by the amygdala that sends danger signals to the hypothalamus. Stress subsequently increases cognitive processing: including arousal, alertness, vigilance and attention [34]. Specifically, the stress response is regulated by the HPA-axis through the actions of various hormones. Briefly, HPA-axis activation releases corticotrophin-releasing hormone (CRH) and vasopressin (AVP) from the hypothalamus. CRH and AVP activate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland into the blood, leading to glucocorticoid secretion by the adrenal cortex. Glucocorticoids such as cortisol engage the glucocorticoid receptor (GR) and form an active complex with it, to function as a genetic regulator. This active complex can activate or repress response elements on target genes and elicit physiological functions specific to stress, including upregulated gluconeogenesis and metabolism, and repressed inflammation. The release of cortisol into plasma then forms a negative feedback loop with the hypothalamus and pituitary gland (where GR density is highest in the body) to terminate stress signalling. The stress response typically declines between 60 and 90 min following the body's perception of a stressor, glucocorticoid release into circulation (peaking at 15–30 min) and activation of the negative feedback loop (Fig. 1).

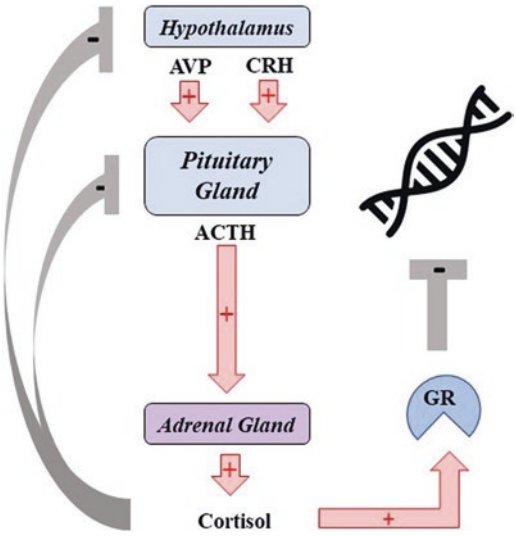

Fig. 1 Positive and negative feedback loops in the HPA-axis that form during a stress response

Cortisol's negative feedback loop becomes perturbed upon chronic stress signalling, leading to HPA-axis dysregulation. Given the breadth of its role in physiological responses (e.g. in metabolism, immunity and the central nervous system), this remains a significant contributor to disease, including psychiatric disorders [34, 86, 132]. As such, the HPA-axis is implicated in the catecholamine hypothesis of depression pathophysiology [113], which argues dysfunctional stress responses can lead to monoamine dysregulation in some individuals. Excess cortisol production, resulting from high stress or dysregulated signalling by the HPA-axis, also has significant effects on the hippocampus, amygdala and frontal lobe [36, 67, 78], resulting in deficits in attention and memory-based cognition [34].

Chronic stress has been associated with a phenomenon known as glucocorticoid resistance, where the HPA-axis becomes desensitised to cortisol [84]. This also occurs in the context of chronic inflammation, which can be related to GR dysfunction [118]. Chronic stress that alters GR expression is associated with hippocampal atrophy, decreased neurogenesis, changes in catecholamine signalling, decreased synaptic plasticity and impaired learning (for review see [34]). This exemplifies the theory of allostasis, where the body becomes maladapted to the stress response after it cannot return to a homeostatic state following the resolution of a stressor [80]. An allostatic load develops when these stress-related mediators remain present in the body (or chronic stress occurs), resulting in damage or 'wear' over time.

2.1 Glucocorticoids and Inflammation

Psychological stress is implicated in increasing the body's inflammatory response. Studies have shown increased C-reactive protein (CRP) and pro-inflammatory cytokine expression is associated with stress, independently of infection or adiposity

[77]. Further, several studies have linked mood and anxiety disorders (including major depressive disorder (MDD) and post-traumatic stress disorder (PTSD)) with pro-inflammatory bodily states [95, 124]. While the underlying pathogenesis for this remains sparsely characterised, there is significant evidence that inflammation causes neurodegeneration, reduced cortical integrity and decreased neural plasticity in association with psychiatric disorders [124]. As inflammation and glucocorticoids are dependent on each other, it is likely that the relationship between stress, the HPA-axis and inflammation predisposes individuals to psychiatric morbidity.

Glucocorticoids are typically regarded as having anti-inflammatory effects. They are known to downregulate immune signalling by engaging directly with immune cells and suppressing pro-inflammatory cytokine and chemokine expression. Interestingly, in the context of psychological stress, a meta-analysis has indicated that human stress tests are associated with increased circulating pro-inflammatory IL-6, IL-1β and TNF-α, and anti-inflammatory IL-10; which peak 30–90 min following exposure to a stressor [77]. Similarly, chronic stressors such as social stress and traumatic life events 'resistant to behavioural coping' are also associated with inflammation [66]. Underlying mechanisms for this may relate to glucocorticoid resistance by immune cells and an increase in stress hormones such as catecholamines and cortisol. It is also suggested that HPA-axis dysfunction conferred by abnormal cortisol expression may lead to long-term, persistent inflammation. Together, these studies demonstrate how consistent increases in glucocorticoid expression perturb inflammatory homeostasis and lead to a pro-inflammatory cytokine milieu in the body.

3 The Physiological Effects of Stress During Pregnancy: Developmental Programming

Stress and mental illness are common in pregnancy, with over half the world's female population of reproductive age living in poverty [127]. This is critical as pregnancy is a sensitive period of development, where the fetus adapts to its perceived *ex utero* environment as driven by physiological perturbations its mother is exposed to. The Developmental Origins of Health and Disease (DoHAD) paradigm hypothesises that *in utero* perturbations alter fetal development and therefore have a 'programming' effect on the fetus [11]. Historically, the DoHAD hypothesis focused on the role of *in utero* perturbations that lead to low birthweight (e.g. intrauterine growth restriction), which are associated with an increased incidence of cardiovascular and metabolic disease in adulthood [10]. Today, these adaptations are reinforced by concepts of epigenetic remodelling, where the maternal environment alters the fetal phenotype to produce offspring that are more robust to adverse *ex utero* conditions. Accumulating evidence suggests *in utero* events such as infection and growth restriction also influence mental health in offspring [3, 5]. As stress alters physiology during pregnancy through HPA-axis signalling, associations between maternal stress and fetal neurodevelopment are increasingly evident and may program psychiatric morbidity during adult life.

3.1 Stress and Inflammation in Pregnancy

Pregnancy involves natural fluctuations in the expression of inflammatory mediators and glucocorticoids to facilitate various stages of gestation. Specifically, implantation and parturition are both pro-inflammatory states and glucocorticoids are involved in organ maturation throughout gestation. These time-dependent effects require strict regulation through endocrine and immune crosstalk, as aberrant inflammation is linked to premature labour, growth restriction and fetal brain damage [47]. When a pregnant mother experiences psychological stress or exhibits HPA-axis dysregulation (potentially due to chronic stress or high allostatic load), fetal exposure to cortisol and inflammation may be increased.

Both chronic and acute stress (including experiencing trauma or violence) during pregnancy are associated with significant elevations in pro-inflammatory mediators (e.g. TNFα, IL-6 and CRP), in maternal and cord blood [7], and the placenta [63] (see [53] for review). The interface between immune and endocrine programming on the fetus is evidenced by animal models that show antenatal exposure to pathogens attenuates the neonatal immune response [13]. Additionally, others have suggested that chronic stress during pregnancy may contribute to immunosuppression that leaves women susceptible to infection [28]. Notably, this latter association has limited evidence, as low income is used as an analogue for chronic stress (rather than psychometric testing) and a small sample size was investigated. Overall, however, there remains a clear link between psychosocial stress and a pro-inflammatory response during pregnancy. This is supported by studies that associated increased CRP and IL-6, and decreased anti-inflammatory IL-10 expression during the third trimester, with self-reported maternal psychosocial stress and poor social support [29]. Further, chronic increases in glucocorticoids during stress or depression have been associated with pro-inflammatory cytokine expression and, therefore, preterm delivery and poor neurodevelopment [31].

The effects of glucocorticoids on inflammation are time and dose dependent [9]. Specifically, glucocorticoids may initially suppress the immune response; however, increased exposure to synthetic glucocorticoids pathologically upregulates inflammation in, at least, the context of ovine pregnancy [62, 70]. This model likely reflects acute maternal stress in humans, which affects the inflammatory response in cord blood. Specifically, cord blood from mothers who scored higher on the Beck Depression Inventory (BDI) in their second trimester expressed increased IL-6 and IL-10 compared to low-scoring mothers, indicating *in utero* immune activation [79]. When these cord blood cells were cultured with allergens, they also increased IL-10 and IL-6 expression compared to cells from pregnancies of non-stressed mothers, suggesting programming of the neonatal response. MDD and anxiety are typically associated with increased levels of circulating pro-inflammatory cytokines [73], an effect which is increased further with pregnancy [30]. Together, these studies show maternal psychological stress can prime neonates towards mounting an increased inflammatory response *ex utero*. Aberrant cytokine expression during pregnancy can also impact fetal brain development via microglial activation and changes to

dendritic and neuronal growth and survival [51]. Inflammatory activation within the central nervous system thereby predisposes the fetus to adverse neurodevelopmental and psychiatric outcomes.

The immunoendocrine interface in human pregnancy is analogous to murine studies that show restraint stress during pregnancy is associated with increased pro-inflammatory cytokine expression in the placenta and fetal brain [52]. This study also observed reduced Brain-derived Neurotrophic Factor (BDNF) expression in the female adult amygdala, indicating perturbed neurodevelopment. Similarly, a study on maternal CRP and IL-6 expression throughout pregnancy found these cytokines were positively correlated with brain connectivity, volume and circuit complexity [121]. Infection during pregnancy can also lead to restricted uterine blood flow infection in association with increased placental CRH [126], inferring an underlying relationship between inflammation and altered fetal HPA-axis activity. Together these studies support maternal immune activation is detrimental to fetal neurodevelopment, where inflammation alters neuronal architecture and functional connectivity.

3.2 Cortisol in Pregnancy

While fetal cortisol levels are correlated with their mother's [12], a majority of maternal cortisol is oxidised into cortisone (its inactive form) before passing into fetal circulation [43]. Murine models of prenatal stress demonstrate programming of the offspring HPA-axis in that they have a hyperactive stress system, disrupted negative feedback loops between cortisol and the HPA-axis, and increase CRH expression in the amygdala (that decreases hippocampal GR expression) [86]. Further, the placenta also expresses endogenous CRH, which increases throughout pregnancy and triggers the expression of maternal cortisol, though its effects on maternal mood are incompletely characterised [53]. Cortisol is catalysed by the 11β-Hydroxysteroid dehydrogenase (11βHSD) 1 and 2 enzymes, which are highly expressed in placenta [20]. Strict regulation of cortisol exposure by the fetoplacental barrier is critical during fetal development, when cortisol surges represent major developmental triggers typical of the pre-delivery period in normal pregnancies [40]. As such, the expression of 11βHSD2 changes throughout pregnancy to accommodate various developmental cues that signal for organ maturation [57]. When pregnancy approaches term gestation, an estimated 75% of cortisol in fetal circulation is endogenously expressed [12].

Increased maternal stress or anxiety can downregulate 11βHSD2, thereby increasing fetal exposure to cortisol [46, 92]. Fluctuations in cortisol exposure can maladapt the HPA-axis *in utero*, increase sensitivity to stress hormones and program negative feedback systems, ultimately modulating the *ex utero* stress response. The theory behind this also involves increased GR expression in the fetal brain in association with maternal stress [71]. Importantly, studies have shown that antenatal stress, including anxiety and depression, is correlated with decreased waking uri-

nary cortisol production in 4-year-old children, independently of 11βHSD2 [116]. 11βHSD2 can also be downregulated by catecholamines [111], inflammation [61] and maternal anxiety and depression [93]. Maternal anxiety has also been associated with increased cortisol levels in amniotic fluid, and decreased placental 11βHSD2 [44, 55]. Subsequently, amniotic fluid cortisol is correlated with decreased performance on the Bayley's mental development index in 18-month-olds, as moderated by secure infant maternal attachment [14]. This suggests infants' predisposition to poor mental health may not be permanent, reflecting positive effects of brain plasticity and/or healthy socialisation. Overall, placental studies provide useful insights into the *in utero* environment, as they reflect physiological events throughout pregnancy and effectively describe the intrauterine environment's 'phenotype'. Placental monitoring is therefore a useful tool for determining offspring disease susceptibility, where 11βHSD2 expression represents a putative biomarker for HPA-axis dysregulation in offspring.

4 How Stress *in utero* Shapes Children

Thirty percent of pregnant women report experiencing stress during pregnancy [129], with up to 12% meeting symptom criteria for at least one psychiatric disorder (an effect exacerbated by low income) [85]. This is critical because maternal stress affects neonatal neurodevelopment including brain anatomy and behaviour. This can be conferred via the damaging effects of aberrant cortisol and/or inflammatory mediator expression. Most directly, the development of fetal brain structures, including neuronal architecture and functional connectivity, can be damaged by inflammation [17]. Increased maternal IL-6 expression throughout pregnancy has been associated with increased neonatal amygdala volume and connectivity; which predict poor impulse control in the same 2-year-old children [49]. This is notable because limbic system function affects the stress response and is implicated in aetiology of poor emotional regulation [102], which can be associated with affective disorders [119].

Chronic or acute exposure to glucocorticoids *in utero* augments postnatal cortisol levels in offspring during stress and infection [33, 83]. This occurs because the developing HPA-axis is highly sensitive to glucocorticoids, which can alter GR density in the HPA-axis [132]. As such, exposure to synthetic glucocorticoids within 12 h of delivery is associated with higher baseline cortisol in preterm-born neonatal serum until 1 week of age [89]. Such findings are also positively correlated with gestational age, fetal distress and low Apgar scores, highlighting an association between cortisol and poor birth outcomes. Similarly, salivary samples from preterm-born infants at 18 months age show differential patterns of cortisol production in those affected by funisitis (acute inflammation of the umbilical cord) [48], reinforcing a role for immune activation in dysregulating the HPA-axis.

The effects of glucocorticoid-related programming depend on the nature of cortisol production (i.e. chronic or acute) and show age-dependent outcomes in children's stress responses. Acutely chronic maternal stress in gestation programs an increased glucocorticoid response to postnatal stress in infants [50] and adolescents [38]. This may begin where neonates demonstrate increased stress reactivity (cortisol expression), which is negatively correlated with diurnal maternal cortisol during pregnancy [88]. Subsequently, elevated maternal cortisol during pregnancy is associated with increased amygdala volume and affective problems in 7-year-old girls (ibid). As the amygdala is involved in HPA-axis modulation of the stress response [76] and mood regulation [24], this suggests a putative origin for increased susceptibility to developing affective disorders.

Maternal mental illness (e.g. anxiety and depression) is linked to higher stress during pregnancy and is also associated with increased baseline [75] and stimulated [105] ACTH and cortisol expression in the neonate. Further, maternal depressive symptoms are associated with decreased developmental index scores in 18-month-olds [69]. A comprehensive systematic review of studies with varying methodologies has shown maternal distress across gestation programs both externalising and internalising symptoms, anxiety, depression and behavioural issues in their children, as moderated by family functioning and support [129]. Further to this, longitudinal studies have found high maternal anxiety doubles the risk of developing psychiatric disorders in children aged between 4 and 13 years, after adjusting for postnatal maternal anxiety and depression, socio-economic status and parenting style [86, 91].

4.1 Exposure to Synthetic Glucocorticoids in utero

As cortisol increases naturally across gestation to drive the final stages of fetal organ maturation [12], perinatal practice guidelines support the administration of synthetic glucocorticoids (betamethasone or dexamethasone) during the management of threatened preterm labour [107]. While their use has decreased morbidity and mortality in preterm neonates, recent studies have shown they have a detrimental effect on neurodevelopmental outcomes [120]. Specifically, both preterm- and term-born neonates exposed to antenatal betamethasone exhibit reduced cortical thickness and affective problems [32]. Reduced cortical convolution and surface area are also thought to be the product of three or more doses of antenatal betamethasone [85]. This glucocorticoid-related programming remains evident in childhood, when antenatal betamethasone exposure is associated with an increased cortisol response to stress in children aged 6–11 years [4]. While preterm neonates are already vulnerable to poor neurodevelopment, the observation of a similar effect in term-born neonates exposed to synthetic glucocorticoids highlights their role in perturbed brain development. It is important to note that altered brain anatomy resulting from high stress (e.g. reduced cortical thickness) are also prevalent in disorders such as schizophrenia [25].

4.2 The Role of Epigenetics in Developmental Programming

Gene–environment interactions can be characterised using epigenetics, a novel field that is particularly informative in the context of pregnancy. There is significant evidence that epigenetic programming occurs transgenerationally in animal models and clinical studies of psychological stress (reviewed in [8, 60]). Epigenetic modifications can lead to changes in how genes are transcribed, where they can decrease or repress the expression of a target gene [46]. This occurs via mechanisms such as DNA methylation, histone modifications, chromatin remodelling and post-transcriptional regulation by non-coding RNAs. The epigenome conferred during pregnancy is modifiable and susceptible to further epigenetic reprogramming throughout gestation, which demonstrates its value as a putative therapeutic target. A majority of studies on transgenerational epigenetics have been characterised using animal models, as they are quick to reproduce. As such, early life stress in rodents (e.g. decreased maternal care) results in GR methylation in the brain and can be inherited by subsequent generations [132]. Seminal work using animal models of intergenerational trauma have determined chronic maternal separation during the early life of mice confers depressive behaviours in two subsequent generations of offspring, in a sex-specific manner [41]. Studies on rats have also demonstrated the transgenerational conferral of depressive-like behaviours [6, 114]. Similar effects of DNA methylation are observed in humans, where maternal anxiety and depressive symptoms during pregnancy are associated with increased cord blood GR methylation [56]. This is also observed in association with maternal PTSD [97] and mothers who experience intimate partner violence during pregnancy [101]. The placenta exhibits adaptations to maternal stress, anxiety or depression through epigenetic change, whereby it increases DNA methylation of the *11βHSD2* gene and GR gene promoter, *NR3C1* [56, 98]. Subsequently, increased placental 11βHSD2 methylation in maternal anxiety or depression is associated with neonatal hypotonia and decreased self-regulation [27, 81]. The inheritance of epigenetic change is subsequently evidenced by studies on cord blood cells that show increased DNA methylation of *NR3C1* in association with maternal anxiety in pregnancy [56].

The link between epigenetic change and its physiological consequences (e.g. hypercortisolemia and inflammation) is not fully understood, and there may also be other factors which influence transgenerational stress dysregulation. Additionally, how these changes are associated with poor birth outcomes and/or compromise infant neuropsychiatry are incompletely characterised. Changes to the fetal stress response may only be evident upon similar postnatal challenge, and therefore, offspring psychopathology may be a part of a two-hit hypothesis moderated by increased susceptibility to a particular psychiatric disorder and decreased resilience to stress.

4.3 Sex-Specific Effects on HPA-Axis Programming

Sex-specific effects contribute significantly to HPA-axis programming, though they are seldom accounted for in developmental psychiatry [2]. Fetal sex confers divergent adaptations to physiological stress *in utero,* where females (unlike males) restrict their physical growth during inflammatory stress [26]. These changes occur independently of sex hormones, and similarly, sex differences are observed with fetal HPA-axis development [110] and immune function [35]. Different antenatal factors related to the immunoendocrine interface appear to predict variable outcomes, which highlights a need for further research in this field. For example, in some studies, pro-inflammatory cytokine dominance during pregnancy is a predictor of MDD in adult male, but not female, offspring [42], while HPA-axis perturbations (e.g. increased maternal stress) predict increased cortisol expression in females across their life course [100, 123, 128]. Interestingly, placental 11βHSD2 expression is increased in pregnancies carrying female fetus compared to males [86], which suggests they encounter decreased cortisol exposure *in utero.* A contributor to these disparities may be sex-specific placental GR isoform expression, which would alter glucocorticoid sensitivity [109].

Sex-specific outcomes are also prevalent in psychiatry, part of which may relate to developmental biology [45]. Males are more likely to exhibit aggressive behaviour [103] and suffer from autism [74], while females are more susceptible to developing anxiety and depression [64]. As such, large cohort studies have shown maternal anxiety during pregnancy programs increased diurnal cortisol expression in female neonates [18]. Subsequently, increased maternal cortisol in pregnancy has been associated with fearful temperament, larger amygdalae and affective problems in females throughout development [24, 110]. Alternately, male offspring demonstrate decreased negative emotionality as infants [18, 19]. While these effects may change over childhood due to brain plasticity and environmental factors, large cohort studies in adults identified low birthweight (commonly associated with stress in pregnancy) as a predictor of depression in females [18]. This highlights a need for longitudinal studies that precisely confirm mechanistic links between stress, fetal sex and neuropsychiatric outcome.

5 Neuropsychiatric Programming following Stress *in utero*

The developmental origins of psychopathology established its own discipline in the 1970s, in careful separation from child psychiatry [59]. While the latter discipline has its own unique focus, some childhood disorders may originate similarly from *in utero* perturbations. Brain development commences early during gestation and consists of ongoing neuronal proliferation, differentiation, synapse development and myelination. The fetal brain is therefore vulnerable to its intra-

uterine environment throughout gestation that may cause permanent changes to brain anatomy. As altered brain anatomy can be associated with various psychiatric disorders, its developmental origins are critical to determining such aetiology. For example, population studies have confirmed intrauterine growth restriction is a significant risk for psychotic symptoms in both children [125] and adults [1]. A possible mechanism for this could be nutrient deprivation, which alters glucocorticoid catabolism and encourages adrenocortical hypertrophy [133], potentially leading to hypercortisolaemia. Unfortunately, this link remains unconfirmed and a common caveat with epidemiological studies is that they are complicated by significant confounders such as socio-economic status [125] and the child's postnatal environment [34]. Nonetheless, some authors have poignantly argued that these findings are useful markers for altered neurodevelopment or endocrine dysfunction [18]. Further, community-based studies have shown acute anxiety during pregnancy is associated with a clinically significant, 6% increased risk of children developing a mental disorder during adolescence, even after correcting for postnatal maternal mood and socio-economic status [90]. Inflammation is also inextricably linked with the HPA-axis, both of which have significant effects on developmental programming and can alter psychopathology throughout life. Overall, these factors align with the diathesis-stress model [82], where the accumulation of different susceptibilities (e.g. genetic risk) and allostatic stressors (e.g. social disadvantage) overload an individual's psychological equilibrium.

Disruptions to HPA-axis function associated with perturbations in pregnancy are central to offspring stress regulation. The severity of psychological stress during pregnancy may have divergent effects on child outcomes. A meta-analysis has supported individuals with MDD express increased ACTH and cortisol [122]. Conversely, PTSD has been associated with decreased levels of urinary, salivary and circulating cortisol [122, 131]. Thus, when women with MDD or PTSD fall pregnant, HPA-axis activity may impact the fetus differently. Ovine models support this, demonstrating that chronic maternal stress allows the fetus more time to adapt physiologically to a stressor and has improved pregnancy outcomes compared to acute stress [37]. In terms of epidemiology, acute traumatic stress during pregnancy has, to date, been more commonly associated with an increased risk for neuropsychiatric disorders, including depression [58], schizophrenia [130] and autism [15, 20].

Neuroendocrine disturbances are postulated to underlie a susceptibility to impaired adult cognition and emotional processing, with HPA-axis dysregulation being implicated in the pathology of depression [122] (i.e. individuals demonstrate increased daily urinary cortisol [34], and CRH and AVP expression in the brain [99]). Poor resilience to stress is therefore implicated in MDD [106], where acute hypercortisolaemia is associated with increased emotional arousal, psychotic symptoms and poor cognitive function. Poor resilience can establish itself early, when infants of mothers who experience emotional abuse during pregnancy demonstrate increased stress reactivity and impaired cognition at 18 months [14]. This

maladaptation is also evident in adolescents who were exposed to maternal stress *in utero,* and express increased cortisol [128]. Notably, most studies on stress in pregnancy described by this chapter do not represent clinical hypercortisolaemia, increases in fetal cortisol may prime certain individuals to experience stress more chronically. These phenotypes demonstrate altered sensitivity to cortisol, which can increase their allostatic load over life.

Maternal infection is also a significant contributor to theories on the developmental origins of psychiatric disorders ([39] for review). However, the link between an increased risk of psychosis in offspring of mothers exposed to viral infections is criticised by meta-analyses for lacking serological confirmation of their exposure to specific viruses [65, 115]. A more general association between experiencing a respiratory infection during pregnancy has instead found a two-fold increased risk for schizophrenia spectrum disorder among their offspring [23]. This has been reinforced by the study of an extensive cohort recruited as part of the 'Prenatal Determinants of Schizophrenia Study' [21], which reported a three-fold increased risk for schizophrenia in the offspring of women who had serologically confirmed influenza during pregnancy [22]. The biological basis for such a relationship may be related to evidence of neuroinflammation, as marked by microglial activation [16], and the increased expression of pro-inflammatory cytokines [96] and transcriptional regulators [104] in individuals with schizophrenia. Additionally, stress during pregnancy can restrict uterine blood flow, and infection is associated with increased placental CRH [5]; compounding any effects on neurodevelopment. Therefore, where maternal infection does not directly lead to fetal neuronal degeneration, it can result in epigenetic changes, program the HPA-axis and/or contribute to a cumulative allostatic burden.

Psychiatric disorders are complex, exhibiting heterogeneous phenotypes and multifactorial aetiologies. The difficulty in separating the effects of psychological stress during and after pregnancy therefore limits research within this area. Primary moderators of *in utero* programming include childhood maltreatment and adversity, which independently increase GR expression [94] and allostatic load [112]. Postnatal depression or anxiety also affect maternal attachment and parenting style, which impacts infant mental health. Similarly, a stressful antenatal environment that includes financial stress, social dysfunction or domestic violence is unlikely to resolve postnatally. Unfortunately, most studies in developmental psychiatry focus on singular stressors during pregnancy and research accounting for mechanistic links or the allostatic load of different stressors is key to closing the gap in discrepancies caused by such confounders. Overall, physiological changes by the fetal HPA-axis to cope with maternal stress may be maladaptive and increase the risk for other diseases. While the developing brain is somewhat plastic and may remain protected from adverse changes earlier in childhood, a multiple-hit hypothesis of psychiatric morbidity may arise following psychological stress during the postnatal period or upbringing, particularly where their mother suffers from chronic stress or psychiatric morbidity herself (Fig. 2).

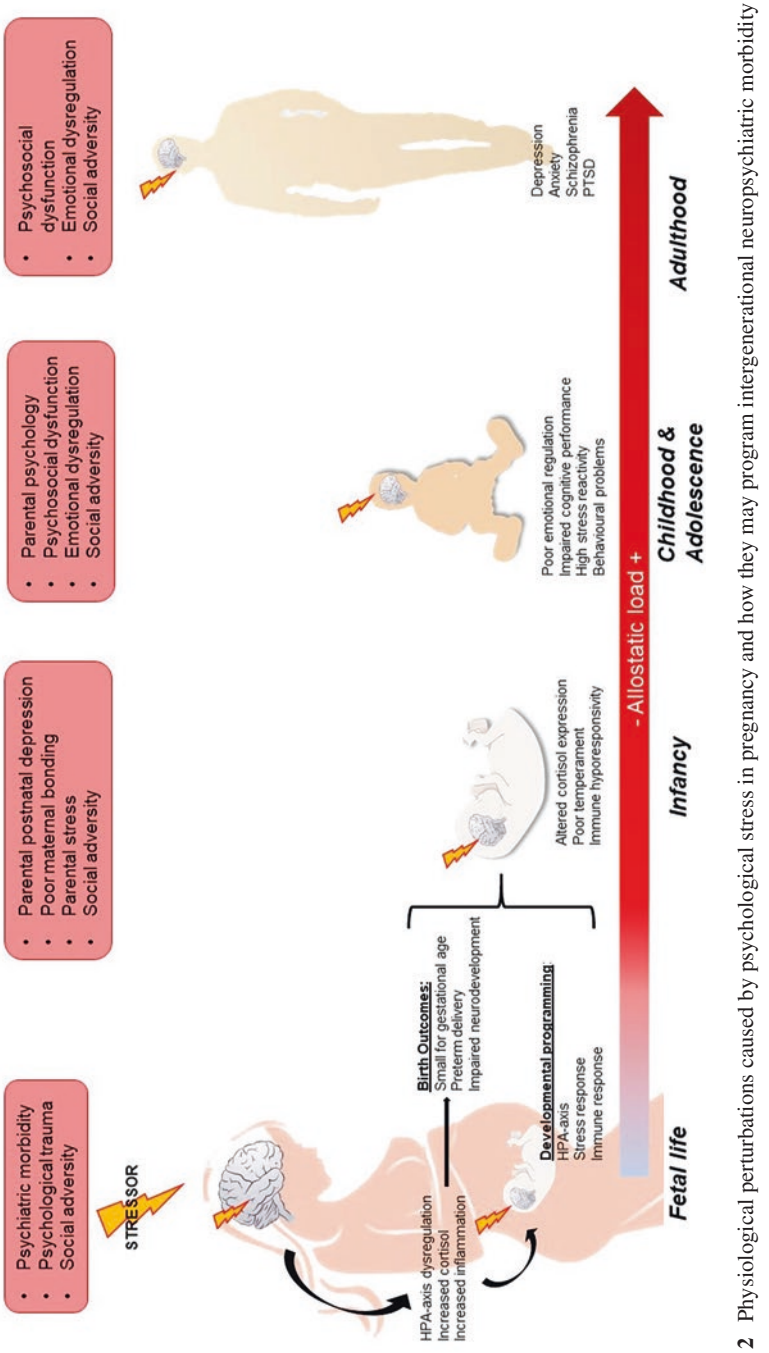

Fig. 2 Physiological perturbations caused by psychological stress in pregnancy and how they may program intergenerational neuropsychiatric morbidity

6 Conclusions and Future Directions

Neuropsychiatric risk is a multifaceted topic that involves interactions between genes, proteins and their environment. This chapter has reviewed the physiology of stress during pregnancy and potential mechanisms for how it programs fetal neurodevelopment in the context of psychopathology. The physiology of psychological maternal stress during pregnancy can place the fetus at risk of poor neurodevelopment, and subsequently, early life exposure to the same stressors could contribute to mental illness under a multiple-hit hypothesis. Individuals already genetically predisposed to mental illness may further inherit a more susceptible epigenome and/or maladapted stress response which makes them more vulnerable to disease.

Currently, most studies in developmental psychiatry are epidemiological or correlational, and further research on direct, causative mechanisms is required. A majority of current findings suggest stressed mothers breed stressed offspring due to biological vulnerabilities created during pregnancy, independently of their postnatal environment (though it can modulate this effect). Specifically, increased inflammation and fluctuations in cortisol can be particularly harmful to the developing brain. As a mediator of maternal cortisol exposure, the placenta may therefore serve as a useful diagnostic tool for determining offspring health outcomes and identifying individuals that require additional psychological support. Following infancy, a majority of research in developmental psychiatry is only beginning to account for neurobiological psychopathology (e.g. using cortisol quantification or brain imaging) and is restricted to childhood or early adolescence. Longitudinal mechanistic studies are required to confirm epidemiological findings that link *in utero* stress to long-term psychiatric outcomes in adults. Deeper clinical phenotyping of prospective cohorts should also occur, in order to account for critical confounders and moderators of this effect: maternal mental illness, social adversity and early life stress.

Overall, investigations in this field to date provide several putative predictive biomarkers and therapeutic targets in pregnancy associated with pathological psychiatric phenotypes. Currently, the prescription of psychotropics to manage depression and anxiety during pregnancy is increasing. However, some authors are concerned with findings that these drugs dysregulate the fetal limbic system and lead to adverse neurodevelopmental outcomes [72], which may increase offspring susceptibility to anxiety disorders [108]. Early interventions that limit allostatic loading in childhood (e.g. addressing maternal postnatal depression and domestic violence) are recommended by authors who favour dyadic approaches to maternal and child psychiatric treatment [86]. Further development of alternative treatment options targeting social determinants of health to ameliorate maternal stress may therefore be more efficacious at decreasing allostatic load across a child's life course.

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Epigenetic Modifications of Early-Life Stress and Adult Life Psychopathology

Chris Murgatroyd

Abstract There is much evidence linking adverse conditions during early life to risk of developing mood disorders in later life. Exposures to high levels of stress during early development are able to impact maturation of pathways regulating stress and immune systems leading to programming long-term changes in stress reactivity and immune functioning throughout later life. Current research is investigating the molecular mechanisms controlling this programming, specifically, how epigenetic mechanisms are able to induce long-lasting changes in gene expression potential at key genes important in modulating stress and inflammatory responses. In this chapter, I discuss the evidence linking how early-life environments drive long-term outcomes through the regulation of neuroendocrine and immune pathways specifically implicated in lasting perturbations in HPA axis and glucocorticoid regulation leading to vulnerability to the development of psychopathology.

Keywords Early-life stress · HPA axis · Immune · DNA methylation · Epigenetic

1 Introduction

Levels of stress and adversity in early life are closely linked to mental health in later life. Numerous translational rodent experiments and human studies provide evidence that variations in early environment can impact physical and mental development leading to alterations in mood, cognition and other aspects of behaviour. Specifically, stressors and adversity during periods of early development can mould individual variations in vulnerability to stress-related disorders throughout later life (*for review see* [1]). This raises the issue as to how mechanistically environmental experiences are able to incorporate at the molecular and cellular levels to program long-term alterations in neurobiological functions, including coordinating responses to stresses that may influence risk to development of psychopathology.

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Within this chapter I discuss and contrast some of the animal and human studies investigating the epigenetic control of gene regulation in programming the effects of adverse experiences in early life. I focus on studies that have examined how early-life stress is able to alter the activity of neuroendocrine stress systems, particularly the hypothalamic-pituitary-adrenal (HPA) axis and immune systems, leading to long-term alterations in stress reactivity. I will explore what we know about the role and identities of epigenetic systems and their functions in programming the development of neuronal and immune systems and disease in response to prenatal and postnatal environmental stress.

2 Early-Life Adversity Moulds Later Life Stress Responsivity

Upon exposure to a stressor, two systems are activated. The autonomic nervous system initiates a rapid and relatively short-lived response, often referred to as "fight-or-flight". The HPA axis on the other-hand is slower, initiating a more prolonged response. A tight regulation of the HPA axis is crucial to the long-term control of systems managing stress responsivity. Following a stressor, the paraventricular nucleus (PVN) of the hypothalamus releases two neuropeptides, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These stimulate the anterior pituitary (or hypophysis) to release the hormone adrenocorticotrophic hormone (ACTH) which in turn acts on the adrenal cortex to release the glucocorticoids cortisol in humans and corticosterone in animals. Through the action of glucocorticoid receptors (GR) a negative feedback loop is formed that allows return to a homeostatic balance when the stress is no longer present. This negative feedback however can become dysregulated, particularly following periods of chronic stress, that can impact the development of stress-related disorders. Altered activity of the HPA axis, and specifically dysregulation in negative feedback control, is one of the most commonly observed neuroendocrine changes in major depressive disorder (*for review see* [20]).

High levels of stress during prenatal, postnatal and early childhood are strong predictors of impaired inhibitory feedback regulation of the HPA axis, with dysregulation lasting into adulthood, long after the early adverse experience (*for review see* [46]). Studies in rodent models further support the notion that exposure to chronic levels of stress can lead to persistent alterations in HPA axis control and behaviour (*for review see* [44]). Such chronic dysregulation of the HPA axis has serious consequences for future mental health being implicated in the pathogenesis of and increasing risk for numerous chronic physical and mood-related disorders.

3 Bidirectional Regulation of the HPA Axis and Immune System

A tight regulation of the inflammatory response is critical to ensure quick protection following infections and injuries that do not become chronic leading to damage of organs and tissues. A dysregulation of the immune system, for example following sustained activity, can lead to chronic low-grade inflammation. Such systemic inflammation has been linked to many chronic diseases of aging, such as diabetes, obesity-related problems, cardiovascular disease, autoimmune disease, and cancer, as well as psychiatric disorders [17].

Between the HPA axis and the immune system, there is a bidirectional communication. Hence, HPA dysregulation generally leads to increased inflammation especially when HPA axis alterations are chronic and long lasting, and this may influence many long-term health conditions (*for review see* [3, 43]). Immune cells, through the production of various cytokines, are able to activate the HPA axis, leading to the release of glucocorticoids (*for review see* [13]). While glucocorticoids have well-known immunosuppressive roles that serve to repress the inflammatory response, they also have an important function in regulating pro-inflammatory functions of immune cells to coordinate inflammatory responses [6]. Hence, glucocorticoids are key immune modulators allowing stress to both acutely enhance and chronically suppress peripheral immune responses [11].

4 Depression and Inflammation

Chronic stress and depression are strongly associated with increased activity of the innate immune system. Numerous studies in patients with depression have shown alterations in the activity of the immune system in the CNS and periphery [19]. For example, depressed individuals exhibit activated inflammatory responses as measured by increased circulating levels of inflammatory cytokines such as IL-1β, IL-6, IFN-γ, TNF-α [12]. A recent study of inflammatory markers in major depressive disorder (MDD) patients, who had never received treatment for depression, revealed elevated levels of 18 pro- (IL-12, TNF, IL-6, IFNγ, IL-9, IL-17A) and anti- (IL-5, IL-15, IL-10, IL-2, IL-13) inflammatory cytokines, chemokines (MIP1α/CCL3, RANTES/CCL5) and growth factors (G-CSF, PDGF, FGF, IL-7), together with lower levels of six cytokines and chemokines (IP10/CXCL10, MCP1/CCL2, IL-8, MIP1β/CCL4) compared to healthy controls. Further, there was a decrease of the activation and cellular memory of healthy donor peripheral blood mononuclear cells (PBMC)s exposed to plasma of major depressive disorder (MDD) patients compared to the plasma of healthy control subjects, supporting cellular immunosuppressive properties of the plasma of MDD patients [64]. Overall, these findings support a major remodelling of the inflammatory landscape in MDD patients.

Several studies support that these serum or plasma changes relate to regulatory changes in the expression of cytokine genes within the peripheral blood cells. For example, higher mRNA levels of TNF-α, IL-1β, IL-6 and INF-α have been found in the leukocytes of patients suffering from MDD [8, 65] while another study found increased expression of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, their receptors, TNFR1, TNFR2, IL-1R1 and the antagonist IL-1RA in lymphocytes of MDD patients compared with controls [56]. A genome-wide longitudinal study on 1846 individuals found the strongest expression differences between the depressed and control groups were in genes enriched for IL-6-signaling and natural killer (NK) cell pathways [23]. Furthermore, many pro-inflammatory cytokines have been significantly correlated with several clinical depressive "traits". In particular higher cytokine levels in serum have been associated with higher depression severity [5] as well as with poor antidepressant response [8].

Increased inflammation (or neuroinflammation) is also found in post-mortem brains of depressed and suicide patients. For example, a gene expression array on prefrontal cortex revealed increases in pro-inflammatory cytokines (IL-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, IFNγ and TNF-α) in depressed suicide patients compared to controls [60]. Finally, further supporting the link between cytokines and immune activation in depression, several polymorphisms in genes encoding immune and inflammatory molecules have been identified in association with depression (*for review see* [4]).

5 Programming Inflammation by Early-Life Adversity

Accumulating evidence suggests that the experience of early-life adversity is a risk factor for a range of poor outcomes across development, including poor physical health in adulthood. Numerous studies support the impact of early-life adversity on programming lasting alterations in inflammatory processes. Genome-wide transcription analysis of adults grown up in environments of high vs. low socioeconomic status in early life revealed that those exposed to low showed significant increased regulation of genes containing CREB/ATF response elements and response elements for NF-kappaB, while there was a reduced expression in genes containing response elements for the glucocorticoid receptor. This was together with increased cortisol levels and stimulated production of IL- 6. Together, this suggests that low socioeconomic early-life environment programs a defensive phenotype characterized by resistance to glucocorticoid signalling, which in turn facilitates exaggerated adrenocortical and inflammatory responses. [38]. A further study demonstrated that an increased IL-6 production in adolescents with histories of childhood adversity preceded subsequent development of depression 6 months later [40]. Ehrich et al. found that monocytes of adolescent girls exposed to early-life adversity, when stimulated in vitro with a bacterial product, displayed larger IL-6 responses and relatively less sensitivity to glucocorticoids compared to those with less early-life adversity [14].

Overall, these studies suggest that childhood adversity programs a pro-inflammatory phenotype in immune cells which results in the exhibition of increased inflammatory responses to stimuli and lower insensitivity to signals that dampen this response. Fitting with the biological embedding model [39], these response patterns over the long term are thought to contribute to the low-grade chronic inflammation implicated in the development and progression of stress-related and age-related illnesses. Thus early stress exposure, it would appear, stimulates inflammatory signalling between the brain and periphery, coupling depression and inflammation and increasing risk for the development of psychiatric disorders. This posits the question of how adversity during early life is mechanistically able to program changes in the stress and immune systems.

6 Epigenetics

This term relates to mechanisms that are able to stably alter gene regulation during development and differentiation, that are under the influence of the environment (*for review see* [47]). Genomes can be thought of containing two layers of information akin to hardware and software of a computer: there is the DNA sequence that is conserved throughout life and mostly identical in all cells of a body, and there are the epigenetic marks that are cell specific and can be dynamic. Epigenetic mechanisms enable regulation of genes, independent of DNA sequence.

DNA methylation and modification of core histones that package the DNA into chromatin represent the best-understood epigenetic marks. These marks are able to control the accessibility of the DNA to the machinery driving gene expression; inaccessible genes become silenced whereas accessible genes are actively transcribed. Organisms and their cells, with these epigenetic mechanisms, are able to integrate intrinsic and environmental signals into the genome, resulting in regulatory control of gene expression and thus facilitating adaptation. In this way, epigenetic mechanisms are able to respond to the early-life environmental signals to allow a way by which early experiences can be integrated into the genome as a kind of memory to program adult hormonal and behavioural responses.

DNA methylation refers to the addition of a methyl group to a cytosine nucleotide in a cytosine– guanine sequence, known as a CpG. This generally forms a silencing mark. Hence, promoters and enhancer elements of transcriptionally active genes are usually unmethylated but may become silenced once targeted by DNA methylation. Mechanistically, the methylation of a cytosine may either directly block DNA binding of specific transcription factors or attract other factors that preferentially bind to methylated or unmethylated DNA to interfere with transcription factor accessibility.

The vast majority (70–80%) of all CpGs are methylated. Around 85% of these are located in repetitive sequences such as transposons that make up about half of the human genome. The other 15% generally cluster within GC-rich regions known as “CpG islands” that are defined as regions of greater than 500 bp that have

cytosine/guanine content of greater than 55%; around 70% of promoter regions of genes contain a CpG island. The process of DNA methylation depends on a family of enzymes known as DNA methyltransferases (DNMTs). DNMT1 recognizes hemimethylated DNA and methylates appropriate cytosines in newly synthesized daughter strands formed during replication, acting as the maintenance DNMT. DNMT3A and DNMT3B can methylate unmethylated DNA supportive of their roles as de novo methylases. DNA methylation can also be reversed. For example, during development there are global and gene-specific increases and decreases in levels of 5mC. The TET family of enzymes can modify 5mC to 5-hydroxymethylcytosine (5hmC) as part of the processes of active demethylation. This modification appears to be particularly abundant in brain [71] and immune cells [22] and might allow dynamic regulation of DNA methylation. In general, patterns of DNA methylation tend to correlate with chromatin structure. For example, regions of hypomethylated DNA associate with active chromatin marks while hypermethylated DNA is found with inactive chromatin.

The major proteins of chromatin, histones, can play both positive and negative roles in gene expression through various modifications, forming the basis of a "histone code" for gene regulation [25]. For example, histone acetylation is known to be a predominant signal for active chromatin configurations while some specific histone methylation reactions are associated with either gene silencing or activation. These are regulated through an array of histone-modifying enzymes that catalyze the addition or removal of an array of covalent modifications.

This leads to the concept that epigenetic changes at sensitive gene promoters for immune regulators could explain the persistence of early-life effects into adulthood of programmed inflammatory and HPA axis dysregulation, increasing risk of psychiatry disorders.

7 Epigenetic Programming of Stress and Immune-Related Genes by Prenatal Stress

Epigenetic mechanisms have been hypothesized to enable fine-tuning of gene expression potential in response to environmental cues, allowing pre- and postnatal environments to induce changes in DNA methylation. This facilitates epigenetic programming of critical genes involved in regulating stress responsivity and immune function that may in turn manifest with psychopathology in adulthood (Fig. 1).

Studies in both animal models and human cohorts provide evidence to show an association with prenatal stress and increased risks in offspring of stress-related disorders, psychopathology and alterations in HPA axis in later life (*for review see* [2]) together with alterations in immune function (*for review see* [21]). Long-term neurological and immune effects of early-life stress appear to be mediated through alterations in the maternal and fetal HPA axes.

One mechanism is that excess maternal glucocorticoids may pass the placental barrier and disrupt fetal brain and immune development. An important factor in

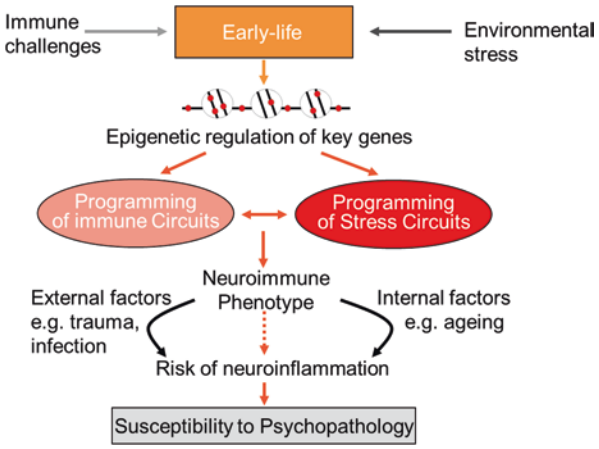

Fig. 1 Programming of stress and immune regulation by early-life stress. Stress and immune challenges in early life can program persistent stress responsivity and immune regulation throughout later life through the epigenetic alteration of the expression levels of key genes involved in stress regulation and inflammation. Levels of stress throughout later life may exacerbate the effects of programming established during early life, resulting in increased vulnerability to psychopathology

regulating the supply of maternal glucocorticoids to the developing fetus is the placental enzyme, 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), that deactivates cortisol as maternal glucocorticoid levels are up to tenfold higher than in the fetus [59]. Rodent studies have shown that this gene is upregulated following acute stress in pregnancy [70] and that chronic stress and prenatal maternal anxiety are associated with increased CpG methylation at the promoter of the *11β-HSD2* gene together with increased expression in the placenta [24]. In humans, a study by O'Donnell et al. [49] revealed that prenatal trait anxiety negatively correlated with placental *11β-HSD2* mRNA expression, while a study by Conradt et al. [10] revealed that intrauterine exposure to maternal depression negatively affected infant behaviour and this was associated with increased methylation of the placental *11β-HSD2* and *NR3C1* (Glucocorticoid Receptor) genes. This suggests that epigenetic regulation of *11β-HSD2* links environmental cues transmitted from the mother to the fetus during pregnancy that could program the response to adverse postnatal environment. Further studies have also identified differential epigenetic regulation of glucorticoids. For example, a study by Oberlander et al. [50] revealed that prenatal exposure to maternal depressed/anxious mood during the 3rd trimester resulted in increased methylation of a CpG-rich region in the promoter and exon1F of the *NR3C1* gene in the cord blood of newborns, which correlated with salivary cortisol levels in infants at 3 months of age. Murgatroyd and colleagues [45] found similar increased methylation in infants exposed to prenatal maternal depression, supporting that prenatal stress can alter epigenetic regulation of genes involved in glucocorticoid control that could program immune and stress responsivity. These studies also support that many results from parental studies in animals have translational value in human studies (See Table 1).

Table 1 Rodent and human studies investigating DNA methylation at stress and immune-related genes following prenatal stress

Reference	Gene	Animal	Form of stress	Model	Tissues	Methylation
[41]	nr3c1	Mouse	Prenatal stress	Chronic stress to pregnant dams	Brain	1–7 ↑
[50]	NR3C1	Human	Maternal depression	At birth	Cord blood	1-F ↑
[10]	NR3C1	Human	Maternal depression	At birth	Placenta	1-F ↑
[45]	NR3C1	Human	Maternal depression	30 years	Saliva	1-F ↑
[28]	Fkbp5	Rats	Prenatal exposure	Perinatal BPA exposure	Hippo	Intron 5 ↑
[33]	Fkbp5	Mouse	Chronic pregnant stress	Chronic exposure to CORT Via drinking water	Blood, hippo	Intron 5 ↑
[27]	FKBP5	Human	Chronic stress, war trauma or prenatal stress	24 mother, newborn 26 years	Blood, placenta	Intron 5 ↑
[42]	FKBP5	Human	Prenatal/postnatal stressors	298 14-months-old infants	Blood	Intron 5 ↑
[24]	11β-HSD2	Rat	Chronic restraint stress during gestational days 14–20)		Placenta	Promoter ↑
[10]	11β-HSD2	Human	Maternal depression		Placenta	Promoter ↑

Prenatal stress may also affect fetal development through epigenetic programming of cytokine genes. Cao-Lei et al., examining prenatal response to maternal stress during the 1998 Quebec ice storm, found that perceived maternal exposure to the ice storm resulted in significant alterations in cytokine levels (including TNF-α, IL-1β, IL-6, IL-4 and IL-13) within their offspring together with DNA methylation changes in T-lymphocytes at genes predominantly associated with immune function [7].

8 Epigenetic Programming of Stress and Immune-Related Genes by Postnatal Stress

Numerous studies in humans provide strong support that stress during early postnatal life and childhood may cause a range of physical and psychiatric problems in adulthood including depressive-related disorders and alterations in HPA axis activity (*for review see* [47]). Although the association between early-life stressful events and depression may arise through numerous processes, a number of studies have posited a role for increased inflammatory responses (*for review see* [9]).

Studies on rodent models have demonstrated that various postnatal stress paradigms can program anxiety and depression-like behaviours together with dysregulation of the HPA axis glucocorticoids [44] together with programming premature activation of the immune system. From the other direction, there is evidence that early-life immune exposure can program HPA axis activity. Sominsky et al., for example, showed in rats that neonatal lipopolysaccharide exposure induces strong increases in HPA axis activity together with increased brain expression of *Crh* and *Nr3c1* genes [62]

One of the first studies to investigate the epigenetic effects of early-life environment on stress programming through variations in the quality of early postnatal maternal care, as measured by levels of licking and grooming, was performed by the group of Michael Meaney. They demonstrated that rat pups who received high levels of maternal care (licking and grooming) showed sustained elevations in *Nr3c1* expression within the hippocampus and reduced HPA axis responses to stress. Further, this associated with a lasting reduction in DNA methylation at specific CpG dinucleotides within the hippocampal *Nr3c1* exon 1–7 promoter that allowed increased binding of the transcriptional activator nerve growth factor-inducible protein A (NGF1a) to this region [69]

A number of human studies show that the epigenetic programming seen in the early-life stress animal experiments translates to humans (*for review see* Smart et al. [61]) (See Table 2). For example, McGowan and colleagues found increased methylation of *NR3C1* promoter among suicide victims with a history of abuse in childhood, but not among controls or suicide victims who did not suffer such early-life stress [36]. Studies have shown that epigenetic alterations following early stress are not limited to brain tissues but may occur in peripheral tissues as well, suggesting that alterations in glucocorticoid receptors in peripheral blood cells that may link to possible changes in glucocorticoid receptor resistance. For example, studies using DNA from blood or saliva of infants, adolescents or adults have shown increased levels of *NR3C1* methylation following postnatal stress or abuse or neglect during childhood.

While some studies have focused on candidate genes involved in HPA-axis regulation, epigenome-wide studies have allowed identification of broad methylation changes that introduce new potential biological pathways related to childhood adversity. Labonte et al. in a genome-wide study of hippocampal tissue from postmortem brains of individuals with a history of severe childhood abuse compared to control subjects identified 362 differentially methylated promoters – genes involved in cellular/neuronal plasticity were among the most significantly differentially methylated [32]. Suderman et al. identified 997 differentially methylated promoters in whole blood DNA of adult subjects were differentially methylated in association with childhood abuse [63]. Most of these were associated in key cell signalling pathways linked to development and regulation of transcription. Provencal et al. identified 448 differentially methylated gene promoters in individual adult men with a history of parental physical aggression from 6 to 15 years of age compared to a control group. Most of these genes have been previously demonstrated to play a substantial role in aggression and were enriched in biological pathways that are affected by behaviour [55].

Table 2 Rodent and human studies investigating DNA methylation at stress- and immune-related genes following postnatal stress

Reference	Gene	Animal	Form of stress	Model	Tissues	Methylation
[69]	Nr3c1	Rat	Increased early maternal care	High licking and grooming	Hippocampus	1–7 ↓
[26]	Nr3c1	Mus	Early-life stress	Maternal separation	Hippocampus	1–7 ↑
[30]	Nr3c1	Rat	Early maternal care	Reduced care by altering litters	Hippocampus	1–7 ↑
[31]	Nr3c1	Mouse	Early-life stress	Maternal separation	Hippocampus	1–7 ↑
[48]	Nr3c1	Rat	Reduced maternal care	Chronic social stress	PVN	1–7 ↑
[53]	NR3C1	Human	Sexual abuse	30–40 years	Blood	1-F ↑
[66]	NR3C1	Human	Early-life trauma	27.3 years	Blood	1-F ↑
[37]	NR3C1	Human	Childhood adversity (depressed)	55 years	Blood	1-F ↑
[52]	NR3C1	Human	Childhood trauma, bipolar	44.6 years	Blood	1-F ↑
[68]	NR3C1	Human	Early-life trauma	16.3 years	Blood	1-D ↓, 1-F ↑
[34]	NR3C1	Human	Childhood abuse	29.4 years	Blood	1-F ↑
[57]	NR3C1	Human	Child abuse and neglect	12 years	Blood	1-F ↑
[35]	NR3C1	Human	Child abuse, suicide	34 years	Hippocampus	1-F ↑
[32]	NR3C1	Human	Child abuse, suicide	37 years	Hippocampus	1-B ↑, 1-C ↑, 1-H ↓
[15]	NR3C1	Human	Childhood stress	15.1 years	Buccal	1-F ↑
[33]	Fkbp5	Mouse	Chronic pregnant stress	Chronic exposure to CORT Via drinking water	Blood, hippo	Intron 5 ↑
[16]	Fkbp5	Mouse	Chronic stress	5 doses of CORT of drinking water	Blood, hippocampus	Intron 1 ↑ Intron 5 ↑
[58]	Fkbp5	Mouse	Depression-like behaviours	Forced stress and tail suspension	Blood	Intron 5 ↑
[72]	FKBP5	Human	Early-life trauma	Pre-treatment, post-treatment, 3 months follow-up.	Blood	Exon 7–8 ↑
[67]	FKBP5	Human	Childhood maltreatment	N = 69 preschool, 3-5 years.	Blood	Intron 7 ↓
[51]	FKBP5	Human	Childhood maltreatment	231 preschoolers	Saliva	Intron 7 ↑

Results from the studies using peripheral cells lead to the question if DNA methylation differences in blood reflect epigenetic changes in the brain. In a study in rhesus macaques, Provencal et al. demonstrated that variations in mothering associated with alterations in DNA methylation, including the homologue of *NR3C1* gene that showed significant correlations between prefrontal cortex samples and T lymphocyte cells with differential rearing-inducing methylation marks common between both tissues [54]. Importantly though, results in general tend to suggest that DNA methylation in lymphocytes do not directly signify methylation in the brain tissue, but probably reflect the response of the immune system to early-life stress, again supporting the important link between blood and brain. Therefore, the possibility that epigenetic responses to environmental stress in early-life stress can be studied in peripheral lymphocytes, as a surrogate for the brain, provides a major opportunity to study DNA methylation in human cohorts and longitudinal studies.

Studies have started to show that risks for the development of depression in later life following childhood trauma can depend upon genetic differences (*for review see* [18]). The hypothesis is that neuroendocrine, particularly HPA activity, resultant from early-life stress could increase risk to develop depression in response to stress later in life dependent on key gene polymorphisms, known as gene-environment (GxE). A study by Klengel et al. showed an increased risk of developing adult stress-related psychiatric disorders associated with allele-specific, childhood trauma-dependent DNA demethylation at glucocorticoid response DNA elements of the FK506 binding protein 51 (*FKBP5*) gene, which encodes a co-chaperone which regulates GR sensitivity [29]. The demethylation of *FKBP5* related to an increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global effect on immune functions and brain areas linked to stress regulation.

9 Conclusions

Exposure to adversity in early life increases risk for the development of stress-related disorders. Within this chapter, I have reviewed the current literature on studies of the role of epigenetic changes altering gene regulation expression that can be programed. This chapter particularly focuses on the role of the immune system with research demonstrating that prenatal and postnatal environments can stimulate inflammatory systems through epigenetic programming. Persistent alterations in gene expression that are maintained into adulthood can lead to an increased susceptibility to develop inflammation and psychiatric disorders. It is crucial to appreciate the core epigenetic mechanisms responsible for programming the long-term reaction to early-life environmental stressors to enable to understand and identify specific alterations at key genes that underlie the development of stress-related disorders. The major hypothesis is that epigenetic regulation during early life in response to adverse environmental exposures could prime genes for reactions to future environment. In this context, this mechanism can allow an animal to adapt to

alterations in environments throughout later life. However, these processes of adaption can elevate the possibility of developing disease in later life particularly if there is a mismatch between the earlier and later life environments.

In order to understand the relationship between inflammation- and stress-related disorders, it is imperative to examine whether elevations in immune activation associated with particular gene pathways involved in psychiatric disorders, which together with changes in immune biomarkers could be used as an approach to screen patients with stress-related diseases. Such individuals may respond to pharmacological interventions that target inflammatory pathways. As it is becoming clearer that immune activation and elevated inflammation are seen in individuals with major depression, especially those with resistance to antidepressant therapies (*for review see* [9]), it would be important to test if elevated inflammation pinpoints a categories of depressed patients that perhaps experienced early-life adversity and are also resistant to particular classes of antidepressants.

In summary, understanding the mechanisms by which adverse conditions during early life can program persistent changes in epigenetic programming regulating risk for psychopathology is a rapidly developing area in psychiatry. The possibility that pharmacological or psychological interventions, or life-style changes, could reverse epigenetic programming previously induced by stressful environmental exposures during early life should be an important focus of future research.

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Hypothalamus-Pituitary-Adrenal Axis Programming by Early-Life Stress: A Role Played by Inflammatory and Epigenetic Mechanisms

Gabriel R. Fries

Abstract Early-life stress exposure, regardless whether pre-, peri-, or post-natal, has been shown to increase the risk for psychiatric disorders in vulnerable subjects. One of the hypothesis that explains this association suggests that early-life stress can induce a programming of the main physiological system responsible for the stress response, namely, the hypothalamus-pituitary-adrenal (HPA) axis. Indeed, several lines of evidence suggest that exposure to early trauma or stressful events can induce permanent alterations in the HPA axis, some of which are also seen in patients with psychiatric disorders. This chapter will discuss clinical and preclinical evidence of HPA programming by early-life stress and the molecular mechanisms suggested to underlie it, i.e., inflammation and epigenetic mechanisms. Future perspectives and clinical implications of the HPA programming and its biological basis are also discussed.

Keywords Stress · Inflammation · Epigenetics · HPA axis · Glucocorticoid receptor · Cortisol · Programming

1 Introduction

Several studies have suggested that exposure to early environmental triggers or stressors can have permanent effects on individuals. The permanent organization of physiological systems by early-life events is known as "programming" [1], and it entails several mechanisms discussed in this and other chapters. Specifically, there

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is strong evidence to suggest that early-life stress (including prenatal, perinatal, and post-natal exposure) increases the risk of psychiatric disorders both during childhood and adulthood [2]. The reasons and mechanisms by which this occurs are still obscure, although it has been hypothesized that such programming and adaptation to environmental triggers involves the permanent modulation of the hypothalamus-pituitary-adrenal (HPA) axis. Accordingly, a dysregulation of the HPA axis is not only known to affect stress reactivity and psychiatric disorders, but has also been linked to several pathological conditions, such as metabolic and cardiovascular disorders, sleep disturbances, obesity, and altered gastrointestinal and immune function [3].

The HPA axis is the main physiological system responsible for the "fight or flight" stress response in humans. In response to stressful conditions of threat to homeostasis, neurons in the paraventricular nucleus of the hypothalamus are activated and secrete the 41-amino acid neuropeptide corticotropin-releasing hormone (CRH), along with the arginine-vasopressin (AVP), into the hypophyseal portal blood [3]. In the pituitary, CRH stimulates the production of the prohormone proopiomelanocortin (POMC), which is later cleaved to form the adrenocorticotrophic hormone (ACTH) and other peptides. Once secreted into the bloodstream, ACTH reaches the adrenal cortex and stimulates the production of the glucocorticoid hormone cortisol, which finally acts as the main driver of the stress response mainly through the glucocorticoid receptor (GR) [3]. Stress-related cortisol effects are widespread in the organism, including alterations in the immune, cardiovascular, and gastrointestinal systems, changes in the feeding and sleep behaviors, and enhancement of memory and attention, among other effects [3]. After a period of time, the cortisol acts in the brain to deactivate the HPA axis and reduce its own levels by a GR-mediated negative feedback loop, ultimately restoring baseline cortisol levels. In situations of chronic exposure to high levels of cortisol, such as during chronic stress or in cases of impaired negative feedback of the HPA axis, chronic cortisol exposure can have deleterious effects, especially in regions with a high concentration of cortisol receptors [4].

The HPA axis is thought to be an important player in the early-life programming that increases the risk for psychopathology later in life [5]. Accordingly, several studies report susceptibility of the HPA axis to pre- and perinatal influences [3]. In addition, multiple studies have shown that such early-life stressors can modify the HPA axis in a permanent way, with cases of early-life-induced mechanisms inducing HPA axis dysfunction detectable in adults [6]. These permanent alterations have been shown to include changes in ACTH responsiveness [7], the HPA axis negative feedback [8], GR expression, CRH and AVP levels, among others [5]. In this chapter, we will review evidence of HPA axis programming by early-life stress and discuss possible mechanisms by which this process can take place. A special emphasis will be given to inflammatory and epigenetic mechanisms, both of which are known to act on the HPA axis and are of particular relevance for psychiatric disorders, as well.

2 HPA Axis Programming by Early-Life Stress

The term "early-life stress" has been used to describe several different situations, including prenatal (fetal), perinatal (immediately before and after birth), and postnatal exposure to stress. Given the different levels of brain development and HPA function, the effects of stressors in each of these developmental stages can vary significantly. In general, a higher risk for psychopathology has been reported in adults exposed to several different types of early stress, including gestational adverse events [3], pre-term birth [9], childhood trauma, maltreatment, neglect, separation, abuse, among others [2]. In this section, we will discuss evidence of HPA programming during each of these developmental stages (pre-, peri-, and post-natal).

The prenatal period is marked by an active brain plasticity and high levels of neurogenesis in the fetus and therefore represents a highly susceptible stage for the fetus to *in utero* exposures [3, 10]. In fact, fetal exposure to maternal stress hormones has been suggested as one of the main mechanisms by which prenatal stress can induce long-term changes in the HPA axis activity of the children [3, 11]. Exposure to excessive concentrations of maternal cortisol has been shown to alter the density and function of the GR and the mineralocorticoid receptor (MR) in the fetus, ultimately interfering with the negative feedback of the HPA axis [3]. Interestingly, the effects of excessive maternal cortisol seem to depend on the exact time of exposure during pregnancy, with early and late gestation representing the highest periods of fetal susceptibility [12, 13]. Typically, the placental enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) acts to protect the fetus from high levels of cortisol in the mother [4], and its levels typically peak in mid-gestation.

Multiple maternal behaviors that can interfere with the mother's HPA axis have been shown to program the offspring's stress reactivity to a certain extent [14]. Infants who were born to mothers with clinically severe major depressive disorder during pregnancy (who show clear alterations in their HPA axis functioning) have been shown to present increased cortisol reactivity to stress and an overall suboptimal neurobehavioral function compared to controls [15]. In a similar way, maternal prenatal depression and anxiety symptoms have been shown to predict higher cortisol levels in 2- to 5-year-old children [16], to alter patterns of diurnal salivary cortisol in 15-year-old children [17], and have been associated with a flatter diurnal cortisol decline in 14–15-year-old children [18], emphasizing the important effect of maternal mood during pregnancy in the HPA axis programming [3]. Subjects who were born to mothers exposed to negative life events during pregnancy have also been reported to present dysfunctional HPA axis later in life, with a notable hyperactivity in the response to stress [19]. Finally, similar effects have been observed in preclinical models, with prenatal restraint stress resulting in increased responsiveness of the HPA axis to stress later in life and an accelerated age-related alteration in the HPA axis [1], among other findings. Of note, even though HPA axis programming has been consistently reported, there is no consensus on the overall effect of prenatal stress on the activity of the HPA axis, with

reports of both hypo- and hyperactivity of the axis [3]. This inconsistency seems to depend upon the sex and age of the offspring, on the species being investigated, the prenatal stress model, and the stage of pregnancy at which the exposure took place [11].

Similar to fetuses, preterm infants are known to be at a particularly high risk for the effects of early stress given that their physiological systems are not yet mature [20]. Accordingly, there is evidence to suggest that the HPA axis can also be programmed by such early stress exposures (including those associated with the frequent invasive procedures during hospitalization at the neonatal intensive care unit) [20], leading to altered basal and nighttime cortisol levels [20, 21]. Moreover, many preterm newborns display deficits in the pituitary responsiveness to exogenous CRH, 11β-hydroxylase activity, and in the interconversion between cortisol and inert cortisone [22].

During childhood and adolescence, even after the first critical years of development, subjects continue to be susceptible to stress-induced programming of the HPA axis. That is possible due to the fact that brain development continues for an extended post-natal period, reaching about 90% of the adult volume by age 6 [10]. As is the case for prenatal effects on HPA programming, the direction of the HPA alterations (hypo- or hyperactivation) is not uniform for all post-natal stressors and seems to depend on a multitude of variables [23]. Early maternal separation stress in rats has been shown to induce hyperresponsivity of the HPA axis in adulthood, similar to the effects of adult stressors [23], and rats reared under reduced maternal care conditions have been shown to present stress hyperreactivity and an impairment in executive function as adults [24]. Making a parallel in humans, adoptees who experienced more than 6 months of deprivation early in life have been shown to present an absence of the cortisol awakening response and a significantly flatter cortisol curve after awakening [25]. Similar findings have been reported in other populations, as well, with lower social care quality in post-institutionalized children being associated with less steep diurnal cortisol slopes [26]. Altogether, these studies strongly suggest that early social deprivation can program HPA axis in children.

3 Molecular Mechanisms Underlying HPA Axis Programming

Now that we have acknowledged that stressful events in different stages of early life can impact the HPA axis in permanent ways, we will turn our attention to the potential mechanisms by which this can take place. Regardless of the developmental stage or the timing of the stress exposure, the HPA axis programming requires the involvement of environmentally plastic and yet fairly stable mechanisms that can be established in response to the stimulus and remain stable (or at least constantly self-maintained) until adulthood. The two main mechanisms hypothesized for the HPA

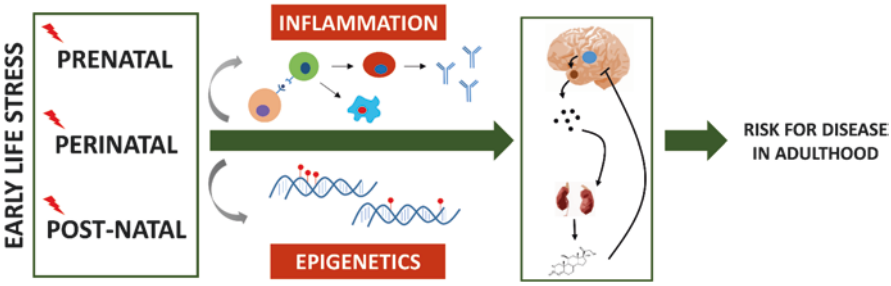

Fig. 1 Schematic representation of the hypothalamus-pituitary-adrenal (HPA) axis programming induced by early-life stress. Pre-, peri-, and post-natal stress are suggested to induce alterations in inflammatory and epigenetic mechanisms that can culminate with significant and stable changes in the HPA axis. By permanently altering the stress response in childhood, adolescence, and adulthood, these effects can interact with genetic vulnerability and increase the risk for disease in adults

axis programming include the effects of inflammatory mediators and of epigenetic mechanisms (Fig. 1), both of which will be discussed in more detail in this section.

3.1 Inflammation

The cross talk between the HPA axis and inflammation has been repeatedly reported by several independent investigators. Stress has been suggested to have a strong effect on the inflammatory response, being activated by both threats from the physical and the social environment [27, 28]. In particular, chronic stress has been shown to activate microglia and astrocytes (neuroinflammation) and increase circulatory damage-associated molecular patterns (DAMPs) [29] that can signal through toll-like receptors and thus activate immune cells [30]. Such association is dynamic in which the stress can induce inflammation but also inflammation can further modulate the response to stress, with evidence of cytokines being able to modulate glucocorticoid production by the HPA axis, as well [31].

Early-life stress can significantly alter inflammatory mechanisms and thereby indirectly program the HPA. For instance, perinatal stress has been shown to produce alterations in immune function (a heightened pro-inflammatory state [32]) occurring in parallel with a long-lasting hyperactivation of the HPA response in preclinical models [1]. Interestingly, at least part of this perinatal stress-induced immune alteration has been reversed during adolescence by changes in the environment [33]. Mechanistic studies have suggested the involvement of the cholinergic system in this early-life immune response [1, 34]. In addition, mice that were born to dams exposed to a polluted diet during pregnancy have been shown to present both chronic brain inflammation as well as high corticosterone levels in a sex-specific pattern, again emphasizing the parallel changes of both systems by such early-life events [35]. Offspring of mothers transvaginally injected with

lipopolysaccharide have been shown to present higher corticosterone levels and CRH expression in the hypothalamus in parallel to neuroinflammatory markers [36]. Similarly, cortisol levels after immunization in 12-month-old infants have been shown to correlate with maternal antenatal inflammatory markers and evening cortisol, supporting a mechanistic link between prenatal environment and the offspring programming of the immune and stress systems [15]. At least part of this immune system–mediated stress programming might be related to its ability to permanently change gene expression, which can be achieved by altering epigenetic mechanisms. In fact, inflammation has been shown to interfere with epigenetic enzymes *in vitro* [37], and an association between immune mediators and epigenetic mechanisms has been repeatedly suggested in clinical samples [38–40]. A detailed discussion on how epigenetics can program the HPA axis will be provided in the next section.

3.2 Epigenetic Mechanisms Driving HPA Programming

An individual's genetic background may modulate the extent to which an adverse event early in life can induce permanent tags and thus program the response to stress [41]. However, the nature of the HPA axis programming, as seen in animal and human studies briefly discussed in the previous section, suggests that more dynamic mechanisms may be relevant, possibly in close interaction with genetic variants underlying resilience and/or vulnerability phenotypes. Epigenetic alterations represent a plausible mechanism by which early-life stress can permanently alter the HPA axis. These alterations are known to dynamically react to environmental stimuli and change gene expression without interfering with the DNA sequence [42]. Specifically, they can interact with the subject's genetic makeup and include changes to DNA methylation, histone post-translational modifications, and the effects of non-coding RNA molecules. The involvement of epigenetic mechanisms in early-life stress-induced HPA axis programming is suggested by several studies that report alterations in the expression of genes related to the immune system and the stress response and in specific epigenetic markers after stress exposure, which we discuss below.

Treatment of juveniles with cortisol or mifepristone (a GR antagonist) during the first two months of life has been shown to persistently downregulate the expression of *crf* and upregulate *mr* in the telencephalon of cichlids, ultimately programming the stress response in this fish [43]. Such gene expression changes suggest glucocorticoids-dependent mechanisms of transcription regulation, which may include epigenetics. After binding to glucocorticoids, activated GR dimers translocate to the nucleus and act as transcription factors through binding to glucocorticoid response elements (GREs) to either induce or repress the expression of specific genes [44, 45]. GR's ability to translocate to the nucleus depends on the action and levels of a series of co-chaperones and proteins that modulate its affinity to glucocorticoids and its action as a transcription factor, such as the heat shock protein

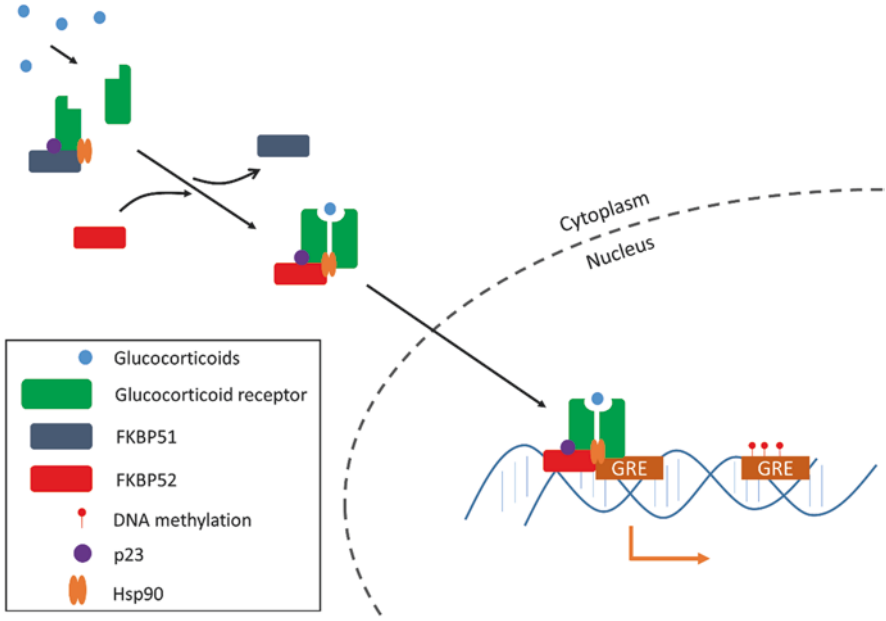

Fig. 2 Schematic representation of the glucocorticoid receptor (GR) signaling pathway. GR typically forms a complex with chaperones (a dimer of heat shock protein 90 (Hsp90), p23, and FK506-binding proteins 51 (FKBP51)) in the cytoplasm. Binding of glucocorticoids to the receptor transfers the equilibrium of the complex to bind FKBP52, which allows GR dimerization and its nuclear translocation. Once in the nucleus, GR acts as a transcription factor by binding to glucocorticoid response elements (GRE). These genomic *loci* can be epigenetically modulated by DNA methylation, which can interfere with the GR-DNA binding and thus with its transcriptional activity

(Hsp) 90, the small phosphoprotein p23, and the FK506 binding proteins 51 (FKBP51) and FKBP52 [46, 47] (Fig. 2). Not only have the binding of GRs to GREs and the ability of GRs to modulate gene expression been shown to be sensitive to DNA methylation [48, 49], but also genes encoding some of GR's co-chaperones are also known to be sensitive to methylation alterations [46, 50].

Several studies report DNA methylation alterations in stress-related genes in response to pre-natal stress. Higher levels of prenatal maternal depression and anxiety have been associated with increased methylation of the *NR3C1* gene (which encodes the GR) in cord blood and predicted increased infant cortisol response to stress [51, 52]. Similarly, exposure to maternal mood disorder *in utero* has also been shown to induce changes in the methylation of placental *NR3C1* and *11β-HSD2* genes [53]. Prenatal malnutrition has also been linked to post-natal epigenome changes that may underlie adverse metabolic phenotypes in later life [54, 55]. Children of mothers who were exposed to the Tutsi genocide during pregnancy have been shown to present lower cortisol and GR levels associated with higher methylation of the *NR3C1* gene [56] compared to children of control mothers, and there is

also evidence of prenatal-induced epigenetic modifications being extended into adolescence and adulthood [3, 57].

As mentioned earlier, the central nervous system remains highly plastic even after birth, and epigenetic alterations induced by post-natal stress early in life have also been shown to be quite stable and related to HPA axis programming mechanisms [58, 59]. Accordingly, post-natal maternal care has been repeatedly associated with permanent epigenetic changes in the offspring. Preclinical models suggest that adult offspring of mothers showing high licking/grooming behavior early in life show methylation changes in the gene encoding the GR [60, 61] with consequent increase in GR expression, which can be reversed by cross-fostering. Epigenetic alterations have also been reported in models of early-life maternal maltreatment [62–64] and in human clinical populations [65–68]. The permanent and stable feature of early-life-induced DNA methylation has been suggested by several preclinical [62, 69, 70] and clinical studies [71, 72], and is likely related to the action of maintenance DNA methyltransferases (DNMT1) in addition to the effect of methylation quantitative trait *loci*. Interestingly, a recent clinical study has also suggested the potential of environmental intervention programs targeting childhood adversity to modulate the epigenome and its long-term consequences [72], and multiple lines of evidence point to the important role of a gene vs. environment interaction in establishing these epigenetic long-term marks [65, 73]. Altogether, these several lines of evidence converge on the common theory that post-natal stressful events target epigenetic mechanisms and thereby program HPA axis.

4 Future Perspectives and Conclusions

Initially proposed by the Austrian psychoanalyst Sigmund Freud [74], the idea that early childhood disturbances can change one's susceptibility to disease later in life is certainly not new. The novelty of the field comes from the growing body of evidence suggesting the molecular mechanisms underlying this link, especially when it comes to those affecting the HPA axis. Programming of the stress axis is thought to be one of the key drivers of psychiatric, cardiovascular, and metabolic diseases after early-life stress [75–78], and this notion is corroborated by multiple studies that report a predictive value of HPA axis alterations in metabolic and psychiatric disorders in adults. As reviewed in this chapter, the two main drivers of HPA axis programming are inflammation and epigenetic mechanisms (with a significant cross talk between both of them).

Of note, while several potential targets and mechanisms have been proposed, several questions still remain. Longitudinal studies of early-life-stress-induced changes in inflammatory and epigenetic mechanisms throughout life are still rare, and that limits the overall understanding and implications of the currently available evidence from cross-sectional studies. A growing body of evidence also suggests a strong sex specificity for the effects of early-life stress [79–82], which has been underexplored. Future clinical studies should also focus more on the genetic variants

contributing to the effects of stress on epigenetic and inflammatory mechanisms, integrating results from single nucleotide polymorphisms, epigenome alterations, and environmental exposure in a single analysis. Understandably, the assessment of this three-way interaction may certainly require larger sample sizes than most currently available cohorts.

A deeper understanding of the molecular drivers of the HPA axis programming can have at least two significant clinical implications. The first one is the exciting possibility of using newly identified molecular targets to prevent (or reverse) the onset of illness later in life, be it through environmental or pharmacological approaches. In fact, several drugs with anti-inflammatory properties are available for testing and repurposing, and preclinical models will be helpful in providing ideal targets. Similarly, epigenetic drugs are being continuously developed to target DNMTs and other enzymes (such as the histone deacetylases) to reverse epigenetic tags. Initial preclinical studies have already suggested the utility of this approach, with early-life-induced epigenetic changes being reversed in adult animals [63]. Finally, another important implication of further understanding the epigenetics of these early-life events has to do with their potential to be transmitted across generations. Accordingly, prenatal inflammatory effects have already been shown to induce transgenerational effects in rodents [83] through stable DNA methylation alterations [84]. In other words, the epigenetic and behavioral effects of an immune activation can be passed on to several generations, even when further generations are not exposed to the initial inflammatory event. That can have several major implications in our understanding of disease transmission, heritability, and prevention. In fact, the possibility of molecularly reversing not only effects induced by early-life stress, but also those established in previous generations, is particularly exciting and with grand societal implications.

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Intergenerational Aspects of Immune and Endocrine Function in Perinatal Depression

Andrew J. Perrin, Carmine M. Pariante, and Patricia A. Zunszain

Abstract Perinatal depression mediates a profound impact on maternal and offspring health. Alterations in endocrine and immune function in depressed mothers have been linked to altered stress responses in offspring and less optimal neurodevelopmental outcomes. This chapter reviews the important changes in immune function that have been documented in depressed mothers and seeks to link changes in immune regulatory and endocrine processes to ultimate outcome in offspring. We identify key interactions between the immune system, the Hypothalamic-Pituitary-Adrenal axis and the oxytocin system that are relevant to understanding the dysregulated immune responses in depressed mothers. Additionally, we review how the above changes have been linked to an increased risk of aberrant development of offspring of depressed mothers, as well as the future manifestation of mental illness. Molecular mechanisms relevant to these processes are highlighted. Our work reinforces the potential importance of biomarkers that could be linked to both immune dysfunction and negative developmental outcomes in offspring in perinatal depression. Through improved screening and intervention protocols that incorporate the above approach, significant progress could be made in reducing the large morbidity associated with perinatal depression.

Keywords Depression · Pregnancy · Offspring · HPA axis · Glucocorticoids · Inflammation · Immune system · Cytokine · Oxytocin · Human development

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1 Introduction

The perinatal period is one of high risk for mothers and their offspring. Pregnancy itself can lead to a variety of medical complications that span the full spectrum of medical science, and illnesses that arise during pregnancy or bracketing gestation are increasingly recognized to impact maternal and offspring health, sometimes years after parturition. This chapter focuses on the immune consequences of depression in mothers and their offspring when depression occurs in the antenatal (i.e., during pregnancy) as well as during the postnatal (i.e., within approximately 1 year of delivery) periods. We review the intergenerational transmission of these processes and link, where possible, events in pregnancy and postnatally with downstream effects in future generations. For clarity, we will specifically refer to the antenatal and postnatal periods when the discussion requires it. Otherwise, we will refer to the overarching entity of depression in pregnancy as perinatal depression. Additionally, we do not discuss the impact of other forms of perinatal mental illness such as psychosis or bipolar disorder on offspring. For this, we refer readers to a recent comprehensive review [1].

2 Epidemiology and Overarching Effects of Perinatal Depression

Between 5% and 15% of women will experience a depressive episode antenatally [2–4] and between 10% and 30% of women will experience a depressive episode within 1 year of delivery [5–7]. Interestingly, there is limited evidence that the prevalence of depression in perinatal women differs from the prevalence of depression in similarly aged women who are not pregnant. This does not mean, however, that the impact of depression in these two populations is entirely similar. Perinatal depression not only impacts the affected mother but can also affect the offspring, either in utero or postnatally. For example, antenatal depression is associated with an increased risk for premature delivery [8, 9] and low birth weight in infants [9], while perinatal depression is associated with increased rates of emotional [10], behavioral [11–17], social, and cognitive difficulties [18] in offspring, as well as potentially disrupted attachment between mother and child as a consequence of postnatal depression [19, 20]. We emphasize that all these reported effects of perinatal depression on offspring can occur alongside inflammatory and immune changes that are the focus of this chapter (Fig. 1).

Historically, the impact of perinatal depression on offspring development was hypothesized to be caused solely by the decreased emotional availability of depressed mothers during a critical period of early offspring development [21]. Such a model was subsequently recognized to be incomplete as additional work identified specific effects of antenatal depression on offspring future mental health that were not shared with postnatal depression [22–26]. Depression confined to the

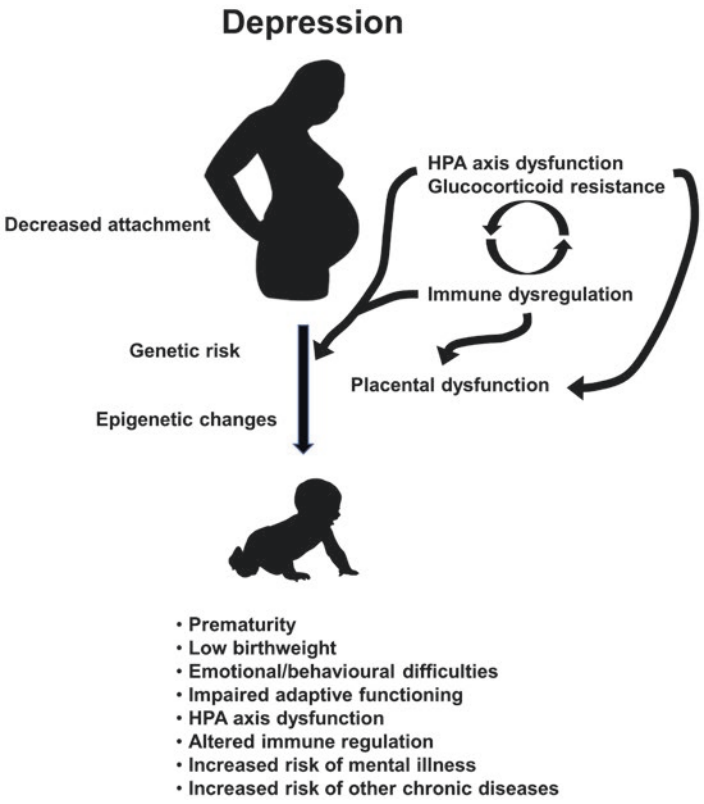

Fig. 1 Immune and inflammatory mechanisms influencing the intergenerational transmission of perinatal depression. The HPA axis, the immune system, and the oxytocin system (see Fig. 2 for a detailed discussion of oxytocin) play individual and interrelated roles in determining the impact of depression on offspring. Some negative biopsychosocial outcomes in offspring are presented

antenatal period is less likely to affect attachment than depression continuing from the antenatal period into the postnatal one or depression that occurs exclusively during the postnatal period; therefore, the full impact of perinatal depression must be driven by factors beyond disrupted attachment. Much follow-on work has identified several processes through which perinatal depression impacts the mother and offspring. These include alterations in the functional connectivity of limbic white matter circuits in the offspring of mothers who were depressed in the perinatal period [27, 28], impairments in full-scale IQ scores in the offspring of mothers who were depressed in the perinatal period [18], the aforementioned impact on behavioral and emotional symptoms in offspring during childhood, the increased risk for the development of mental illnesses, including depression, in the adolescent offspring of depressed mothers [22, 29], alterations in endocrine processes such as the Hypothalamic-Pituitary-Adrenal (HPA) axis and oxytocin signaling, and changes to offspring immune function that we discuss below (Fig. 1).

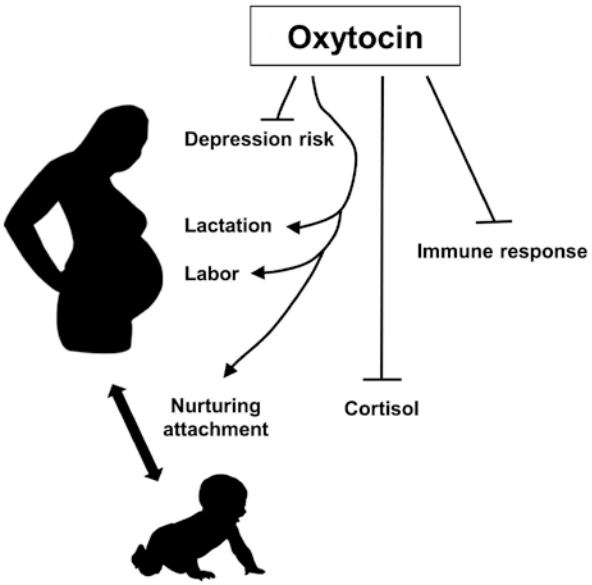

Fig. 2 The proposed outputs of oxytocin in perinatal depression. Activating functions are represented by arrows, restraining functions by cross-hatches

3 Transmission of Effects Involving the HPA Axis

The intergenerational effects of perinatal depression most clearly demonstrated in the literature are those within the HPA axis. This body of evidence is particularly relevant to inflammation and immune function in depressed mothers and their offspring because outputs of the HPA axis interface with many systems throughout the body, including other hormonal systems and the immune system. Thus, a discussion of HPA axis changes in mother and offspring during perinatal depression, as well as how these HPA axis changes impact immune function in mother and offspring, is a fruitful endeavor.

Programming of offspring in utero by maternal glucocorticoids is an established model of normal developmental regulation. For example, endogenous glucocorticoids provide an essential developmental trigger in the normal maturation of fetal lung, thyroid, kidney, and brain [30–33]. Unfortunately, aberrant glucocorticoid levels can also produce adverse developmental effects such as the cognitive decline and disruptions in hippocampal neuronal function that are seen when the fetal brain is exposed to excess levels of glucocorticoids [31]. Concurrently, stress-induced changes in maternal HPA axis function, such as increased reactivity to stress in nondepressed mothers, have been linked to similar changes in the HPA axis in their offspring, even years after parturition [34–36]. This programming of dysfunctional HPA axis response to stress can impact offspring behavioral and developmental outcomes [37–39], as well as predispose offspring to the later development of chronic diseases such as diabetes, obesity, and cardiovascular disease [31].

Therefore, the fact that hyperactivity of the HPA axis and elevations of serum cortisol above normal levels are seen in mothers who are depressed antenatally [40–42] means that fetal exposure to high levels of glucocorticoids could drive some developmental consequences of perinatal depression (Fig. 1). Corticotropin-releasing hormone (CRH) is the primary trigger of increased HPA axis output, and CRH presumably produced both by the maternal hypothalamus and the fetal placenta [43] is noted to increase normally through pregnancy, peaking during the third trimester [44, 45]. Elevation in CRH beyond that seen normally has been linked by at least one study to an increased risk of experiencing antenatal depressive symptoms when antenatally depressed mothers were compared with healthy pregnant women [42]. Our own work has examined aspects related to this process, showing that in women who were depressed antenatally, increased cortisol secretion, which may occur due to increased CRH function, was observed. This increased cortisol secretion in depressed mothers was, in turn, associated with sub-optimal developmental outcomes and elevated cortisol responses to stress in their offspring [46].

The relative resistance of Adrenocorticotropic Hormone (ACTH) secretion to CRH action in non-depressed postnatal women highlights the changes to HPA axis output that normally occur during pregnancy. Further decreased sensitivity to CRH occurs in depressed women in the post-partum weeks, demonstrating that decreased responsiveness to HPA axis actions is important to perinatal depression, much as it can be in depression not associated with pregnancy [47]. Interestingly, reduced reaction to HPA axis output and/or glucocorticoid resistance can be a component of depression as well as other inflammatory illnesses such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis [48]. It is hypothesized that glucocorticoid resistance impacts mechanisms that normally restrain the immune system in the face of high HPA activity, leading to an elevated level of chronic inflammation in these diseases [49]. This is supported by observations of greatly exaggerated inflammatory and immune responses in studies of animals with intentionally disrupted adrenal function [50–53]. Multiple mechanisms are thought to contribute to the final outcome of glucocorticoid resistance [see [48] for a detailed review]. Ultimately, however, alterations in glucocorticoid receptor (GR) function likely represent the final common pathway of glucocorticoid resistance in depression [54]. How this occurs at the molecular level is still an ongoing area of study. Alterations in GR intracellular localization, stability, and transcriptional function are all possible mechanisms to be engaged. For further detailed discussion, we refer the reader to an excellent recent review [55].

4 Inflammatory Consequences of Perinatal Depression in Mother and Child

Stress experienced during the perinatal period can change inflammatory pathways. We recently found elevated levels of the cytokines Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α), and IL-10 in a group of women with antenatal

depression, mirrored by raised cortisol levels and blunted cortisol awakening responses [46]. Interestingly, maternal cortisol responses in this study correlated with respective infant cortisol responses, suggesting that the inflammatory response patterns observed in these mothers might be associated with HPA axis activity as well.

Experiencing early-life trauma seems to feed into the patterns discussed above, especially with regard to IL-6. A history of childhood abuse of mothers has been linked to higher than normal IL-6 levels when pregnant [56]. This may consequently elevate further the risk that these mothers become depressed in pregnancy through two mechanisms: the contributory effects that childhood trauma plays in increasing the risk of developing depression [57]; and the impact that childhood trauma has on increasing IL-6 levels and how this may feed into IL-6-dependent depressive mechanisms in the perinatal period. Furthermore, a recent report has provided evidence that increased plasma cytokine levels (TNF-α and IL-18 in this case) can be correlated with postnatal depressive symptoms in postpartum women [58]. The timing of cytokine measurement during pregnancy may play an important role as well, as women in the third trimester who displayed depressive symptoms also showed evidence of an inflammatory burst of IL-6 that was not as evident during earlier trimesters [59]. When inflammation was assessed in mothers who experienced depressive symptoms rather than full depression, some differences from the above were found. For example, two studies found negative correlations between the presence of depressive symptoms and the levels of IL-1β, IL-17, and TNF-α [60, 61]. The fact that depressive symptoms are not the same as criteria-fulfilling major depression must be considered in the interpretation of these findings. The balance of evidence therefore suggests that inflammatory factors present in the mother play an important role in the pathophysiology of perinatal depression. In turn, this can be linked to the known effects of antenatal maternal inflammation on behavioral outcomes in toddlers [62, 63].

How altered immune responses are transmitted from depressed mothers to affected offspring and how this can lead to less optimal developmental outcomes and mood disorder presentation in the later lives of offspring are intriguing questions. Data have been presented suggesting that the patterns of pro-inflammatory cytokines that are observed in depression can alter enzymatic pathways that change the availability of serotonin precursors. For example, cytokines can induce the activity of indoleamine 2,3-dioxygenase (IDO), one of the enzymes that catalyze the first step in tryptophan degradation. This would then divert tryptophan away from being transformed into serotonin, possibly leading to serotonin depletion in depressed mothers [64]. The elevated pro-inflammatory cytokines that have been observed in postnatally depressed mothers suggest the possibility for such a scenario to develop, but to date, we are unaware of work that simultaneously measured cytokine levels and activity of the tryptophan metabolism pathways in depressed mothers. Nonetheless, it is tempting to speculate that durable effects on serotonin metabolism could be initiated through aberrant inflammation in depressed mothers and thereafter transmitted to offspring to serve as possible contributing factors to illness development.

Epigenetic modifications have been proposed as a major mechanism by which durable changes in immune pathways are transmitted from depressed mother to adult offspring [65, 66]. Early changes in DNA methylation in offspring occur in response to specific events such as maternal pregravid obesity [67, 68], maternal exposure to toxins (cigarettes, for example) [69], difficulties during the process of birth [70], and exposure to early-life adversity [71] and abnormal parenting behaviors [72, 73]. Pre-clinical evidence even suggests that some of these changes can be transmitted through the paternal germline [74], possibly influencing gene expression in multiple future generations. If this is the case in humans, epigenetic changes in genes involved in immune activation could modify the function of the immune system years, even decades, after exposure to maternal depression and stress [71]. For example, when Nemoda et al. [75] examined genome-wide DNA methylation profiles from cord blood T lymphocytes in neonates of depressed mothers and compared this with methylation profiles from the same cells in neonates born to non-depressed mothers, they noted differential methylation of several regulatory regions associated with immune genes such as *TNF*, the interferons (*IFN*), and those controlling T helper cells. Further comparison of differential methylation profiles from cord blood T lymphocytes with those from postmortem hippocampi of adults whose mothers were depressed maternally revealed enrichment for genes also involved in immune function such as *IL2* and *IFNG*. Combined with the observation that elevated cortisol leads to detectable changes in infant DNA methylation profiles, these data suggest that offspring epigenetic marks acquired *in utero* could be drivers of future immune and HPA axis function [76]. How these changes directly link to mechanistic changes in inflammatory pathways in depressed offspring still needs to be clarified, but this work highlights the exciting impact that epigenetic research has had on reformulating our understanding of how the inheritance of traits can occur independently of changes to the coding segments of genes.

It is important to also highlight that mothers and offspring exposed to similar environmental circumstances can develop similar epigenetic signatures independently of inheritance [76] and additional mechanisms beyond DNA methylation have been invoked to explain inheritance. For example, work from our group has implicated another potential epigenetic mediator in the inheritance of the effects of depression – microRNAs (miRNAs) [77]. We found that prenatal stress drove changes in miRNA levels in the brains of rats, with possible implications for the future development of depressive behaviors. Interpreting epigenetic findings in the context of common environmental triggers and miRNA, in addition to DNA methylation changes, only scratches the surface of an exceedingly complex field of study. Intergenerational transmission of altered immune function from the depressed mother to offspring is likely to be mediated by epigenetic mechanisms, but it will be many years before we fully understand this process.

In addition to epigenetics, traditional inheritance mechanisms play an essential role in the transmission of depression risk. Up to 40% of the risk for offspring to develop depression later in life has been shown to run in families [78], and a recent systematic review [79] linked known depression genetic risk variants to postnatal depression risk. In support of perinatal depression being a unique variant of depres-

sion, a recent genome-wide association study identified the hemicentin-1 locus as being specifically associated with postpartum depressive symptoms [76, 80], while some studies have reported that the heritability of perinatal depression is higher than that seen in major depression not associated with pregnancy [81]. Overall, up to 14% of the total variance in perinatal depression appears to be unique for perinatal depression [76, 81], showing that genetic contributions to offspring risk of depression can come from both traditional inheritance mechanisms and epigenetics. The overlapping genetic predispositions for different sub-types of depression nonetheless make it difficult to fully differentiate genetic inheritance effects from the impact of environment, possibly due in part to the moderating effects of genetic variants on the effects of the prenatal environment. A number of studies have supported the contention that intergenerational transmission of the effects of depression is moderated by such effects. For example, low birth weight, which itself is associated with depression in pregnancy [9], portends a greater risk of developing depression in the offspring of depressed parents compared with the offspring of non-depressed families [82], highlighting the cyclical intergenerational effects that genes and the environment can impart upon each other. Several genes have been found to moderate the relationship between birth weight and offspring neurodevelopment, including polymorphisms in the serotonin transporter and the D4 receptor [83, 84]. Trying to disentangle this web of gene–gene and gene–environment interactions has proven challenging. For example, the emergence of depressive or anxious symptoms in children seems unaffected by whether prenatal maternal anxiety or depression occurred in mothers who were genetically related to their offspring or in mothers who were genetically unrelated to their children [85]. Resolving such dissonance requires more work focusing on the combined impact of traditional inheritance mechanisms, epigenetics, and gene–environment interactions on perinatal depression and its intergenerational transmission. We have begun to explore these complexities in a recent study that integrated data from rodent models of prenatal stress and humans exposed to childhood maltreatment. This work showed significant gene-by-environment interactions between exposure to stress and depressive symptoms [76, 77].

5 Fetal Aspects of Intergenerational Transmission

The placenta influences the transmission of the maternal effects of depression to the fetus. Hydroxysteroid dehydrogenase 2 (HSD-2) is a key enzyme that controls how much cortisol the fetus is exposed to. Placental expression of HSD-2 is reduced by maternal prenatal stress, including depression [86, 87], and a mechanism implicated in this process is increased methylation of placental *HSD-2* [88]. Impairing HSD-2 function potentially reduces the conversion of active cortisol to its less potent derivative, cortisone, and could result in increased fetal exposure to cortisol in depressed mothers. Fetal consequences of experiencing higher cortisol levels include decreased birth weight and altered responses to stress, both of which have been detected in

human [86, 89] and animal studies [90]. The effects of cortisol on the offspring are believed to be derived from, at least in part, changes in *GR* expression in the brain [91] and consequent neurodevelopmental effects. In fact, increased methylation of *GR* was observed in the placentae of offspring whose mothers were depressed, suggesting that altered fetal *GR* expression can be induced very early in development [88, 92].

Being a protean regulator of the immune interface between mother and offspring, the placenta also helps to regulate early immune responses in the offspring [55]. While certain levels of immune regulators are necessary for proper fetal implantation [93], when overwhelming levels are present in depressed mothers, normal placental expression levels of CRH and HSD-2 are overridden [94, 95], excess placental expression of IL-1β, IL-6, and TNF-α is activated [55, 96] and adverse obstetrical outcomes such as pre-eclampsia [97] and premature labor [95] become more common (Fig. 1). Stress applied to pregnant mice has been used to model the effects of maternal depression on placental immune regulation. In this system, maternal stress was found to be associated with increased placental IL-1β expression as well as increased IL-1β levels in the whole fetal brain [98]. This finding supports the view that fetal-protective functions of the placenta can be disrupted by processes such as depression and that this may represent another mechanism by which fetal inheritance of depressive effects occurs.

6 Linking Parenting Effects to the Intergenerational Transmission of Perinatal Depression

Even in classical descriptions of intergenerational transmission of psychopathology, the importance of the developmental environment in early life, especially the quality of parenting, was central to the models created. It was not until seminal studies in rodents uncovered the impact of parenting on the endocrine system that a molecular understanding of the environmental regulators of development began to take shape.

Oxytocin, a hormone known to influence uterine contractions during delivery and lactation postnatally, was found to be stimulated in the offspring of attentive maternal rats [99]. This attention to pups was manifested by several factors including licking and grooming. High licking-and-grooming mothers also manifested higher levels of oxytocin in certain areas of their own brains, including components of the limbic system [100], and attentive maternal behavior has been further linked to increased densities of oxytocin receptors in the maternal brain [101]. The aspects of oxytocin function in parenting that were explored in rats were subsequently shown to be relevant in human mother–infant interactions too. For example, mothers with low oxytocin levels during pregnancy are more likely to show lower positive attachment interactions with their children [102]. Furthermore, low oxytocin antenatally is associated with an increased risk of developing postnatal depression [103] and antenatal depression is associated with low oxytocin levels after birth

[104], possibly impacting parenting interactions and portending an increased risk for the development of postnatal depression. The maternal responses to oxytocin are thought to be influenced by differences in oxytocin receptor function, even in non-depressed mothers [105]. As is the case for maternal cortisol levels during pregnancy, maternal and offspring plasma levels of oxytocin coincide [106], with higher conjoint levels being associated with secure attachment and better developmental outcomes [107]. This higher level of oxytocin in mothers corresponds with activation of areas of the maternal brain known to be influenced by oxytocin, such as portions of the limbic system and pituitary [108]. Thus, oxytocin has been proposed as a master hormone of successful parenting.

Interestingly, evidence suggests a link between oxytocin action and the regulation of both the HPA axis and the immune system in perinatal depression. Insufficient oxytocin-related signaling in the brains of women with postnatal depressive symptoms, if not depression, is thought to impact the regulation of the HPA axis, possibly through the hypothalamus [109]. Indeed, lower levels of oxytocin in women with postnatal depressive symptoms have been associated with higher cortisol levels in response to an experimentally applied stressor [110], and modulation of oxytocin levels through breastfeeding is thought to be a mechanism by which HPA axis activity can be tempered [111]. These observations are consistent with known homeostatic links between hypothalamic, oxytocin and CRH action at the anterior pituitary [112].

As already discussed in this chapter, the function of the HPA axis has profound impacts on the regulation of the immune system in depression. How oxytocin impacts this balance between the HPA axis and the immune system, as well as how oxytocin may regulate the immune system on its own, presents a fascinating crossroad for exploration. While we have already touched on central interactions between oxytocin and the HPA axis, we note that oxytocin plays a bivalent role in immune function. Sufficient peripheral oxytocin signaling is required for proper thymic T cell maturation and the induction of self-tolerance [112], but central and peripheral oxytocin both also exert strong anti-inflammatory effects through oxytocin receptors expressed on activated immune cells [113]. For the purposes of this chapter, we focus on the anti-inflammatory effects of oxytocin. Other aspects of oxytocin function in immune regulation can be explored in a recent review [112].

Two studies in particular demonstrated that oxytocin is able to reduce the production of several cytokines in healthy humans and rodents that have been exposed to inflammatory stimuli [114, 115]. Significantly, the cytokines for which such an effect has been reported include IL-1β, IL-6, and TNF-α, molecules that have been linked to the pathogenesis of perinatal depression. Interestingly, evidence supporting a reciprocal interaction of cytokines with the oxytocin system in humans has also been presented, namely, the ability of IL-1β to inhibit oxytocin receptor mRNA expression [116]. Together, this work suggests that the interface between HPA axis dysfunction, oxytocin action, and immune system function is important to depression (Fig. 2). The capacity for outputs of the HPA axis and the oxytocin and immune systems to be transmitted from depressed mother to offspring, and, in some cases, even to the second filial generation, reinforces that further study of all three path-

ways and their respective overlaps is essential if we are to fully understand this complex intersection of regulators.

7 Concluding Remarks

Depression is transmitted from mother to offspring through many conduits. In this chapter, we focused on the immune and endocrine factors that are relevant to this process. We highlighted how these factors are relevant to the transmission of the effects of depression from mother to offspring and reviewed how these factors may interface with each other to mutually reinforce dysfunction in homeostatic mechanisms. How changes in immune and endocrine function ultimately lead to the relatively poor neurodevelopmental outcomes observed in the offspring of depressed mothers requires further investigation. We certainly now have the benefit of long-term cohorts through which we can follow change intergenerationally [e.g., refs. [117, 118]], but many questions remain. For instance, how do we integrate potential inflammatory markers, such as IL-6 and TNF-α [46], found in mothers with perinatal depression with better diagnostic assays for perinatal depression risk? How do these same biomarkers link to long-term neurodevelopmental outcomes and depression risk in future generation(s)? Can we capitalize on the potential interactions of the immune systems with oxytocin pathways to develop better treatments for the inflammatory consequences of depression? How will our recent understanding that the intergenerational effects of depression extend into the second filial generation [117] change our appreciation of the urgency that underlies work in this field? A worthy goal of the community's work is to develop combined interventions that focus on all aspects of perinatal depression, including the immune consequences across generations. By targeting inflammatory pathways in depressed mothers, we can hopefully mitigate the harms of perinatal depression on offspring. Translating the research described in this chapter into preventative strategies, early-stage interventions and acute treatments will be an exciting journey.

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Conflicts

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Neonatal Meningitis Mechanisms and Implications in Adult Life

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Abstract Neonatal meningitis (NM) is a serious infectious disease that accounts for elevated mortality and morbidity rates in low- and middle-income countries. Despite decreased mortality rates due to the advancement in antimicrobial therapy, the incidence of morbidity has not reduced; rather a decrease in mortality increases the number of survivors after NM. Nearly half of all meningitis survivors suffer from complex neurological or neuropsychiatric sequelae later in life. Neurologists and microbiologists are continuously searching to improve the quality of life after this dreadful infection. The experimental NM demonstrated positive effects of various pharmacological approaches using antioxidants, matrix metalloproteinase (MMPs) inhibitors, kynurenine metabolites inhibitors, and antidepressants in addition to antibiotics and supportive therapy. To understand the long-term complications after NM, it is necessary to have profound knowledge of the mechanisms behind its pathology. Hence, in this chapter, we aim to enumerate experimental neonatal and infant meningitis models and enlist possible mechanisms associated with behavioral alterations. We also demonstrate the links between NM, inflammatory mediators, and brain injuries in clinical studies. This chapter will also highlight

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currently available effective therapy to reduce neurological complications and discuss the possible treatment regimen in the future.

Keywords Neonatal meningitis · Inflammation · Redox imbalance · Behavioral impairment · Neuropsychiatric consequences

1 Introduction

Neonatal meningitis (NM) is the inflammation of meninges due to an invasion of microorganisms, especially bacteria in neonates [1]. NM is an uncommon, dreadful infection, which contributes substantially to neurological sequelae worldwide. Lack of immunity and the absence of clinical signs in neonates increase the risk of meningitis and make its diagnosis more challenging as compared to children and adults [2]. Other common causes associated with NM are prematurity, postnatal age, geographic region, gestational age, and clinical setting.

NM is categorized as early-onset meningitis (EOM) when the signs of infection and isolation of pathogen from cerebrospinal fluid (CSF) cultures occurred before 72 h, while later than 72 h of life defined as late onset meningitis (LOM). In the case of infants, characterization of culture before 7 days is regarded as EOM, and between 7 and 89 days is defined as LOM [3]. Common challenges for pediatricians in diagnosing NM include lack of clinical signs, compromised CSF by prior antibiotic exposure, negative blood cultures, and normal CSF parameters [4].

In developing countries, NM incidence ranges from 0.8 to 6.1 per 1000 live births, with a high mortality rate of 58%. In developed countries, the culture-proven NM is estimated at 0.3 per 1000 live births with a mortality rate of 10–15%, and high morbidity. About 50% of neonates or infants who survive from meningitis develop acute to chronic neurological impairment that include seizures, cognitive deficits, motor problems, as well as hearing, and visual impairment. Although the mortality from meningitis has dropped tremendously in the past four decades, there is no change in morbidity, especially regarding the neurological sequelae [4, 5].

During birth, neonates are exposed to a vast number of pathogens. The transmission of microorganisms may occur when the neonate aspirates the amniotic fluid infected from maternal genitourinary tract or due to contact of the neonate's skin with the mother during passage through the birth canal [6]. Transplacental transmission is also possible for *Listeria monocytogenes* [7]. Group B Streptococcus (GBS) remains the first common cause of meningitis, and the transmission occurs through maternal bacteremia. *Escherichia coli* (*E. coli*) remains the second most common cause of EOM infection among very low birth weight (<1500 g birth weight) infants [4, 8].

The most common pathogens that cause EOM in infants and children include GBS, *E. coli, L. Monocytogenes,* and *S. pneumoniae.* The pathogen for LOM includes *coagulase-negative Staphylococcus, S. aureus, E. coli, Klebsiella* sp.,

Enterococcus sp., *Enterobacter* sp., *Pseudomonas* sp., and GBS [4]. Advancement in microbiology enhanced the efficacy of conjugate vaccines, which increases the number of survivors from meningitis. Nevertheless, survivors are at risk for neurological complications and neuropsychiatric sequelae. The most common sequelae include seizures, encephalomalacia, cerebral infarctions, ventriculitis, hydrocephalus, abscess formations, brain edema, subdural effusion and hearing loss, vision loss, cognitive and motor delay, speech and language disorder, behavioral problems [9–11].

In addition to active prevention, the rational use of antibiotics, supportive therapy, regular and continuous monitoring of pathogens in a clinical setting is essential to minimize the neurological complications associated with NM. In this chapter, we aim (1) to enumerate experimental neonatal and infant meningitis models and enlist possible mechanisms implicated in behavioral alterations and (2) to show links between NM, inflammation, and brain injury in clinical studies. This chapter will also highlight the currently available effective therapy to reduce neurological complications and discuss the possible treatment regimen in the future.

2 Neonatal Meningitis and Later Consequences in Preclinical Models

A number of evidence from preclinical models confirmed later behavioral alterations when the neonates have meningitis [12–14]. Most studies used single strains to induce NM in rodent models. The age of the animals during infection was postnatal day (PND) 3–4 or PND 11. The most common strains utilized to induce NM are *S. pneumoniae* [13, 15], *E. coli K1* [16, 17], and *S. agalactiae* [18, 19]; a few studies used *L. monocytogenes* [20] and GBS type III [21, 22]. Similar to single-strain bacteria, the infection also induced by a synthetic double-stranded RNA analog, Poly I:C simulates viral infection [23]. A study by Maffioli et al. used Langat virus, closely related to tick-borne encephalitis virus (TBEV), which induces tick-borne encephalitis in humans. Infections with Langat virus were used as an experimental model for meningitis [24].

2.1 Behavioral Impairments Observed After Neonatal and Infant Meningitis

The infant male Wistar rats infected with *S. pneumoniae* on PND 11 demonstrated depressive-like behavior in sweet food consumption and forced swimming tests during their adult life. In this study, Barichello et al. reported improvements in depressive symptoms after treatment with the antidepressant imipramine [12]. Adult life depressive-like behavior was also demonstrated in Wistar male rats' injected

with *E. coli K1* suspension on PND 3–4 [16]. Impairment in habituation memory was demonstrated after *S. pneumoniae* infection in male Wistar rats [25]. However, 30 days of environmental enrichment successfully reversed the memory deficits in their adulthood as compared to *S. pneumoniae*-infected rats [13]. Similarly, infection with *E.coli K1* also induced habituation memory deficits in adult rats, as evaluated by an open field test [16]. Infections from different sources of pathogens including *S. pneumoniae*, *E. coli K1* and *S. agalactiae* in neonatal age demonstrated decreased aversive memory in step-down inhibitory avoidance task in meningitis rats when compared to controls in their adult life [13, 16, 18, 25]. Impairment in spatial memory performance was also demonstrated after *S. pneumoniae* NM infection. Treatment with daptomycin, lithium chloride and BB-1101 (hydroxamic acid–based inhibitor of matrix metalloproteinases (MMP) and tumor necrosis factor-alpha converting enzyme (TACE)) significantly reduced the spatial memory impairments in meningitis rats [14, 26, 27].

In the treatment of bacterial meningitis, the use of dexamethasone remains controversial [28]. The results of the meta-analysis of published controlled trials support the use of dexamethasone in the treatment of bacterial meningitis [29]. Recent studies report that the beneficial effects of dexamethasone only applied to adult patients with pneumococcal meningitis in high-income countries [30]. Moreover, a study by Leib et al. reaffirmed that adjuvant therapy with dexamethasone after pneumococcal meningitis increased hippocampal neuronal damage and demonstrated behavioral deficits in the Morris water maze task [31].

To explain alterations in behavior, experimental NM models propose different mechanisms that include redox imbalance, altered neurotrophic factor levels, alteration in cytokine and chemokine signaling, and increase in apoptosis.

3 Mechanisms Proposed in Experimental Neonatal and Infant Meningitis

3.1 Evidence of Redox Imbalance and Nitrosative Stress After NM in Preclinical Models

Redox imbalance is one of the most common disruptions of brain homeostatic processes observed in a number of neurological diseases [32]. The balance between antioxidants and free radicals was disrupted after NM. The lipid-peroxidation marker malondialdehyde (MDA) increased after *S. pneumoniae* post-infection at 12 and 24 h in the cortex. Protein carbonyls increased at 24 and 48 h in the hippocampus [33]. An increase in cortical lipid peroxidation was demonstrated after 21.5 ± 1.5 h post-infection by *S. pneumoniae* [34]. Increased thiobarbituric acid reactive substance (TBARS) levels occurred at 24, 48, and 72 h in the hippocampus

of *E. coli K1*-induced meningitis rats. *E.coli K1* infection also increased the protein carbonyl levels in the hippocampus of the meningitis group at 6, 12, 24, 48, 72, and 96 h than the control group [17]. Infection with *S. agalactiae* elevated the TBARS levels in the hippocampus at 6, 12, 24, 48, 72, 96 h, and the cortex at 72 and 96 h. Protein carbonyls were elevated in the hippocampus and cortex at 6, 24, 48, 72, and 96 h [19], with a marked increase of the concentration of lipid peroxidation end products. Increased levels of MDA and 4-hydroxy alkenals were demonstrated after 18 h post-infection with GBS type III [21]. Eighteen hours after infection with *S. pneumoniae,* elevated levels of lipid peroxidation were observed in the CSF of neonatal mice [35]. In the infant rat model of pneumococcal meningitis, infection with *S. pneumoniae* increased the carbonyl content 20 h after infection. However, pre-treatment with vitamin B6 reduced the carbonyl levels in the cortex and increased the higher carbonyl content in the hippocampus at 20 h after infection [36]. Schaper et al. reported that increased protein carbonyls were not evident until 21 h after infection, but there was a marked increase in carbonyls in the cerebral vasculature; additionally marked upregulation of oxidative stress protein manganese superoxide dismutase (MnSOD) in cerebral vasculature ensured elevated oxidative stress during bacterial meningitis [35].

On the other hand, an increase in free radicals diminished the antioxidant defense after NM. *E. coli K1* infection-induced NM demonstrated a decrease in superoxide dismutase (SOD) activity in the rat hippocampus of NM survivors but was not observed in the frontal cortex [17]. Barichello et al. reported that SOD activity increased in the hippocampus at 12 and 48 h and decreased at 24 h after infection [33]. Infection with *S. agalactiae* also significantly reduced SOD activity in both the rat hippocampus and cortex [19]. Pneumococcal meningitis elevated the levels of catalase (CAT) activity in the hippocampus and cortex [19, 33]. However, Giridharan et al. reported no change in CAT activity after NM [17]. The study by Christen et al. reported that xanthine oxidase is not a major cause of oxidative stress, and the elevated urate levels due to induction of xanthine oxidoreductase after *S. pneumoniae* bacterial meningitis may have a protective response [37]. The contribution of reactive oxygen intermediates for the necrotic and apoptotic neuronal injury in the infant rat model of meningitis was demonstrated by Leib and colleagues [21].

The study by Ghielmetti et al. suggested that energy depletion, rather than parenchymal oxidative damage, was involved in experimental bacterial meningitis [38]. *E. coli K1*-induced experimental meningitis increased the nitrate/nitrite concentration in the hippocampus of the rat, but not in the cortex [17]. Christen et al. and Pfister et al. reported increased nitrate/nitrite concentration in CSF after *S. pneumoniae* infection. The treatment with antioxidant α-phenyl-tert-butyl nitrone or N-acetylcysteine and endothelin antagonist bosentan demonstrated no effect on nitrosative stress [34, 39]. An increase in CSF nitrite concentration was observed after GBS type III infection [40]. Altogether these data evidenced the increased oxidative and nitrosative stress and decreased antioxidant defense after NM.

3.2 Altered Neurotrophic Factors Levels After NM in Preclinical Models

The family of neurotrophic factors plays a crucial role in neuronal survival, differentiation, and cell death during development. Brain-derived neurotrophic factor (BDNF) has been known for its neuroprotective effects in several models [41]. In the experimental meningitis model, the levels of BDNF were found to be decreased in the hippocampus [12, 18, 25, 26]. Conversely, some studies reported increased BDNF levels after meningitis [13, 16, 42]. Bifrare et al. tested the survival-promoting effect of the neurotrophic factor BDNF in bacterial meningitis models. The results demonstrated that BDNF plays an endogenous protective role against meningitis; however, the parallel administration of antibiotic treatment to meningitis has the efficacy to reduce neuronal cell injury [43].

Another neurotrophic factor, glial cell–derived neurotrophic factor (GDNF), is critical in the maintenance of dopaminergic and motor neurons [44]. Barichello et al. reported decreased levels of GDNF after *S. pneumoniae* infection in the rat hippocampus; however, treatment with imipramine reestablished the GDNF levels 60 days after infection [12].

3.3 Cytokine, Chemokine, and Other Inflammatory Markers Alteration After NM in Preclinical Models

Infections from different sources of pathogens activate inflammation, which is one of the important biological responses of the immune system. The first line of defense in response to meningitis includes the activation of macrophages, production of cytokines and chemokines, and migration of leukocytes to the site of infection [45]. When the pathogen reaches the subarachnoid space, it reproduces rapidly and releases highly immunogenic bacterial compounds recognized through toll-like receptors (TLRs). This biological cascade translocates the nuclear factor kappa B (NF-kB) to the nucleus, thereby stimulating the synthesis of cytokines, chemokines, and other proinflammatory molecules. Cytokines are multifunctional pleiotropic proteins with crucial roles in cellular activation and cell-to-cell communication. The release of cytokine results in blood-brain barrier (BBB) permeability and the recruitment of leukocytes from the circulation into the brain [46].

Tumour necrosis factor (TNF)-α is one of the major cytokines with 158 amino acids being reported after meningitis infection in preclinical models [13, 14, 16, 19, 22, 23, 26, 27, 33, 42, 47–61]. Increased levels of TNF-α were observed until 96 h after meningitis initiation [62]. Additionally, higher level of CSF TNF-α during meningitis has been positively correlated to an increased hearing threshold because TNF-α alone is able to induce a predominant loss of outer hair cells [14, 63]. TNF-α and bacterial compounds stimulate the production of interleukin (IL)-1β, a proinflammatory cytokine, in the cortex and hippocampus, by perivascular mononuclear

phagocytes, macrophages, and glial cells [62]. Increased levels of IL-1β have also been demonstrated in preclinical studies [14, 19, 23, 26, 33, 42, 48, 50–52, 54, 56, 57, 60, 64].

IL-6 is one of the important cytokines reported after meningitis infection. Depending on the context, IL-6 plays a pro- and anti-inflammatory role. During infection, IL-6 increases the influx of neutrophils and stimulates the synthesis of the acute phase proteins, serum amyloid A, fibrinogen, and C-reactive protein (CRP). Studies have demonstrated the specific role of IL-6 in the development of mental disorders, specifically schizophrenia [65]. In experimental models of neonatal or infant meningitis, many studies reported elevated levels of inflammatory cytokine, IL-6 [13, 14, 16, 19, 23, 24, 26, 33, 42, 47–56, 64].

IL-10 is a potent immune-suppressive cytokine that increased during experimental bacterial meningitis [13, 14, 16, 19, 23, 26, 33, 42, 47–55, 64]. Usually, the release of IL-10 inhibits the production of pro-inflammatory cytokines including TNF-α and IL-6, as well as the release of ROS [66]. IFN-γ [14, 24, 26, 42, 49, 51–55, 64] is another important pro-inflammatory cytokine elevated during meningitis through the activation of the NOD-like receptor (NLR) inflammasome pathways [67]. Other cytokines expressed during neonatal and infant experimental meningitis include IL-4 [13, 16, 23, 55] and IL-5 [23]. Both the IL-4 and IL-5 belong to the group of T-helper cell type 2 (Th2) cytokines [68].

Chemokines are also known as chemoattractant cytokines and are involved in the recruitment and regulation of the leukocyte traffic during meningitis [69]. Multiple chemokines as cytokine-induced neutrophil chemoattractant (CINC)-1 [13, 16, 19, 33, 50], monocyte chemoattractant protein (MCP)-1 [24, 26, 48, 49, 54, 64], macrophage inflammatory protein (MIP)-1a [26, 48, 49, 54, 64], CCL2 [42], CCL3 [42], CCL5 [24, 42], CXCL10 [42], GM-CSF [55, 64], CXCL1 [64], IL-18 [48, 64], TIMP-1 [70] have been reported to be upregulated in NM. The low-molecular-weight chemotactic cytokines play a central role in the perivascular transmigration and accumulation of specific subsets of leukocytes at sites of tissue damage. In an experimental bacterial meningitis model, Diab et al. [71] demonstrated that the blocking of the bioactivity of chemokines MIP-2 or MIP1-a results in decreased neutrophil influx.

A study demonstrated an elevated hippocampal myeloperoxidase (MPO) levels, which is an index of leukocyte infiltration after 24, 48, 72, and 98 h infection and in the cortex at 6, 12, 24, 48, and 96 h after meningitis [17, 19]. Christen et al. reported peak MPO levels 12 h after infection when Sprague Dawley rats were infected with *S. pneumoniae* [34]. An increase of CSF MPO was also observed after 18 and 24 h of *S. pneumoniae* infection [39, 47]. However, no change in MPO activity was reported in the cortex and hippocampus at 6, 12, 24, and 48 h after *S. pneumoniae* infection in neonatal rats [33]. Similarly, Sury et al. reported no change in CSF MPO activity after *S. pneumoniae* post-infection [72]. Treatment with daptomycin, a non-bacteriolytic antibiotic, or rifampin, 24 h post-infection reduced the CSF MPO levels as compared to ceftriaxone treatment on neonatal rats [48]. Liechti et al. reported that when fluoxetine (antidepressant) was assessed for its

neuroprotective effect against pneumococcal meningitis, the levels of MPO escalated at 18 h and then decreased at 27 and 42 h after infection [49].

Other inflammatory proteins, such as iNOS, were also upregulated after experimental meningitis by *L. monocytogenes* infection and GBS type III infection [20, 40].

3.4 Evidence of Apoptosis and Related Signaling After NM in Preclinical Models

An accumulating amount of evidence has shown hippocampal apoptosis after neonatal and infant meningitis in rodent models [22, 60, 73]. In a mouse model of infant meningitis, Grandgirard et al. demonstrated that the peak of apoptosis is at 30 h of *S. pneumoniae* infection [74].

Cortical necrosis after infant meningitis was significantly reduced in rats treated with daptomycin and combined daptomycin with trocade (MMP, inhibitor) compared to ceftriaxone monotherapy. The use of daptomycin, a non-bacteriolytic and bactericidal lipo-peptide antibiotic, in infant rats with meningitis increased the bacterial clearance of CSF, thereby reducing the inflammatory parameters and decreasing cortical injury compared to ceftriaxone treatment [14, 48]. Similarly, another MMP inhibitor, RS-130830, significantly attenuated the cortical necrosis in the infant rat model of meningitis, with no effect on hippocampal apoptosis [53]. Ro 32–3555, BB-1101 (MMP inhibitor), and Ro 32–7315 (TACE inhibitor) significantly reduced hippocampus apoptosis [27, 54].

MMPs play a significant role in response to infections by activating inflammatory cytokines. Increases in MMPs during infection degrade components of the basal lamina and weaken the BBB, thereby facilitating the leukocyte extravasation and BBB leakage. Thus, the pharmacological inhibition of MMPs facilitates neuroprotection by downregulating hippocampal apoptosis and cortical necrosis [54, 75]. Perny et al. reported the role that the infection severity plays in hearing loss. The results from a quantitative cochlear histology revealed a significant loss of spiral ganglion neurons (SGN) and outer hair cells [51]. Liechti et al. investigated the two second-generation enzymes, MMP (Ro 32-3555) and TACE inhibitors (Ro 32-7315), against *S. pneumoniae* infection. The treatment with Ro 32-3555 inhibits MMP-1, -8, -9 and -13 levels, while Ro 32-7315 is an efficient inhibitor of TACE. TLR-2 agonist, Pam3CysSK4 stimulation increased MMP-9 within the CSF in sham-infected infant rats [58]. The role of MMP is considered important, as it facilitates the degradation of BBB components after meningitis. Sellner et al. investigated the association of cortical brain damage with the parenchymal MMP-9/TIMP-1 ratio and collagen IV degradation. These findings provide support to the hypothesis that the protection of the vascular unit after meningitis might have a beneficial effect [70].

The antidepressant fluoxetine and mood stabilizer lithium reduced the hippocampus apoptosis in infant models of experimental meningitis. Treatment with lithium also improved the spatial memory performance in the Morris water maze.

Fluoxetine plays a neuroprotective role by enhancing neurogenesis, dampening inflammatory response, and reducing hippocampal apoptosis in *S. pneumoniae*-induced experimental meningitis models. The neuroprotective role of lithium is elicited by enhancing the functional integration of surviving neurons and by reducing apoptosis in the hippocampus in *S. pneumoniae*-induced experimental meningitis models [26, 49].

Bellac et al. reported that the activation of the kynurenine pathway provided neuroprotection by preventing energy failure and apoptosis in the hippocampus in infant rat models of meningitis [57]. The study by Sury et al. demonstrated that treatment with the phosphatase and tensin homolog (PTEN) inhibitor bpV(pic) restored Akt activity and significantly attenuated hippocampal apoptosis. Treatment with TLR-2 agonist Pam3CysSK4 and the blockade of NMDA receptors had no effect of apoptosis in *S. pneumoniae*-induced experimental meningitis [58, 76]. In contrast, dexamethasone and α-phenyl-tert-butyl nitrone adjuvant therapy increased the apoptosis and demonstrated learning deficits in Sprague Dawley rats subjected to *S. pneumoniae* infection [15, 31]. A study by Sury et al. demonstrated that during NM, c-Jun N-terminal kinase (JNK) was activated, but hippocampal neuronal apoptosis was not mediated by JNK [72].

3.5 Miscellaneous Markers Associated with NM in Preclinical Models

Increased blood levels of adrenocorticotropic hormone (ACTH) in adulthood rats subjected to meningitis by *S. pneumoniae* during the early life period were observed [12]. Infection with *S. agalactiae* decreased the levels of nerve growth factor in the hippocampus of the rats [18]. The levels of DNA repair protein apurinic/apyrimidinic endonuclease (APE1) increased in the cortex and hippocampus of the rats after pneumococcal meningitis. However, treatment with vitamin B6 did not affect APE1 levels [36].

Pneumococcal meningitis caused significant loss of type I neurons in the spiral ganglion. Adjuvant treatment with dexamethasone had no effect on the loss of type I neurons and ABR threshold (highly correlated with hearing sensitivity) in infected animals as compared to treatment with saline and ceftriaxone [77]. Similarly, adjuvant treatment with doxycycline attenuated the hearing loss and neuronal death in the cochlear spiral ganglion rat model [59].

Coimbra et al. investigated on the genetic program that regulates the host response during bacterial meningitis, which might be responsible for the neurological consequences. The results from temporal and spatial analysis of gene expression identified differentially expressed gene in infant rat model of pneumococcal meningitis. Among 598 differentially regulated genes after experimental pneumococcal meningitis genes responsible for growth control/neuroplasticity, signal transduction, cell death/survival, cytoskeleton, and immunity were upregulated and genes related to neurotransmission and lipid metabolism were transiently downregulated [78].

4 Neonatal Meningitis and the Late Consequences in Clinical Studies

NM patients, especially those who have a relatively earlier age at the onset of meningitis, and those who are preterm/low birth weight have a higher mortality rate, as well as higher neurocognitive and hearing sequelae rates [79, 80]. The three most common organisms causing bacterial meningitis are pneumococcal meningitis, *Hemophilus influenzae* type b, and meningococcal meningitis [11]. In infants, EOM is defined as meningitis occurring within 7 days after birth, and most commonly caused by Group B Streptococcus (GBS) [81, 82].

Cerebrovascular involvement is very common in neonatal group B streptococcal meningitis. A case series of eight newborns with NM identified arterial ischemic stroke with dual patterns causing either the deep perforating arteries stroke to basal ganglia, thalamus, periventricular white matter, or superficial injury with focal cortical infarcts [83]. Another retrospective cohort study of nine patients demonstrated ischemic and hemorrhagic strokes after NM [84]. A case report of a 36-day-old infant with GBS meningitis demonstrated vascular deficits in addition to inflamed meninges [85]. In another case report, GBS meningitis led to transverse myelitis [86]. Blood stream infections such as GBS meningitis can cause hypoxic-ischemic encephalopathy that result in neurodevelopmental problems [87]. In a NM study conducted in Northern Jordan, where *Klebsiella sp.* and *Enterobacter* sp. (40% and 19%, respectively) were the most common organisms, the mortality rate and neurological consequences were 32 and 39%, respectively, among survivors. Among the many clinical features analyzed, reduced arousal was predictive of post-meningitis consequences ($p = 0.016$) and a bulging anterior fontanelle was predictive of mortality ($p = 0.009$) [79].

NM might lead to hypoxic-ischemic insults, microglial and astrocytic activation, release of proinflammatory cytokines such as TNF-α and IL-6, which may cumulatively increase the susceptibility of oligodendrocyte precursors, leading to periventricular leukomalacia (PVL). PVL is a major problem for neurological and intellectual impairment and cerebral palsy [88].

A long-term follow-up study of bacterial meningitis in France depicted increased risk of sequelae in *Pneumococcal meningitis* compared to other organisms. Hearing disorders in 15% of the cases, and neuro problems such as mental retardation, motor deficit, or epilepsy were seen in 3–4% of the cases [80]. On an analysis of a 12-year outcome after bacterial meningitis, there were only subtle differences in intellectual, scholastic, and higher cognition at 7 and 12 years of follow-ups, while behavioral problems worsened and lower order skills improved [89]. On a longitudinal analysis of *H. influenzae* meningitis, patients with acute phase neurological deficits performed poorly at a final follow-up on IQ tests, academic and scholastic performance, psychomotor skills, visual memory, attention, executive function, and abstract reasoning [90]. A case-control study performed on outcomes of invasive serogroup B demonstrated an increase in bilateral sensorineural hearing loss, decreased IQ, executive function, and memory. An increased incidence of psychiat-

ric problems such as separation anxiety disorder, conduct disorder, attention deficit disorder, specific phobias, and generalized anxiety disorder were noted in meningitis cases as compared to the control group [91]. A bacterial meningitis study of African children showed that one fourth of the children with pneumococcal and *H. influenzae* type B meningitis showed neuropsychological sequelae; this rate was higher when compared to meningococcal meningitis. All cases showed hearing loss, vision loss, motor delay and seizures, whereas *H. influenzae* type B showed cognitive delay, and meningococcal meningitis additionally showed behavioral problems [11]. On a systematic review of high-risk newborns, survivors of NM with birth asphyxia had a higher percentage of cerebral palsy, neurodevelopmental and cognitive impairment, when compared to NM survivors with prematurity/very low birth weights [92]. On a neuropsychological assessment of cognitive domains, *non-Haemophilus influenzae* type B patients with academic and behavioral limitations had poor performance on cognitive functioning, as well as speed and motor steadiness when compared to patients with no limitations [93].

A systematic review conducted recently on bacterial meningitis showed that the incidence of hearing loss was 11%, and almost 5% of those affected had profound hearing impairment [94]. Seizures, serum CRP levels (an index of inflammation), and the severity of meningitis were some of the risk enhancers [95]. Some infants with normal or moderate hearing loss worsened after bacterial meningitis, suggesting that late onset hearing loss should be considered seriously in NM, and a repeat hearing screen test should be performed after the Universal Newborn Hearing Screening (UNHS) [96, 97].

On a study conducted to compare single and recurrent episodes of pneumococcal meningitis, among 1634 pneumococcal meningitis episodes in children ≤18 years of age, 24 (1.5%) children had recurrent episodes of pneumococcal meningitis. The patients from recurrent episodes of pneumococcal meningitis have significantly less ear, nose, and throat infections when all or just the first episode was considered. CSF leakage was frequent in recurrent episodes of pneumococcal meningitis cases, whereas immune deficiency, which was expected to be higher, was absent in recurrent episodes of pneumococcal meningitis cases and present in 15% of controls. However, death rates or neurological outcomes were not significantly different between these cases and controls [98].

4.1 Neuropathological Injuries of NM Leading to Neuropsychological Deficits

Some findings of the brain pathology as seen on magnetic resonance imaging (MRI)/computed tomography (CT) imaging in NM include ischemic/hemorrhagic stroke, ventriculitis, leukomalacia, asymmetrical periventricular space, and temporal edema [84]. In addition, focal cortical infarcts and deep perforating arteries strokes in basal ganglia, thalamus, and periventricular white matter can also be seen [83]. A preterm neonate infected with meningoencephalitis caused by *Bacillus*

cereus demonstrated cerebral edema and bright cortical sulci, representing meningitis on a CT scan. Liquefactive necrosis with abundant neutrophilic infiltration was also seen on a post-mortem histological examination [99].

The risk factors associated with poor outcome in bacterial meningitis cases are differing degrees of coma, need for ventilator support, cranial nerve palsy, bulging anterior fontanel, altered level of consciousness, high protein and low glucose content in CSF, high erythrocyte count, thrombocytopenia, leukopenia, low leukocyte count in CSF (< 600–1000 per microliter), positive CSF cultures, gestational age <37 weeks, birth weight <2500 gm, EOM, and neurological complications such as epilepsy, stroke, brain edema, hydrocephalus, or hemodynamic failure [80, 100].

As meningitis causes neurological injury in term and preterm infants, MRI images consistently show cerebral tissue and vascular abnormalities that are associated with poor neurodevelopmental outcomes at 2 years of age such as cognitive and psychomotor delay, cerebral palsy, and neurosensory impairment. Moderate-to-severe white matter abnormalities are better predictors of neurodevelopmental impairments compared to gray matter abnormalities [101]. A retrospective cohort study and a case series of 8 term infants with GBS meningitis and ischemic stroke had abnormal MRI findings including a deep perforating arterial infarction and more superficial cortical injuries [83, 84]. Neuroimaging in a couple of case reports about GBS meningitis in term infants demonstrated cerebral vasculopathy and transverse myelitis [85, 86].

4.2 Treatments to Reduce Neurological Sequelae with NM

The three leading causes of bacterial meningitis, pneumococcal, meningococcal, and *H. Influenzae* type B are vaccine preventable, so routine use of conjugate vaccines could help prevent meningitis cases, deaths, and neurological sequelae [11]. Replacement of childhood pneumococcal conjugate vaccine (PCV7) with PCV13 demonstrated significant reduction in PCV13-serotype invasive pneumococcal disease (IPD). Increase in childhood invasive pneumococcal disease cases are due to non-vaccine serotypes in England and Wales [102]. The introduction of meningococcal serogroup A in Africa, B in the United Kingdom, and C in several countries has demonstrated successful results. However, outbreaks of serogroup C and W meningococcal disease occurred in recent years in African and European countries [103]. Thus, continuous monitoring facilitates the introduction of vaccines against the endemic serogroups to the affected regions.

As *Klebsiella* sp. species is an important pathogen causing NM, antibiotics against *Klebsiella* sp. such as cefotaxime or ceftazidime plus ampicillin have to be used [79]. Patients with non-communicating hydrocephalus received ventriculoperitoneal shunts, whereas those with communicating hydrocephalus received oral acetazolamide and furosemide [104]. A meta-analysis conducted by Brouwer et al. in 2015 demonstrated that corticosteroids significantly reduced hearing loss and neurological sequelae in children and adults [105]. Another neonatal study with two

randomized controlled trials expressed an equivocal efficacy of steroids in reducing death toll and hearing loss [106]. In another study, steroids showed a bad prognostic influence on bacterial meningitis caused by Group B Streptococcus and *E. coli* [107]. Therefore, the uncertainty of steroid efficacy in neonatal bacterial meningitis alerts us to be cautious while administering them. Thrombocytopenia complicating NM should be treated with platelet transfusion, which is not related to mortality or any other risks and adverse events [108].

5 Conclusion

Neonatal meningitis is a potentially fatal infection of the meninges surrounding the brain and spinal cord that affects the neonates. NM considered being a public health challenge for pediatricians. About 50% of children who survive an episode of neonatal or infant bacterial meningitis experience persistent behavioral, intellectual, or neurological complications. Experimental NM studies demonstrated the beneficial effect of antioxidants, MMP inhibitor, and antidepressant (imipramine and fluoxetine) treatment in terms of decreased apoptosis and improved behavioral effects. However, current treatment with NM includes empirical antibiotic therapy and steroids. Hence, treatment targeting the modulation of redox imbalance, cytokine levels, BBB integrity, and inflammatory mediators in addition to conjugated vaccine and supportive therapy in meningitis of diverse pathogenic etiologies may be a useful strategy to reduce the mortality and to improve its lingering neurological complications.

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Toxoplasma gondii Infection as a Risk Factor for Major Psychiatric Disorders: Pre-clinical and Clinical Evidence

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Abstract The link between toxoplasmosis and major psychiatric disorders, such as schizophrenia and bipolar disorder, has been an important field of investigation in immunopsychiatry. *Toxoplasma gondii* is a parasitic protozoan that lodges in parenchymatous tissues like the central nervous system, disrupting their normal functioning and activating immune cells. *T. gondii* infection may occur in two different ways: (i) acquired through consumption of *T. gondii* as a foodborne pathogen and (ii) vertically from mother to fetus. Maternal toxoplasmosis infection activates the immune system of both mother and fetus. Fetal brain can be affected by such immune activation, explaining in part the association between congenital toxoplasmosis and schizophrenia. Moreover, *T. gondii* may induce a disruption in dopaminergic signaling pathways in the brain, which may lead to psychotic episodes. In this chapter, we discuss the pre-clinical and clinical evidence on the association between perinatal and postnatal *T. gondii* infection and the development of neuropsychiatric disorders, as well as the pathophysiological mechanisms.

Keywords Toxoplasma gondii · Psychiatry · Inflammation · Dopamine, Glutamate · Congenital

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1 Introduction

Toxoplasmosis is an infectious disease caused by the apicomplexan protozoan *Toxoplasma gondii,* which affects approximately one third of the world population. It is more widespread than diseases regarded as "serious global threats," such as tuberculosis and malaria [1–3]. Its incidence varies based on geographical location and its rate of infection may oscillate from 10% to over 86% depending on the studied population [2]. In North and Latin America, seroprevalence rates vary quite largely. In South America, the *T. gondii* prevalence is estimated to be high, i.e., above 60%, in some countries like Brazil, while it remains low, around 20–40%, in countries such as Chile. Such discrepancy is possibly related to different eating and drinking habits as well as sanitary practices [4]. Also, the warm weather may favor survival of the parasite's oocysts [5]. In the United States and Canada, the seroprevalence of *T. gondii* is between 10% and 20%. The seroprevalence of *T. gondii* in China is less than 10% [2]. Owning a cat, being male, and having a body mass index above 30 are risk factors, whereas being vegetarian and falling into a high socioeconomic class are protective factors against T. *gondii* infection [6].

T. gondii's definite host consists of members of the family *Felidae*, but its ability to infect most warm-blooded animals, including humans, is well-known [7]. Human infection may occur vertically, from mother to fetus via the placenta, or acquired as either a foodborne pathogen or contact with cats' feces [8]. Perinatal infection by *T. gondii* is an established risk for miscarriage, fetal malformation, and congenital complications such as intellectual disability, microcephaly, hydrocephaly, and chorioretinitis [9]. Routine pregnancy laboratory exams including detection of either IgM or IgG antibodies against *T. gondii*-derived antigens are used worldwide to evaluate fetal safety and viability [10].

There is a significant body of evidence linking infection by *T. gondii* and the emergence of neuropsychiatric symptoms and psychiatric disorders, especially schizophrenia and bipolar disorder [11]. Such observation dates back to the middle of the twentieth century when *T. gondii* infection was found to affect rodent behaviors, leading rats to exhibit decreased defensive mechanisms and to become attracted to cats' urinary odor [12, 13]. In more recent years, independent studies have supported a link between *T. gondii* infection after birth and the onset of psychiatric disorders and/or behavioral changes [14, 15].

In this chapter, we aimed at discussing the current evidence regarding the potential role of congenital and postnatal *T. gondii* infection in the development of neuropsychiatric disorders. We also provided an overview of the potential underlying molecular and cellular mechanisms.

2 Biology of the Parasite and *Toxoplasma gondii* Infection

The apicomplexan *T. gondii* is an intracellular coccidium protozoan parasite. Its definite host includes several members of the family *Felidae,* i.e., domestic cats and their relatives. Intermediate hosts are most warm-blooded animals, including humans [16]. Infection by *T. gondii* is more prevalent in developing countries, such as Brazil and Argentina, than in developed ones, except for some European countries [2]. *T. gondii* infection usually remains asymptomatic in immunocompetent, non-pregnant individuals.

In immunocompetent subjects, macrophages and dendritic cells induce the development of Th1 and antigen-specific killer $CD8^+$ T cells. These cells synthesize interferon-γ (IFN-γ), which suppresses intracellular parasitic growth [17]. During pregnancy due to an immune environment dominated by Th2 and T regulatory cells, the parasite can escape from an effective defensive immune response, increasing the chances of maternal pathology and congenital transmission [18]. In immunocompromised patients, such as organ transplant recipients, HIV/AIDS patients, and cancer patients, *T. gondii* infection can be fatal [19]. In such individuals, Toxoplasmosis is often a consequence of reactivation of latent infection, usually presenting as intracranial mass lesions causing focal and intracranial hypertension syndromes [20, 21]. Acute toxoplasmosis in immunocompromised patients may also involve different organs and lead to disseminating systemic diseases, such as pneumonia and retinochoroiditis [22].

T. gondii may reproduce sexually (feline host) and asexually (non-feline host) and has three different life forms: oocytes, rapidly diving tachyzoites, and slowly dividing bradyzoites. Feline infection occurs via consumption of the protozoan in any life form. If ingestion occurs by animals belonging to the family *Felidae*, the bradyzoites will sexually reproduce inside their intestine and form schizonts (sexual life cycle). Merozoites are organisms that form the male and female gametes and are released from schizonts. Oocyst wall develops around the fertilized egg [23].

The asexual life cycle (non-feline) of *T. gondii* begins upon the formation of oocysts in the digestive tract of the definite host. Oocysts are resistant to adverse environmental changes and undergo sporulation outside felids' intestines. Sporulation refers to an increase in the parasite's volume due to an internal synthesis of sporozoites, the infective form. Sporulation produces a total of two sporocysts that must contain four sporozoites inside each oocyst [23]. Within the intestines of intermediate hosts, infectious oocysts release sporozoites that penetrate enterocytes. Once inside these cells, sporozoites become tachyzoites, form that asexually reproduces until the host cell bursts. Newly formed tachyzoites are released to infect new cells in the bloodstream and several tissues, which may include the central nervous

system (CNS) [24]. In the asexual cycle, tachyzoite infection forms intracellular bradyzoites. Tachyzoites will keep infecting cells until the intermediate host develops specific immunity against them. Although bradyzoite reproduction (chronic infection) is much slower than that of tachyzoites (acute infection/toxoplasmosis), bradyzoites are less accessible to the immune system since they are hidden as tissue cysts. Tissue cysts usually remain latent and toxoplasmosis is considered an asymptomatic disease in immunocompetent hosts [23, 25].

3 Infection with *Toxoplasma gondii* and Development of Neuropsychiatric Disorders

T. gondii has the ability to lodge in the CNS and remain latent for years. In recent years, it has been noticed that *T. gondii* may disrupt synaptic communication, especially affecting dopaminergic systems, which are implicated in behavioral changes. Maternal infection may lead to immune activation, possibly affecting fetal brain development and behavioral impairment later on.

4 Insigths from Clinical Studies

4.1 Prenatal

One of the very early studies in the field evaluated the incidence of anti-*Toxoplasma* antibodies in human subjects admitted to a mental hospital through complement-fixing and dye-tests. Among 116 children evaluated, *T. gondii* infection was implicated as the cause of "congenital mental deficiency" (hydrocephaly, microcephaly, post-encephalitic disorder, and schizophrenia) in 7–8% of children [26]. A study conducted in a large birth cohort born between 1959 and 1967 showed that maternal infection by *T. gondii* is a possible risk for schizophrenia [27]. Such association was also observed by several other independent studies [28–30]

Perinatal research currently evolves around the vertical exposure to anti-*Toxoplasma* antibodies rather than the intrauterine exposure to the parasite itself, and the available evidence indicates that maternal seropositivity to *T. gondii* is associated with schizophrenia. This association is probably mediated by the parasite-induced immune response rather than exposure to the parasite, and may be dependent on the interaction between genetic and environmental factors [31].

The relationship between maternal anti-*Toxoplasma* antibodies and the development of autism in the offspring has also been investigated. Maternal anti-*Toxoplasma* IgM antibodies were associated with a 60% decrease in the odds of childhood

autism development in the offspring. In contrast, low anti-*Toxoplasma* IgG maternal antibodies titers were associated with an increase in the chance of childhood autism [32]. It is worth mentioning that IgG antibodies can cross the placenta whereas IgM antibodies cannot. The relationship between congenital toxoplasmosis and the development of bipolar disorder was not confirmed [33].

4.2 Postnatal

After behavioral alterations were described in *T. gondii*-infected rodents, research around the possible effects of *T. gondii* infection in human behavior began. The association between postnatal infection with *T. gondii* and development of psychiatric disorders has been documented [14, 15]. In 1953, the first association between *T. gondii* infection and schizophrenia was reported [12]. Additional studies on acquired toxoplasmosis in humans described a wide range of symptoms that could vary from "neurosis" to severe psychosis [34, 35]. Currently, toxoplasmosis has been associated with the development of schizophrenia and bipolar disorder [36, 37].

Interestingly, patients with psychiatric disorders treated with psychotropic drugs that also exhibit anti-*Toxoplasma* activity may display better prognosis. Bipolar disorder patients treated with drugs that have anti-*Toxoplasma* activity exhibited a less number of depressive episodes [38]. Indeed some drugs used to treat schizophrenia and bipolar disorder, such as haloperidol and valproic acid, inhibit *T. gondii* replication in vitro [39].

Asymptomatic individuals who were seropositive to T. *gondii* were more likely to cause motor vehicle accidents as compared to non-seropositive healthy subjects, possibly reflecting subtle cognitive impairment and/or impulsive traits [40–43]. In line with the assumption of cognitive dysfunction, *T. gondii* seropositive subjects are more likely to display poorer performance on the simple reaction time test, the symbol-digit substitution test, and the serial-digit learning test as compared to matched controls for age, sex, and ethnicity [44]. Finally, HIV patients infected with *T. gondii* display worse neurocognitive performance than patients with HIV without toxoplasmosis [45].

5 Insights from Pre-clinical Studies

Experimental Models

Toxoplasma-induced behavioral changes can be modeled in animals. Both rat and mice display behavioral impairment after *T. gondii* infection (Table 1).

Table 1 Toxoplasma-induced behavioral abnormalities

Author	*T. gondii* strain and inoculum	Infection pathway	Rodent line	Sex	Age	Behavioral test	Impairment	Proposed mechanisms
Spatial learning and memory								
Piekarski et al. 1978 [46]	Avirulent strain 300–350 cysts	Intraperitoneal	**Mouse**: NMRI/HAN **Rat:** Wistar AF/HAN	Female	15 weeks old	Deep labyrinth	Impaired learning	Possible indirect toxic effects from *T. gondii*
Witting 1979 [47]	Avirulent strain 300 cysts for rats and 30 for mice	Intraperitoneal	**Mouse:** CF1/W74 **Rat:** Wistar TNO/W74	Female	6 months old	Deep maze	Impaired learning	No mechanism proposed
Hodkova et al. 2007 [48]	Avirulent HIF strain and 0.5 mL of brain suspension in saline containing 10 tissue cysts	Oral	**Mouse**: F1 cross between BALB/c (females) and C57/BL (males)	Female	10 weeks	Radial arm maze	Impaired recognition memory	*Toxoplasma*-induced dopamine imbalance
Kannan et al. 2010 [49]	Prugniaud and ME49 strains 400 tachyzoites (2 parasites/μL)	Intraperitoneal	**Mouse:** BALB/c	Female	9 weeks	Y-maze	Impaired working memory but no impaired recognition memory	Immunological reactions that lead to disrupted neurotransmission

Olfactory-based learning memory								
Xiao et al. 2012 [50]	Prugniaud strain 400 tachyzoites (2 parasites/μL)	Intraperitoneal	**Mouse:** BALB/c	Female and male	9 weeks	Social transmission of food preference	Female: No impairment Male: Impaired learning and memory	Altered dopamine receptor 4 (D4) expression in males Sex-difference: different locations for bradyzoite lodging; different sex-related neuroimmunological responses
Associative learning and memory								
Wang et al. 2010 [51]	Prugniaud strain Each mouse was infected with 5 cysts by the/or on the 5th, 10th, and 15th day after gestation	Oral	**Mouse:** NIH for congenital transmission and BALB/c mice for *T. gondii* maintenance	Not provided	N/A	Passive avoidance	Impaired memory	Disrupted neurotransmission cell and tissue damage secondary to *T. gondii* infection

5.1 Rodents

Behavioral changes, especially rodents' sudden attraction to feline urinary odors, have been consistently reported in *T. gondii* infection [13]. Infected rats also exhibit decreased rate of defensive behaviors and tend to spend longer times in vulnerable areas, thus becoming fearless to novel stimuli [52]. Such collection of unexpected behaviors brings "advantageous" consequence to *T. gondii* as rats become more susceptible to predation by felines, thus allowing the parasite to complete its sexual life cycle. This phenomenon known as the "Fatal Feline Attraction" has been interpreted as evolution-driven [13, 53].

Much of the pathophysiology underlying this uncanny attraction to cats' urinary odor is due to an increase in limbic system activity, similar to the one observed in sexual arousal. Uninfected rats display an increase in neuronal activity in the posterodorsal medial amygdala (MEApd) upon exposure to an estrous female rat. When exploring cat urine, *T.gondii*-infected rats not only display an increase in activity in the MEApd, but also in other areas, including the ventromedial hypothalamus dorsomedial region (VMHdm) and the basolateral amygdala (BLA). Conversely, when exposed to an estrous female, infected rats do not exhibit increased MEApd activity, still displaying increased neuronal activity in the VMHdm and BLA regions [54]. Moreover, *T. gondii* induces greater production of testicular testosterone in rats by upregulating the expression of steroidogenic enzymes of the smooth endoplasmic reticulum and enzymes involved in the synthesis of precursor pregnenolone [55]. Testosterone enhances sexual attractiveness in males and reduces fear.

Overall, infected female rats display similar behavioral changes as males, but attraction- and averse-related behaviors are largely influenced by their estrus cycle. Uninfected female rats displayed a preference toward rabbit urine as opposed to bobcat urine throughout the cycle, except at estrus and metestrus stages. Infected female rats lose this preference, except during the estrus stage. Such behavior was supposed to be dependent on the levels of circulating progesterone, hormone known for its anxiolytic effects [56]. However, a more recent study suggested that loss of predator aversion in infected female rats is not dependent on ovary-derived hormones [57]. Intriguingly, infected rats usually display preference for wildcat odor (e.g., cheetahs [*Acinomyx jubatus*] or pumas [*Felis concolor*]) over domestic cats (*Felis silvestris catus*) [53].

The Flinders Sensitive Line (FSL) rats are an animal model of depression since these animals are supersensitive to the effects caused by cholinergic agonists like humans with depression [58]. A recent study found that *T. gondii*-infected animals from both the sensitive and Flinders Resistant Line (FRL) strains displayed an increase in anxiety-like behaviors. Nevertheless, only FSL rats exhibited depressive-like behaviors secondary to *T. gondii* infection. Since FSL rats are genetically modified to model human depression, such finding corroborates the hypothesis of genetic and environmental interaction in the pathogenesis of neuropsychiatric symptoms, specifically depressive symptoms [59]. Other unusual behaviors observed in infected

rats include: (1) deficits in task-associated memory as for performing functions that required access to such; (2) defective learning abilities; (3) improved locomotor activity; (4) and reduced neophobia [60–62].

6 Mechanisms

These behavioral changes in infected rodents have arisen many hypotheses around the pathogenesis of neuropsychiatric disorders and their association with *T. gondii*. *T. gondii* tissue cysts are known for their ability to lodge in the brain. A study showed that *T. gondii* cysts were mainly (75% of the total cysts) distributed within rat telencephalon, which comprises 56% of its total brain volume. Conversely, 5% of cysts were found in the metencephalon, which comprises 12% of the total brain volume [63]. The amygdala, the brain region responsible for fear processing, is also known to concentrate great volume of *T. gondii* cysts in rats [64]. In outbred mice, behavioral and neurological changes were secondary to inflammation and loss of brain parenchyma due to chronic infection with *T. gondii*. Inflammation was contiguous to the hippocampus and aqueduct of Sylvius [65]. Besides cyst location and related inflammation, other hypotheses on the CNS effects of *T. gondii* have been proposed as discussed below.

6.1 Prenatal

During pregnancy, *T. gondii* infection is associated with lower levels of progesterone [66]. Progesterone, in turn, stimulates NK and T cells to synthesize progesterone-induced blocking factor (PIBF), which promotes Th2 expansion and reduces NK cell activity [67]. Early pregnancy infection by *T. gondii* increases the likelihood for abortions, stillbirth, and premature birth. Infection during the third trimester increases the chances of congenital transmission of the parasite [66]. Although the mechanism still remains unclear, low levels of progesterone and estrogen may lead to a severe infection [68].

T. gondii infection induces an inflammatory state in the mother. Innate macrophages are stimulated upon microbial stimulus, like *T. gondii* infection, and synthesize tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and nitric oxide (NO) [69]. Increased maternal levels of IL-6 are associated with alterations of the fetal salience system, which has been implicated in schizophrenia [70]. The mechanism by which increased IL-6 levels alter fetal neurodevelopment is unknown [71]. IL-6 has gained attention since genetic knockout model and maternal administration of anti-IL-6 inhibited behavioral impairment in the offspring [72]. Maternal immune activation may also result in offspring's CNS dopaminergic abnormalities [73].

Infectious agents, like *T. gondii*, with antigens similar to CNS components (sialic acids or gangliosides, for example) would sensitize the mother and induce the

maternal synthesis of IgG antibodies. IgG antibodies to these common antigens would cross the placenta as well as the fetal blood-brain barrier. These antibodies would attack the developing nervous system, leading to neuropsychiatric disorders later in life [74].

6.2 Postnatal

6.2.1 Inflammation

T. gondii infection induces an inflammatory state in murine models. In the first 7 days after *T. gondii* infection in 4-week old mice, rodent energy expenditure was increased and such elevation was associated with increased brain and splenic levels of TNF-α, IL-1, IL-5, and IFN-γ. Conversely, latent toxoplasmosis was associated with elevated brain and splenic concentrations of TNF-α and IL-10. These findings were observed in adult mice that regained partial body weight after *T. gondii* infection [75]. Systemic inflammation induces behavioral changes, such as depressive-like symptoms in rodents. Inflammatory stimuli increases the tryptophan-degrading enzyme idoleamine-2,3-dioxygenase (IDO) activity, which promotes the activation of the kynurenine pathway. Besides degrading tryptophan and, as consequence, reducing the synthesis of serotonin, the kynurenine pathway generates several neuroactive metabolites with glutamatergic effects, playing a key role in the genesis of depressive-like behaviors [76]. Clinical evidence has shown that there might be a "Th1-Th2 seesaw" response generated by glial cells on tryptophan and kynurenine metabolic enzymes, which leads to abnormalities in the serotonergic and glutamatergic abnormalities that are features in major depressive disorder and schizophrenia [77]. Also, cognitive deterioration in *T. gondii* seropositive bipolar disorder patients is associated with circulating levels of IL-6 [78].

6.2.2 Neuromodulation

6.2.2.1 Dopamine

Cyst-containing brain cells accumulate great concentrations of dopamine, and in vitro infection induces synthesis of large amounts of dopamine in neural cells [62]. Rodents infected by *T. gondii* exhibit increased non-physiological concentrations of dopamine, a neurotransmitter known to mediate primarily reward circuits [62, 79, 80].

The reward circuit is known to be mediated via dopaminergic signaling. Tyrosine hydroxylase (TyrH), the rate-limiting molecule for dopamine biosynthesis, is encoded by two genes found in the genome of *T. gondii* [81]. This rate-limiting molecule converts tyrosine to DOPA by using tetrahydrobiopterin, also known as sapropterin, and molecular oxygen. Normally, TyrH is inhibited through a negative

feedback loop, in which dopamine binds to TyrH competitively and interacts with the R domain of the enzyme [82]. TyrH expression increases during brain and muscle cyst-forming stages of *T. gondii* infection [81]. Upregulation of miR-132 upon *T. gondii* infection altered dopaminergic signaling via downregulation of D1-like dopamine receptors, monoamine oxidase, and other intracellular proteins that are related to dopamine-mediated signaling transduction [79].

It is worth mentioning that disruption in dopaminergic signaling has been implicated in the pathophysiology of schizophrenia. More specifically, psychotic symptoms are related to hyperactive dopaminergic signaling in mesocorticolimbic pathway [83].

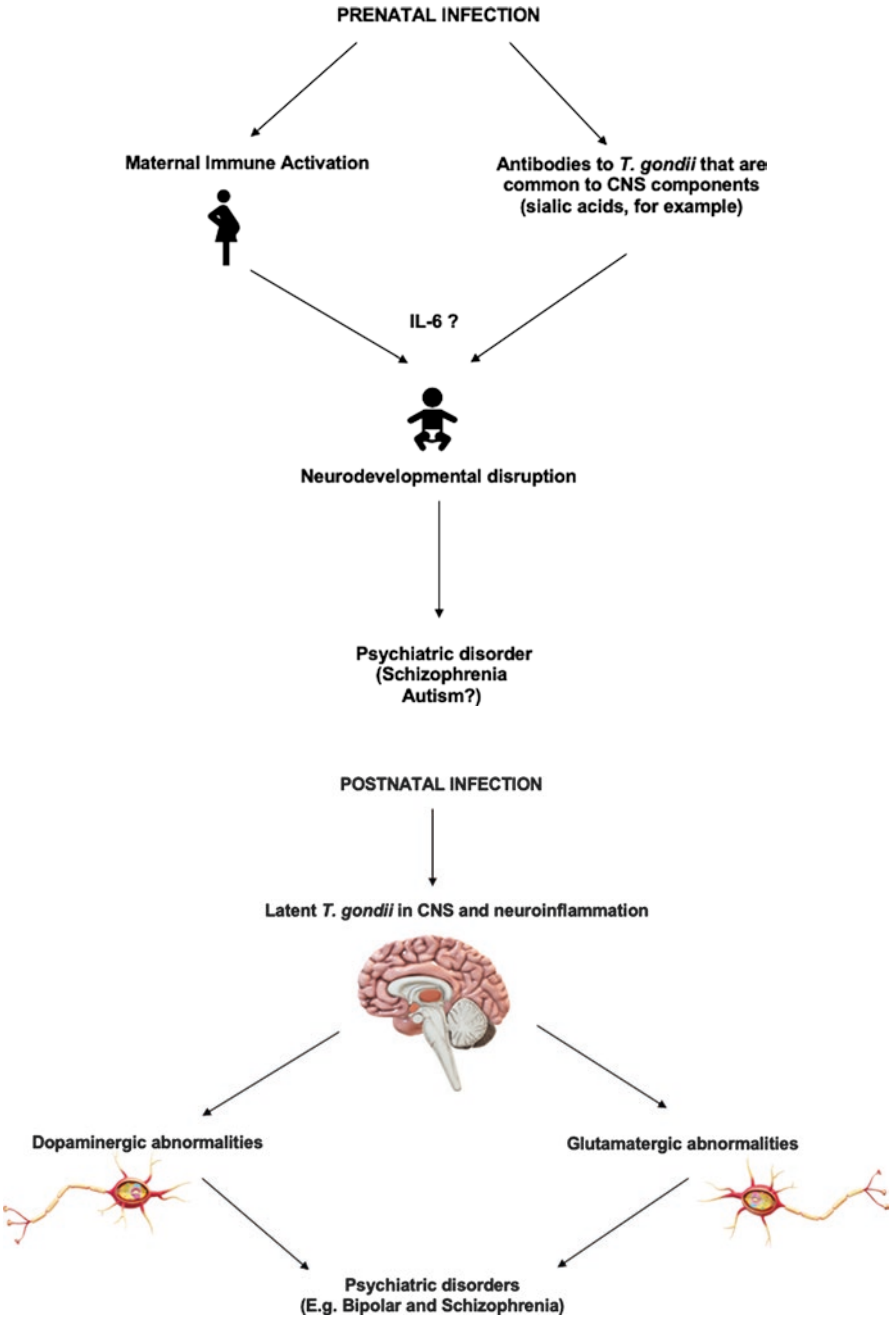
6.2.2.2 Glutamate

Chronic toxoplasmosis in mice downregulates synaptic protein expression in the hippocampus and neocortex. In the hippocampus, proteins such as the glutamate transporter EAAT2, post-synaptic scaffolding protein Shank3, GluA1, GluA2, and GluN1 were downregulated. In the cortex, proteins downregulated included EAAT2, Shank3, GluA1, GluN1, and GluN2B [84]. *T. gondii* infection also downregulates the expression of GLT-1, which is the astrocytic glutamate transporter, thus increasing amounts of extracellular glutamate [85]. Tachyzoites have the ability to manipulate Ca^{2+} signaling, resulting in hypo- or hyper-responsive neuronal cells in chronically infected mice [86].

Deficits in glutamatergic signaling have gained attention as a key factor of schizophrenia pathophysiology. Postmortem tissue from schizophrenic patients presented reduced density of NMDAR, a glutamatergic receptor [87]. However, an additional study showed that abnormal glutamate receptor localization as opposed to a generalized deficit is what possibly underlies the pathophysiology of schizophrenia [88]. One clinical study found reduced concentrations of CSF glutamate in bipolar and depressive patients, thus establishing a possible link between this neurotransmitter and these mood disorders [89].

7 Concluding Remarks

In this chapter, we discussed the association between *T. gondii* infection and development of neuropsychiatric diseases. Whether the infection occurs in uterus or later in life, it seems to influence the CNS and, as a consequence, lead to cognitive and behavioral symptoms. Prenatal infection is mostly associated with schizophrenia and autism, as opposed to postnatal infection, which has been linked not only to schizophrenia but also to bipolar disorder and other mood disorders. Neuromodulation of dopamine and glutamate, and neuroinflammation are some of the mechanisms proposed by which toxoplasmosis may affect behavior. Besides a better understanding of these mechanisms, it must be defined whether effective anti-*Toxoplasma* treatment could prevent and/or improve prognosis of neuropsychiatric disorders.


PRENATAL INFECTION
Maternal Immune Activation
Antibodies to T. gondii that are common to CNS components (sialic acids, for example)
IL-6 ?
Neurodevelopmental disruption
Psychiatric disorder (Schizophrenia Autism?)
POSTNATAL INFECTION
Latent T. gondii in CNS and neuroinflammation
Dopaminergic abnormalities
Glutamatergic abnormalities
Psychiatric disorders (E.g. Bipolar and Schizophrenia)

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A Critical Appraisal on the Epidemiological Evidence Linking Perinatal Inflammation and Risk of Psychosis

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Abstract Since the dawn of psychiatry as a medical discipline, physicians and researchers struggle with theories that could explain the origin of schizophrenia. Among several hypotheses, perinatal inflammation remains one of great importance not only for the schizophrenia syndrome but also to major neurodevelopmental disorders as autism. In this chapter, a summary of the evidence and relevance to support neuroinflammation as an important factor increasing the risk for schizophrenia is highlighted. The limitations of this theory are discussed together with other synergistic factors that could influence the diathesis of schizophrenia.

Keywords Schizophrenia · Inflammation · Perinatal · Virus · Bacteria · Etiology

1 Introduction

Genes and environment interact to increase the risk of schizophrenia and psychotic disorders. Although genetic predisposition is important to the genesis of schizophrenia, environmental influences account for the 40–55% monozygotic twin discordance [1]. Since Menninger described an association between psychosis and influenza in 1919 [2], numerous studies have investigated the link between schizophrenia and infections [3]. These efforts have not identified a specific pathogen for schizophrenia but suggested that immune dysregulation may play an important role in the development of this disorder. Epidemiological data have repeatedly indicated the impact of environmental factors, such as prenatal infections and inflammation,

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on the pathogenesis of schizophrenia [4]. Multiple hits seem to accumulate during critical periods of central nervous system (CNS) development to cause schizophrenia symptoms and other psychotic disorders [5]. The link between prenatal infection and schizophrenia is derived from ecological studies that searched historical evidence for gestational viral infection exposure during influenza pandemics. Nevertheless pioneer studies showed substantial proof for an association between second-trimester influenza exposure and psychotic outcome, and more recent meta-analysis concluded that evidence needed clinical caution and more investigation [3–5].

Infections requiring hospitalizations are associated with subsequent increased risk of mental disorders [6], including schizophrenia. Gestational exposure to influenza, rubella, and toxoplasmosis and elevations of specific proinflammatory cytokines also increase the risk of schizophrenia [7]. Antibody levels of cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus, *Mycoplasma*, chlamydia, and *Toxoplasma gondii* are higher in patients with schizophrenia than in health control subjects [8]. Moreover, several schizophrenia susceptibility genes have been directly implicated in the life cycles of these pathogens, suggesting an interplay between genes and environmental risk factors [9].

Many schizophrenia-related genes are part of the immune network [8–10], and autoantibodies to dopamine, serotonin, acetylcholine, and NMDA receptors have been reported in schizophrenia [11]. Maternal immune activation in animal models generates phenotypes in the offspring that have proved relevant to schizophrenia research [12]. Preclinical studies have also shown that intranasal infusion of influenza in mid-pregnancy reduced exploratory and social behavior and induced prepulse inhibition deficit in offspring, which is reversed following treatment with clozapine and chlorpromazine [13].

A growing body of literature supports a role for neuroinflammation in the pathophysiology of psychosis. Neuroinflammation is caused by the accumulation of circulating and local immune cells in the neuronal tissue, and it is often associated with tissue injury [14]. Peripheral immune response to inflections can activate microglia and cytokines that have destructive effects in the brain [15]. Physiologic levels of cytokines play critical roles in brain development, but elevations due to maternal infection increase vulnerability to developmental brain damage [16], which might explain associations between different prenatal infections and schizophrenia. Infections increase the levels of several proinflammatory cytokines, including IL-8 and TNFα, which have been associated with schizophrenia [17].

In this chapter, we discuss the putative mechanisms by which perinatal inflammation may lead to psychosis and review preclinical and clinical studies that support a role for inflammation in the pathophysiology of schizophrenia and psychotic disorders.

2 Pathophysiology

Ventricular enlargement and reduced hippocampal and parahippocampal volume strongly suggest brain tissue loss in the course of schizophrenia [18]. There is an ongoing debate as to whether brain abnormalities result from direct fetal brain

infection or from maternal immune response [4]. The prevailing view is that neuroinflammation results from the maternal immune response to viral and bacterial infection [19]. In fact, the induction of the maternal immune response in the absence of an infectious agent is enough to impair brain development in offspring [20, 21]. Nevertheless, there are several reports of deleterious effects due to direct viral, bacterial, or parasitic infection into the fetal brain [4]. The mechanisms by which infections might lead to schizophrenia have not been well delineated, but include teratogenic effects of maternal antibodies on neurodevelopment and a rise in the levels of cytokines causing disruption of neuronal layer migration [7]. A parsimonious pathophysiological model for schizophrenia postulates that infections alter fetal brain development and increase vulnerability to schizophrenia by acting through common pathways [17] that involve neuroinflammation through infection-induced cytokines. The most important event is the host's elevation of cytokines, which function as the main chemical mediators of the host's immune response against the infectious agents. Nevertheless, besides their crucial roles in the modulation of T and B lymphocytes in the periphery, cytokines also exert multiple effects on the developing brain by disrupting the neurotrophin signaling. Cytokines released by the maternal immune system can cross the placenta and enter the fetal circulation. Maternal infection can result in toxic elevation of cytokines in the fetal brain and thus exposing the fetus to possible neurodevelopmental impairment [22].

There is converging evidence of a hyperactive proinflammatory system in schizophrenia [23]. Infections raise the levels of proinflammatory cytokines such as IL-8 and TNFα, which have been implicated in the pathogenesis of schizophrenia [17]. IL-8 is important for the adherence of neutrophils to endothelial cells and in free radical formation [24], and fetal infection increases [25] amniotic fluid levels of TNF-α that has been associated with later risk of autism and schizophrenia [26]. Regarding anti-inflammatory responses, there are reports of reduction in the levels of anti-inflammatory cytokines (IL-4) [27] as well as increase in the levels of anti-inflammatory cytokines soluble IL-1RA (sIL-1RA), IL-2R, IL-10, and TGF-β in the sera of patients with schizophrenia [28]. Reduced anti-inflammation suggests an inability to limit inflammatory response, while excessive anti-inflammation may reduce patients' resistance to infectious agents [4].

As a multifactorial disorder, multiple events must occur during critical developmental periods to cause schizophrenia [5]. At least for a significant group of patients, changes in the CNS may result from neuroinflammation and abnormal immunological responses [5]. It is known that immune activation elevates maternal and fetal cytokines [17], but is there a direct causal connection between cytokines and brain–behavioral abnormalities?

Epidemiological studies of the 1957 influenza pandemics were some of the first to show a strong association between maternal infection in pregnancy and schizophrenia in the offspring [29], an effect that seems to depend more on immune activation and maternal cytokine release than on the specific infectious agent. In later epidemiological studies, oscillations in the incidence of influenza have been compared with the dates of birth of schizophrenic patients. Most, but not all, studies have demonstrated correlation between maternal exposure to the influenza virus and higher risk of development of schizophrenia in the offspring.

It is worth mentioning that studies that clearly described cases of influenza in pregnant women followed by the investigation of the incidence of schizophrenic disorders in the offspring during adulthood are almost inexistent, but the few available [30–34] failed to show any association. The most likely reason for these negative results concerns their methods. These studies took into account only the influenza cases reported by the mothers, with the likelihood of underestimation due to memory bias relating to the retrospective evaluation and asymptomatic influenza infection. Moreover, the small number of cases of schizophrenia subsequently diagnosed among the infants surveyed considerably restricts the interpretation of the results [30]. As epidemiological studies have enormous data limitation, the translational observation with animal exposure to infections, cytokines, and schizophrenia-like risk can ameliorate our understanding.

In this regard, an animal model, a single maternal injection of the proinflammatory cytokine IL-6 in mid-pregnancy resulted schizophrenia-like phenotypes, such as prepulse inhibition and latent inhibition deficits, in adult offspring [31]. These effects were prevented by administration of anti-IL-6 antibody and in an IL-6 genetic knockout, suggesting a key role for this cytokine in the schizophrenia pathogenic process.

Deleterious effects of inflammation are likely caused by oxidative stress, and vice versa. Oxidative stress is an imbalance between reactive oxygen species (free radicals) and antioxidant defenses, which can lead to chronic inflammation [32]. Oxidative stress activates the nuclear factor κB (NF-κB), a transcriptional activator of inflammatory response that also triggers the production of free radicals [33, 34]. Conversely, the immune system causes oxidative stress because activated microglia generate free radicals to destroy pathogens, which can also damage the brain in the absence of proper antioxidant defenses [35]. In fact, immune activation in animal models shows that the imbalance between pro-oxidants and antioxidants mediates the development of psychosis [36]. Maternal immune activation (MIA) elevates multiple markers of oxidative stress in the hippocampus of male offspring [37]. Inflammation and oxidative stress seem to have a reciprocal relationship in the development of psychosis.

But how exactly inflammation could lead to psychosis? Barrow and colleagues propose that psychosis results from alterations in cellular homeostasis due to oxidative stress and immune dysfunction [5]. Neuroinflammation causes aberrant growth and/or pruning of N-methyl-D-aspartate receptor (NMDAR)-containing parvalbumin interneurons (PVI) in the prefrontal cortex and hippocampus. PVI disruption disinhibits pyramidal cells in the hippocampal subiculum, which, in turn, leads to stimulation of the nucleus accumbens, followed by inhibition in ventral pallidum, resulting in ventral tegmental area (VTA) dopamine release [38]. The model is plausible, considering that subclinical doses of NMDAR antagonists, such as phencyclidine and ketamine, mimic positive and negative symptoms, as well as cognitive deficits in healthy subjects [39]. Moreover, NMDAR blockade by autoimmune antibodies in NMDAR encephalitis leads to severe psychosis and cognitive deficits [40]. NMDAR disruption is upstream from the well-characterized hyperactivity of dopamine (D2) receptors in mesolimbic and mesocortical projections in patients

with schizophrenia [41]. The best framework to explain how an excess in dopamine makes someone paranoid comes from the aberrant salience attribution account of psychosis [42]. Dopaminergic hyperfunction leads to aberrant assignment of novelty and saliency to objects and associations. Delusions then arise as a cognitive scheme that the patient develops to explain aberrant salience experience.

(NMDAR)-containing interneurons in the prefrontal cortex and hippocampus are likely disturbed during important developmental windows [43], which fits to the neurodevelopmental hypothesis of schizophrenia. Oxidative stress and immune dysfunction could result in aberrant growth and/or pruning of these interneurons and lead to psychotic symptoms [5]. Decreased synapse density in the downstream pyramidal neurons could occur through decreased perinatal growth or increased peripubertal pruning of these connections [44]. NMDARs mediate long-term potentiation dependent on neuronal activity level, deciding which neurons mature and which are pruned [45]. Even mild postnatally antagonism of NMDARs in rodents alters PVI number [46, 47]. Low neuronal activity due to inflammation or oxidative stress could cause long-term changes in PVIs in schizophrenia [5]. PVIs are the last subset of interneurons to develop, which may explain how general effects of oxidative stress and inflammation may lead to the specific alterations seen in schizophrenia [39, 48, 49].

3 Clinical Considerations and Perspectives

For one century, researchers have been searching for a comprehensive and coherent explanation for psychotic experiences and prognosis in schizophrenia. Exposure to prenatal infection and traumatizing experiences during the brain-body development have been linked to them. Even though prenatal infection leading to neurogenesis disruption has been replicated by many later studies, inconsistent findings have been reported as well. Nevertheless, the clinical phenomenon cannot be ignored and physicians must be alert to the association between infections, immune alteration, and psychosis. Until now there is no single microorganism that could be directly implicated in schizophrenia pathogenesis. A multitude of germs could be related to the syndrome acting in the inflammatory pathway during brain development. Hence, the precise etiological role of virus, parasitic, or bacterial infection in schizophrenia remains elusive. One major hypothesis suggests that a common pathogenic mechanism involving increased production of cytokines and other inflammatory mediators causes the link between prenatal infection and subsequent risk of schizophrenia. Although some researchers debate (this is controversial), in our understanding, this risk should be always addressed [50–52].

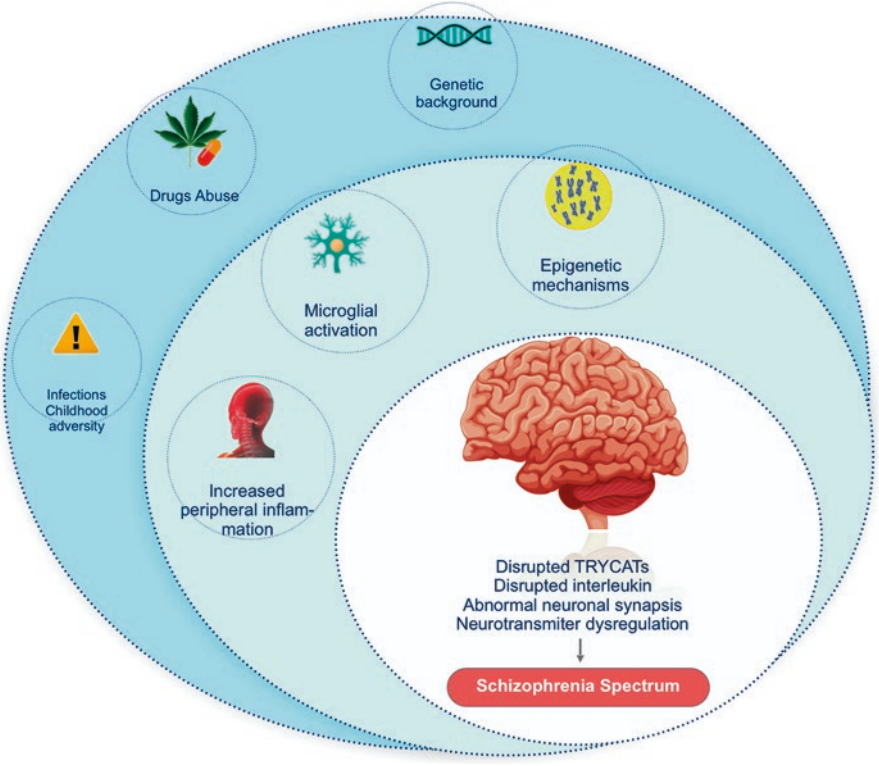
Exposure to trauma events during childhood development is another environmental insult that has received enormous recognition in the etiology of neurodevelopmental disorders and could act as a second hit increasing the risk for schizophrenia. Factors such as abuse, parental somatic illness, family crime, divorce, drug abuse, and socioeconomic status have all been associated with adverse mental health outcomes and schizophrenia. Much emphasis has been given to early exposure to infections, but

time around puberty has recently emerged as a highly sensitive period to the disruptive effects of environmental insults such as traumatizing experiences [49, 53, 54].

Neither in utero infection alone nor exposure to traumatizing experiences alone can cause psychosis. Vis a vis, most studies investigating these factors have estimated only the relative effects of single exposures or in combination with genetic factors and did not evaluate the naturalistic effect of several influences happening in a pleiotropic manner, contributing in small parcels to the risk of schizophrenia.

Accordingly, a better comprehension of the role these risk factors play in the etiology of schizophrenia needs efforts moving beyond analyses of single exposure only [51, 55, 56].

Recent animal studies have shown synergistic effects between prenatal immune activation and childhood or pubertal stress, leading to anatomic and pathological changes similar of those frequently seen in schizophrenia spectrum. Consequently, trauma must be analyzed and linked to other prenatal risks in the etiology of schizophrenia and related psychotic disorders. The major consequence of those new insights is that children in high risk of schizophrenia (due to genetic, prenatal, or childhood risks) should be regularly monitored before the onset of full psychotic symptoms. This is a great task and involves ethical and enormous economic planning, but would be the state of the art to a better treatment and quality of life in those patients [57–60].



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Maternal Immune Activation as a Risk Factor for Schizophrenia: Evidence From Preclinical and Clinical Studies

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Abstract Maternal immune activation (MIA) has been implicated as a risk factor for schizophrenia by several epidemiological studies. Animal models have confirmed this association between MIA and long-term neuropathology as well as behavioral abnormalities in the progeny. This chapter describes outcomes from the preclinical MIA models as well as results from recent clinical studies corroborating the effects of MIA on the neurodevelopment of the offspring. We have described various neurochemical, structural, and behavioral changes occurring in the developing brain of the MIA model offspring. Clinical studies delineating the effects of various maternal infections on fetal brain development and association of genetics

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with the development of schizophrenia have been summarized. We have also reviewed various neurobiological alterations induced by MIA in the fetal brain that play a role in the manifestation of schizophrenia. More research in this field and effective management of maternal infections are needed to reduce the future risk of schizophrenia in the offspring.

Keywords Maternal immune activation · Pre-clinical MIA models · Clinical studies · Neurodevelopment · Neuroinflammation · Schizophrenia

Abbreviations

5-HT1B	5-hydroxytryptamine receptor 1B
5-HT2A	5-hydroxytryptamine receptor 2A
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
C4	Complement component 4
CMV	Cytomegalovirus
CNS	Central nervous system
CNVs	Copy number variants
COMT	Catechol-*O*-methyltransferase
CSF	Cerebrospinal fluid
D1R	Dopamine receptor D1
D2R	Dopamine receptor D2
DAO	D-Amino acid oxidase
DAOA	D-Amino acid oxidase activator
DAT	Dopamine transporter
dsRNA	Double-stranded RNA
DTNBP1	Dysbindin/dystrobrevin-binding protein-1
EBV	Epstein-Barr virus
GABA	γ-Aminobutyric acid
GABAA	γ-Aminobutyric acid type A
G-CSF	Granulocyte colony-stimulating factor
GD	Gestational day
GFAP	Glial fibrillary acidic protein
GLT-1	Glutamate transporter
GluR1	Subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor
GluRδ2	Glutamate receptor delta 2
GM-CSF	Granulocyte/monocyte colony-stimulating factor
Grin1	Glutamate receptor ionotropic NMDA type subunit 1
Grin2a	Glutamate receptor ionotropic NMDA type subunit 2A
GRM3	Glutamate receptor metabotropic 3

HERV	Human endogenous retrovirus
HIV	Human immunodeficiency virus
HPA	Hypothalamic–pituitary–adrenal
HSP60	Heat shock protein 60
HSV-1	Herpes simplex virus type 1
IFN	Interferon
IKK	Ikappab kinase
IL	Interleukin
LCMV	Lymphocytic choriomeningitis virus
LPS	Lipopolysaccharide
MIA	Maternal immune activation
MIP-1γ	Macrophage inflammatory protein–1. Gamma
mRNA	Messenger ribonucleic acid
NF-κB	Nuclear factor kappa B
NMDA	*N*-methyl-d-aspartate
NR1 subunit	NMDA receptor NR1 subunit
NRG1	Neuregulin 1
P	Period day
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
PET	Positron emission tomographic
PFC	Prefrontal cortex
Poly (I:C)	Polyinosinic–polycytidylic acid
PPI	Prepulse inhibition
PRODH	Proline dehydrogenase
PSD	Postsynaptic density
PSD-95	Postsynaptic density protein 95
RGS4	Regulator of G-protein signaling 4
SNPs	Single-nucleotide polymorphisms
SynGAP	Brain-specific RAS GTPase-activating
TAAR6	Trace amine-associated receptor 6
TLR3	Toll-like receptor-4 (TLR)-4
TLR4	Toll-like receptor-3 (TLR)-3
TNF-α	Tumor necrosis factor alpha
TRAX/DISC1	Translin-associated factor X/disrupted in schizophrenia 1

1 Introduction

Schizophrenia is a chronic mental illness with low prevalence but a substantial burden [37]. It is a disorder considered to have neurodevelopmental origins, although the typical positive and negative symptoms usually appear in late adolescence or early adulthood [97]. In general, men have an earlier age of onset, around 15–25 years than in women, in whom it is 20–30 years [53]. Figure 1 shows the difference in

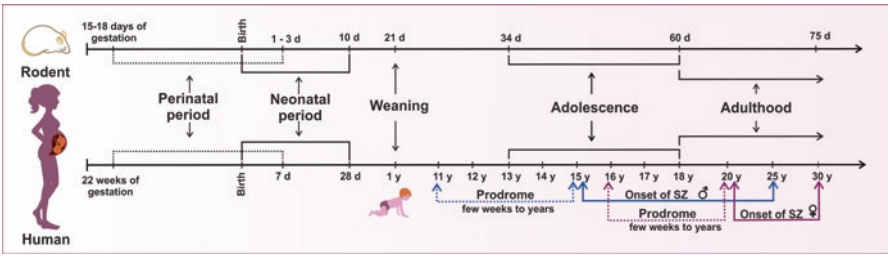

Fig. 1 Timeline of schizophrenia development
SZ Schizophrenia

onset between men and women. The prodromal period that precedes the onset of schizophrenia can be a few weeks to several years long. During prodrome, the patient exhibits subclinical behavioral and psychological changes [59]. Clinical symptoms include delusions, hallucinations, social withdrawal, alogia, and flat affect, and cognitive deficits [106].

The pathophysiology of schizophrenia is complex and not completely understood. It is believed to involve genetic/epigenetic and environmental factors that interact intricately, especially during the perinatal period [15]. Perinatal factors such as exposure to environmental insults, including maternal exposure to stress, infections, and immune activation, maternal malnutrition, and obstetric complications [12] increase the risk for schizophrenia.

Epidemiological evidence has shown an elevated risk of schizophrenia in the offspring of mothers exposed to viral infections (influenza, measles, herpes simplex virus type 2, rubella, and poliomyelitis), bacterial infections (pneumonia, respiratory infections), and parasitic infections (toxoplasmosis) [1]. Furthermore, after the 1964 rubella pandemic, the prevalence of schizophrenia rose from the expected approximately 1–20% in this pandemic-affected population [29]. Fetal immune system and, ultimately, the fetal brain's immune status might be permanently changed by maternal infections because some of the fetal hematopoietic stem cells originate from the placenta. These pieces of evidence suggest that immune activation, in general, rather than a specific pathogen, disrupt the healthy brain development [34, 86].

Thus, the prenatal period is crucial for brain development, and any vulnerability during this period may lead to long-term changes in fetal behavior. The occurrence of maternal infections and subsequent maternal immune activation (MIA) causes several structural and functional changes in the brain of the offspring that may predispose individuals to psychiatric disorders such as schizophrenia in postnatal life [40]. Research in animal models has confirmed this association and demonstrated that MIA is sufficient to induce alterations in offspring neurodevelopment [39]. The maternal viral infection is associated with a three- to sevenfold increased risk of schizophrenia in the offspring [28], and both first- and second-trimester exposures have been implicated in increased risk for schizophrenia [86]. Specifically, differences between exposure in early/middle gestational day (GD) 9 and late GD 17 have been identified in a mouse model of MIA, which corresponds to the mid-first and early-second trimester in humans, respectively [70].

According to the neurodevelopmental hypothesis of schizophrenia, genes involved in brain development would be vulnerable to environmental risk factors, especially during the second trimester of pregnancy, a period of vulnerability to disruption of brain developmental pathways, limbic disorganization, and neurochemical imbalances [30]. Hence, a greater understanding of the pathobiological alterations underlying MIA, as a first hit for the development of psychiatric disorders, is vital to the development of future preventive strategies. Therefore, epidemiological studies and animal models of MIA such as polyinosinic:polycytidylic acid—Poly(I:C)—and lipopolysaccharide (LPS) are promising in the integration of knowledge.

2 Maternal Immune Activation As a Risk Factor for Schizophrenia

2.1 Poly(I:C) and LPS Preclinical Models of Maternal Immune Activation

Rodent models of MIA are increasingly used as experimental tools to study neuronal and behavioral dysfunctions related to infection-mediated neurodevelopmental disorders [79]. The structural and functional brain abnormalities emerging in the offspring of mothers exposed to viral or bacterial infections during pregnancy may be accounted for the effects that are specific to the immune responses to the particular pathogen [24]. These effects may include direct responses in the fetal brain, against the presence of virulent pathogens or detrimental long-term outcomes on brain mechanisms and behavior by the activation of the maternal immune system and increased interleukin (IL)-6 levels [114].

In order to induce MIA without biological risk, bacterial and viral-like particles, also called pathogen-associated molecular patterns (PAMPs), have been used in experimental settings. In this regard, the two most commonly used methods are based on maternal exposure to the bacterial endotoxin, lipopolysaccharide (LPS), and the double-stranded RNA (dsRNA) analog polyinosinic:polycytidylic acid, Poly(I:C) [4, 124]. LPS is a gram-negative bacterial cell wall component that mimics bacterial infections binding to toll-like receptor-4 (TLR-4) [28, 42], while Poly(I:C) is a synthetically generated dsRNA analog binding to TLR-3. The dsRNAs are exclusively produced in the context of viral infection and constitute potent activators of the mammalian immune system [63], eliciting a plethora of intracellular signaling pathways including activation of the IkappaB kinase (IKK) complex, extracellular signal-regulated kinase, and c-Jun N-terminal kinase, among others [85]. LPS exposure leads to a cytokine-associated innate immune response that is typically seen after infection with gram-negative bacteria [124], whereas the administration of Poly(I:C) mimics the acute phase response to viral infection [121]. Additional relevance for both approaches (TLR4- and TLR3-dependent) MIA animal models is conferred by independent observations linking individual molecular

elements of the signaling cascades elicited by TLR-4 and TLR-3 activation to the pathophysiology of schizophrenia [98].

A number of studies evaluated LPS and Poly(I:C)-induced MIA as an experimental model for neurodevelopmental disorders [23]. At different dosages and distinct times of Poly(I:C) or LPS injection, the protocols can lead to varying results by altering brain development at different stages.

The study from Meyer et al. demonstrated that when pregnant mice were challenged with the Poly(I:C), the histology of the fetal brain was not similar when the exposure was on GD 9 compared with GD 17. On GD 9, a distinct cytokine response was observed together with decreased corticogenesis/neurogenesis, whereas challenge on GD 17 caused increased apoptosis, which was associated with a different cytokine response and behavioral pathology, including higher amphetamine sensitivity [68, 72]. The selected GD 9 and 17 in mice correspond to the first-to-second and second-to-third trimesters of a human pregnancy, respectively [39]. Most notably, mice injected intraperitoneally (i.p.) 20 mg/kg Poly(I:C) into GD 9.5 was sufficient to induce a deficit in the prepulse inhibition of the startle reflex (PPI), whereas a lower dose 10 mg/kg failed to do so [23]. Many protocols of MIA in mice induced by Poly(I: C) also use i.p. administration of 20 mg/kg dose at GD 12.5 [46, 84].

In rats, many studies expose the pregnant rats to Poly(I:C) at GD 15 using a dose of 4 mg/kg intravenous (i.v.) [45, 66, 132, 136] and to LPS at GD15–16 using a typical dose of 100 μg/kg i.p. [11, 131]. This mid-late gestational exposure results in a range of behavioral changes that overlap with both mid and late gestational MIA in mice, and support the model's face validity for positive, negative, and cognitive symptoms of schizophrenia [132, 133].

Dose – response analysis of cytokine mRNA levels in maternal blood and fetal central nervous system (CNS) from Poly(I:C) injection at two different stages of pregnant rats in early/mid-pregnancy (GD 9) or in mid-/late pregnancy (GD 15) showed that the most significant overall pro-inflammatory response was obtained at GD 15 with 4 mg/kg intravenous [75]. Mid-gestation MIA induction by LPS injection (100 mg/kg) at GD 10–11 may lead to motor impairments in the offspring while late-gestation MIA by the same modality at GD 18–19 can cause altered reward-seeking behavior in the pups [119].

3 MIA-Induced Brain Alterations in the Offspring

3.1 Cytokines

Many cytokines have been reported to be involved in MIA models for schizophrenia. Indeed, interleukin (IL)-6 was found to be elevated in the maternal blood, as well as in the amniotic fluid, placenta, and brain of the fetus after MIA exposure [114]. Notably, a single injection of IL-6 leads to similar effects in the offspring, as observed in Poly(I:C) or LPS models [114].

The initial immune dysregulation occurs as early as 3 h after Poly(I:C) injection and is characterized by elevated levels of IL-6 in the fetal brain [135]. Although IL-6 seems to play a crucial role in MIA, changes in many other inflammatory mediators such as IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-17, Eotaxin-2, tumor necrosis factor-α (TNF-α), macrophage inflammatory protein-1 gamma (MIP-1γ); GM-CSF (granulocyte colony-stimulating factor), G-CSF (granulocyte/monocyte colony-stimulating factor) have been identified in various areas of the brain of the offspring after challenging with Poly(I:C) [33, 35, 71, 89]. Figure 2 depicts the primary altered inflammatory mediators.

The LPS model of MIA also exhibits evidence of immune activation in the brain of the fetus. Various genes related to *interferon* (IFN) signaling were overexpressed 1 day after injection of the third dose of LPS [47]. Offspring from the LPS model also demonstrated many cytokine alterations in the whole brain, including increased mRNA levels of IL-1β and TNF [21], increased mRNA levels of IL-1β, IL-6, TNF-α, and IL-10 at embryonic day (ED) 12 that continued up to early adulthood in the amygdala [83]. Furthermore, maternal LPS exposure induced persistent fetal inflammatory reactions associated with significant white matter injury in offspring at postnatal days 1 and 7 [104].

3.2 Microglia

Many studies reported changes in the density or the activation state of microglia and astrocyte in MIA offspring from the Poly(I: C) model [36, 41, 50, 62, 64, 126, 137]. An almost equal number of studies found that MIA offspring from the LPS demonstrated increased microglia density and other microglia markers in various brain regions [21, 103]. Alterations in microglia after MIA are detailed in Fig. 2.

3.3 Neurotransmission

Altered neuronal function in MIA offspring involves dysregulation of the components of neurotransmitter systems (neurotransmitters, receptors, and transporters). The most affected systems include dopaminergic, glutamatergic, GABAergic, serotonergic, and cholinergic systems [13].

Offspring from Poly(I:C) exhibited brain changes in the dopaminergic system such as increased dopamine levels [35, 129], increased D1R (dopamine receptor D1) and D2R (dopamine receptor 2) immunoreactivity, as well as reduced DAT (dopamine transporter) levels in the nucleus accumbens [66, 73, 128]. They also showed changes in various glutamatergic receptor subunits, for example, NR1 subunit (subunit of the *N*-methyl-D-aspartate [NMDA] receptor) and the GluR1 (subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptor), as well as changes in mRNA levels of Grin1 and Grin2a (which encode

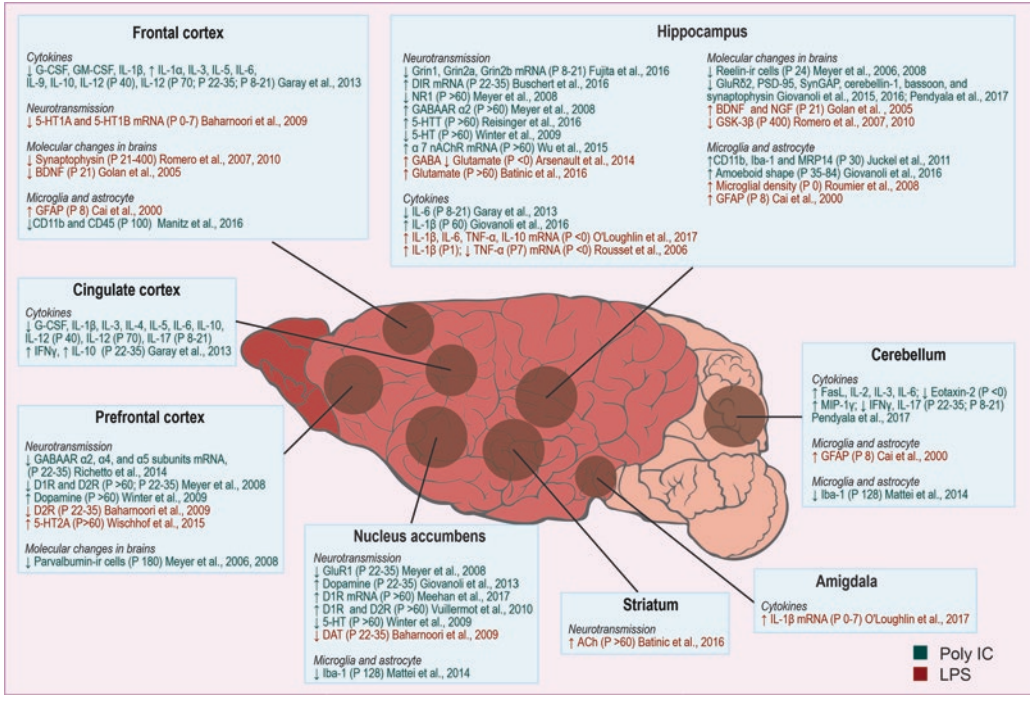

Fig. 2 Alterations in the brain during the development of MIA offspring
5HT 5-hydroxytryptamine, *D1R/D2R* dopamine receptor 1/2, *DAT* dopamine transporter, *G-CSF* Granulocyte colony-stimulating factor, *GM-CSF* Granulocyte/monocyte colony-stimulating factor, *GluRδ2* Glutamate receptor delta 2, *Grin1* Glutamate receptor ionotropic NMDA type subunit 1, *Grin1* Glutamate Ionotropic receptor NMDA type subunit 1, *Grin2a* Glutamate receptor ionotropic NMDA type subunit 2, *Grin2b* 5HT1B: 5-hydroxytryptamine receptor 2B, *PSD-95* Postsynaptic density protein 95, *SynGAP* Brain-specific RAS GTPase-activating, *IFN* interferon, *GluR1* AMPA receptor GluR1 subunit, *FasL*: Fas ligand, *GFAP* Glial fibrillary acidic protein, *Iba-1* Ionized calcium-binding adaptor protein-1, *MIP-1 γ* Macrophage inflammatory protein-1 gamma, *ACh* acetylcholine, *MRP14* Myeloid-related protein

glutamate receptor ionotropic NMDA type subunits 1 and 2A, respectively) [32, 95, 120]. Also, changes in γ-aminobutyric acid (GABA) system were reported such as in the mRNA levels of γ-aminobutyric acid type A (GABAA) receptor α1, α2, α4, and α5 subunits [32, 100, 101]. Changes in the serotonergic system included decreased levels of serotonin [129] and increased levels of the serotonin transporter [98] and, finally, changes in nicotinic acetylcholine alpha 7 receptor mRNA levels [134]. All these changes have been reported in different areas of the brain and at different postnatal periods. For more details, see Fig. 2.

Offspring from the LPS model exhibited similar changes such as increased dopamine levels in striatum [56], decreased D2R expression in PFC [8, 9], decreased DAT [9], increased glutamate in hippocampus [10], reduced glutamate and increased GABA in the whole brain [10], increased 5-HT_{2A} (5-hydroxytryptamine receptor 2A) in PFC [130], decreased levels of 5HT1A (5-hydroxytryptamine receptor 1A) and 5HT1B (5-hydroxytryptamine receptor 1B) mRNA in frontal cortex [9], and increased acetylcholine in striatum [10].

3.4 Synaptic Development, Neuroplasticity, and Brain Abnormalities

After prenatal Poly(I:C) exposure, there are decreased hippocampal neurogenesis [71] and reduced levels of BDNF (brain-derived neurotrophic factor) in the offspring [35] as well as reduction in the expression of presynaptic proteins (cerebellin-1, bassoon, and synaptophysin) and postsynaptic proteins (GluRδ2, postsynaptic density protein 95 [PSD-95], and SynGAP) in the cerebellum and hippocampus [35, 89]. Besides, MIA causes a specific reduction in the inhibitory parvalbumin cells [71, 73].

In MIA LPS offspring, other long-term molecular changes such as changes in growth factors [38], synaptophysin [102], neuroleukin [7], and reelin and parvalbumin [71, 73] following prenatal immune activation have been reported.

3.5 The Long-Term Behavioral Consequences of MIA

MIA induction in animals, primarily rodents, with LPS, Poly(I:C), or other agents capable of inducing a strong maternal immune response has been demonstrated to elicit behaviors in the offspring that are reminiscent of schizophrenia [67, 68]. These include difficulties in communication and socializing, elevated anxiety, reduced sensorimotor gating (the process of the brain to filter out irrelevant or unrelated stimuli), defects in cognitive performance and working memory, and elevated response to amphetamines [67, 115]. Schizophrenia patients have cognitive deficits that are quite similar to these changes observed in rodents. Also, in favor of the

relevance of these models, many of these behaviors can be mitigated by antipsychotic medications [68].

4 Maternal Immune Activation As a Risk Factor for the Development of Schizophrenia

The impact of perinatal exposure to a vast array of infections and inflammation may affect fetal and neonatal brain development, generating both short- and long-term neuropsychiatric complications. In this regard, the teratogenic TORCH pathogens (i.e., *T. gondii, others (Treponema pallidum, Varicella zoster, parvovirus B19), rubella virus, cytomegalovirus* [CMV], *and herpes simplex virus*) are also risk factors for schizophrenia. Not only TORCH pathogens but also perinatal viral, bacterial, and parasitic infections may lead to behavioral changes via direct toxic injury to neurons or through indirect damage by immune cell activation, cytokine production, and oxidative stress [2].

4.1 Perinatal Viral Infections and Schizophrenia

The hypothesis that periconceptional viral infection increases the likelihood of adult schizophrenia dates back to the 1957 type A2 influenza epidemic in Helsinki, which left the aftermath with an increased number of schizophrenia cases [65]. The possible candidate perinatal viruses causing schizophrenia in the offspring are *influenza virus,* CMV*, Epstein-Barr virus* (EBV), *herpes simplex virus type 1* (HSV-1) *and type 2* (HSV-2), *coxsackie-B virus, mumps, measles and rubella virus, parvovirus, hepatitis virus, human immunodeficiency virus* (HIV), *lymphocytic choriomeningitis virus* (LCMV), *bornavirus*, and *human endogenous retrovirus* (HERV) [48, 52, 81, 87, 96, 127]. Notably, HERVs in several neurological diseases are activated by pro-inflammatory changes, which need to be better evaluated in animal models of MIA [108].

These viral infections disrupt hippocampal circuits and cause selective neuronal loss, leading to an increased risk for schizophrenia [87]. Perinatal viral infections are more often seen in winter months, increase pregnancy and birth complications, which might be a cause for the high stats of winter-born patients with schizophrenia [60]. However, in another study that measured serum antibody titers to eight neurotropic viruses, a seasonal variation with a peak incidence between March and April was noted in schizophrenic births [55]. As per a systematic review conducted by Khandaker and his team, a causal association between HSV-1, CMV and schizophrenia was not established, the link between HSV-2 and schizophrenia was mixed, and influenza infection showed more association during the first trimester than second and third trimesters [54].

The description of the connection between maternal influenza and an increased risk for schizophrenia in their descendants dates back to more than 30 years [2]. Perinatal exposure to serologically proven influenza exposure leads to decreased gestational growth and low birth weight that is associated with later schizophrenia [31]. Preterm birth and low gestational weight from perinatal infections, and the first 2 weeks period after measles, mumps, and rubella vaccines are a risk factor for febrile seizures, which have a slight potential towards schizophrenia development, even in those without epilepsy [127]. Prompt administration of the seasonal influenza vaccine may help to reduce perinatal influenza infection and the risk for fetal brain injury [2]. A decrease in mumps antibody titers was found in people with schizophrenia, which may indicate an impaired immune response. Thus, perinatal mumps viral infection of the CNS might lead to schizophrenia later in life [55].

Maternal exposure to HSV-2 infection and the presence of antibodies to HSV-2 glycoprotein gG2 renders the offspring liable to increased risk for psychosis. This risk is even higher in women with more sexual activity during pregnancy. However, schizophrenia was not shown to be related to the presence of maternal antibodies against HSV-1, CMV, rubella, human parvovirus B19, or human papillomavirus type 16 [18 , 19]. CNS infections, especially viral as Coxsackie B5 during the neonatal period, had increased risk for schizophrenia and psychosis [96].

In a preclinical study in rats infected with LCMV, the infection resulted in inhibitory circuit breakdown, causing neuronal hyperexcitability and the excitotoxicity leading to hippocampal dentate granular cell death [87].

4.2 Perinatal Bacterial Infections and Schizophrenia

Data analysis of maternal infections from the Copenhagen Perinatal Cohort and the Danish National Psychiatric Register established a link between perinatal bacterial infection and the risk for schizophrenia in the descendants, which was mainly significant for first-trimester maternal infections followed by second ones. Bacteria causing upper respiratory tract and genital infections such as gonococcus were predominantly implicated, followed by urinary tract infections and other bacterial infections [116].

Placental transfer of maternally produced IgG antibodies and cytokines, especially IL-8, released in response to the bacterial infection might be a leading cause of this connection [16, 81]. The bacterial strains most often involved in this connection are *Streptococcus pyogenes*, *Campylobacter jejuni*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*, and *Clostridium tetani* [81, 116]. *S. pyogenes* infections are future contributors to neuropsychiatric disorders such as schizophrenia, obsessive-compulsive disorder, autism, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), and movement disorders such as tic disorders [77].

Periconceptional *N. gonorrhoeae* infection may lead to late-life schizophrenia in offspring via an immune-mediated mechanism. Antigonococcal serum is directed towards Snap 23 protein that is involved in vesicle-directed exocytosis in SH-SY5Y cells, and in papilloma cells of human choroid plexus, anti-NG antibodies (α-NG) bind to mitochondrial proteins heat shock protein 60 (HSP60) and ATP synthase subunit beta (ATPB) and interfere with cellular energy metabolism. Notably, these in vitro alterations triggered by antigonococcal serum in SH-SY5Y cells mentioned earlier were already demonstrated in schizophrenia [6, 99]. Similarly to *N. gonorrhoeae* antiserum, *N. meningitidis* antiserum has the potential to interact with mitochondrial HSP60 protein and to reduce the neuritic length [99].

4.3 Perinatal Parasitic Infections and Schizophrenia

T. gondii is the most common in utero parasitic infection that affects fetal brain development and increases the susceptibility to develop schizophrenia at a later time in life.

T. gondii is a single-celled obligate intracellular eukaryotic parasite that resides, in a latent form, in the human CNS. It elicits neuronal changes by direct parasitic invasion or by indirect changes that occur because of the activation of the peripheral immune system in response to CNS inflammation [125]. Schizophrenia has been related to increased maternal toxoplasma IgG levels rather than the parasite itself [17, 78]. Microglial cells eliminate the parasites via phagocytosis associated anti-toxoplasma activity, while nitric oxide production and IFN-γ signaling inhibit intracellular parasite replication; however, astrocytes contain the *T. gondii* cysts [49, 90, 109, 125].

In the acute and chronic stages of *T. gondii* infection, there is an increase in the levels of homovanilinic acid, a dopamine metabolite, and dopamine levels, respectively [117]. There is also an increase in extracellular glutamate and a gradual reduction in the astrocyte glutamate transporter (GLT-1) in the forebrain [26]. *N*-methyl-D-aspartate (NMDA) receptors play a vital role in schizophrenia pathophysiology. Serum toxoplasma IgG antibodies target NMDA receptors that underlie the reduced function of glutamate receptors and related impairment found in schizophrenia. NMDA IgG titers are more in *T. gondii*-seropositive patients with schizophrenia, rather than seronegative schizophrenia and seropositive ones without schizophrenia [51]. Toxoplasma also alters GABA-related synapses and neurotransmission [122]. Thus, *T. gondii* can cause macroscopic changes such as brain lesions, and cysts, alteration in fiber and grey matter density, cellular changes such as microglial and immune cell activation, reduced dendritic spines, axonal damage, and kynurenic acid and quinolinic acid discrepancies in the neurons. *T. gondii* can also cause microstructural alterations such as microtubule and postsynaptic density (PSD) alterations and functional changes like neurotransmitter fluctuations and postsynaptic signaling leading to gene expression alterations [125].

The effect of toxoplasma in causing schizophrenia is more potent than any schizophrenia-associated gene variant associated with genome-wide analyses [94].

4.4 Genetics As a Risk Factor for Schizophrenia

Genetic inheritance of schizophrenia in families was supported by many twin and adoption studies. Schizophrenia is a complex multigene trait, where alleles are weak when expressed individually, but they interact synergistically on combined expression leading to typical clinical symptoms with varying behavioral phenotypes.

Genetic errors in schizophrenia such as single-nucleotide polymorphisms (SNPs) and copy number variants (CNVs) within a group, or mutations such as insertions/deletions can change the functionality of metabolic or cellular processes leading to alterations in cognitive functions such as memory, attention, language, execution, and visuospatial abilities via effects on neurotransmitters, cerebral structural, metabolic, or connectivity abnormalities [88]. So far modifications in chromosomal areas such as 1q, 8p, 6p, 22q and 13q, including sequences that code for neuregulin 1 (*NRG1*), dysbindin/dystrobrevin binding protein-1 (*DTNBP1*), catechol-*O*-methyltransferase (*COMT*), D-amino acid oxidase activator (*DAOA*), D-amino acid oxidase (*DAO*), translin-associated factor X/disrupted in schizophrenia 1 (*TRAX/DISC1*), V-AKT murine thymoma viral oncogene homolog 1 (*AKT1*), glutamate receptor metabotropic 3 (*GRM3*), and regulator of G-protein signaling 4 (*RGS4*), proline dehydrogenase (PRODH), trace amine-associated receptor 6 (TAAR6), and zinc finger for putative palmitoyltransferase enzyme containing an aspartate-histidine-histidine-cysteine (DHHC) domain (ZDHHC8 gene) [58, 88].

4.5 Neurobiological Mechanisms of Behavioral Abnormalities in Schizophrenia

Apart from the most common dopamine and glutamate hypothesis, multiple other mechanisms are proposed to be involved in the pathogenesis of schizophrenia, such as inflammation and immune system activation. Maternal immune activation due to prenatal infections, obstetric complications, or maternal stress, in general, is reported to interfere with fetal neurodevelopment and contribute to the risk of adult schizophrenia by various mechanisms [54].

4.5.1 Neuroinflammation

Neuroinflammation is the chronic continuous activation of the neuroimmune system along with the infiltration of the brain tissue by peripheral immune cells. Microglia are the resident cells of the innate immunity of CNS, which get activated because of various insults such as infections, autoimmunity, toxins, brain trauma, psychosocial stress, and exposure to proinflammatory mediators like IFN-γ or TNF-α. Activated microglia release reactive oxygen species [93] and proinflammatory

chemokines and cytokines such as IL-1α, IL-1β, IL-6, IFN-γ, and TNF-α [22]. These proinflammatory mediators not only cause damage to the neurons but also lead to the disruption of the blood-brain barrier (BBB) (Fig. 3).

Cytokines such as IL-1β activate the astrocytes, which are a major component of the BBB. These activated astrocytes further release proinflammatory mediators such as IL-1β, TNF-α, and chemokine (C–C motif) ligand (CCL) 5 and show increased expression of the *glial fibrillary acidic protein* (GFAP), which is a marker for astrocyte activation [123].

Perinatal microglial activation makes these cells very sensitive to the stressors in adult life and might lead to their overactivation, a phenomenon called "priming of microglia." This microglial overactivation on exposure to a stimulus leads to excessive synaptic pruning and damage of the hippocampus, prefrontal cortex, and loss of cortical gray matter, which in turn leads to various clinical features of psychosis [44].

The positron emission tomographic (PET) scan can be used in an adult schizophrenic patient to evaluate the translocator protein (TSPO), which is a marker of microglial activation. However, there are mixed results with some studies using radioligand [^{11}C] PBR28 reporting higher levels of microglial activation in schizophrenic patients as compared with controls [14], whereas other studies using radiotracer [^{11}C] DPA-713 were not able to confirm these results [82]. It is also important to note that many other cells, such as microvascular endothelial cells and astrocytes, also express TSPO, making it a less specific marker for microglial activation [82].

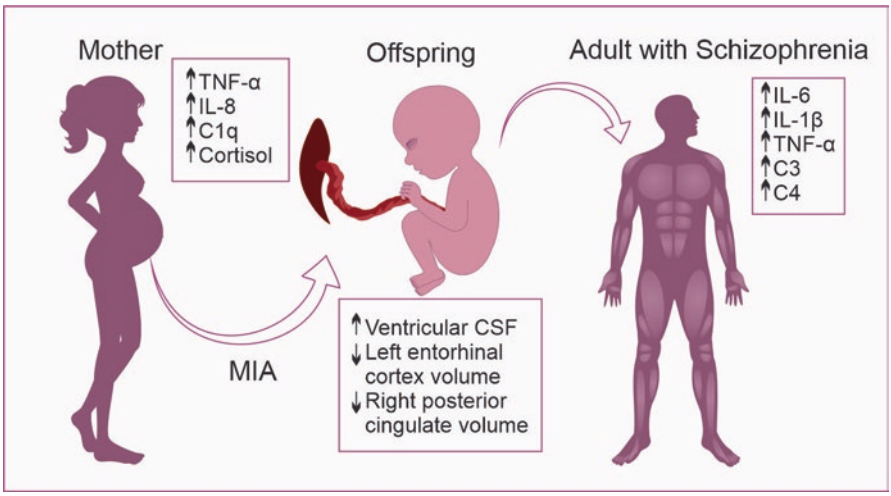

Fig. 3 Neurobiological mechanisms of schizophrenia
TNF-α Tumor necrosis factor-alpha, *IL* Interleukin, *C1q* Complement component 1q, *CSF* Cerebrospinal fluid, *C3* Complement component 3, *C4* Complement component 4

4.5.2 Effects of Inflammatory Cytokines

Innate immune system activation and the release of pro-inflammatory cytokines can lead to various abnormalities in the mesocorticolimbic dopamine system of the fetus, and these changes are associated with the psychosis-related alterations in the adult brain [69].

Various studies have found significantly elevated cytokine levels during pregnancy in the mothers of patients with schizophrenia when compared with matched controls, which shows a significant association between inflammatory cytokines and the risk of psychotic illness in the offspring. One study involving mothers of schizophrenia patients and healthy controls reported significantly increased TNF-α levels in case mothers and also described higher odds of developing schizophrenia in the offspring associated with higher maternal cytokine levels [20]. Another study showed a significantly elevated value of IL-8 during the second trimester in mothers of patients with schizophrenia spectrum disorder as compared with control mothers [16]. In a study involving patients with schizophrenia and matched controls, it was reported that increased IL-8 level in prenatal sera was associated with significant structural brain changes such as increased ventricular cerebrospinal fluid (CSF), diminished left entorhinal cortex volumes, and right posterior cingulate volumes in the cases. These regions are postulated to be involved in schizophrenia pathophysiology [27].

Several studies have also evaluated cytokine levels in the blood of schizophrenia patients to support the association of inflammation and schizophrenia. IL-6 was found to be significantly elevated in the blood of schizophrenia patients in two independent meta-analyses. One of these meta-analyses also showed elevated IL-1β and TNF-α levels in schizophrenia patients, whereas the other showed otherwise. These are the cytokines released due to neuronal damage due to astrocyte proliferation and can, in turn, cause neuronal cytotoxicity [74, 92].

4.5.3 Blood-Brain Barrier

Neuroinflammation leads to the disruption of BBB due to the release of various chemokines and cytokines. These inflammatory mediators also attract the peripheral immune cells such as macrophages, T cells, and B cells to the site of injury. These cells freely pass through the damaged BBB and cause further inflammation and destruction of neural tissue [57].

BBB damage during neurodevelopment may be involved in the onset of schizophrenia in adult life. Animal studies have shown that early postnatal systemic inflammation increases the permeability of the BBB to proteins for the short and long terms, leading to brain damage. With the first hit being perinatal brain injury due to inflammation and second hit being long-term, increased permeability of BBB to proteins and toxic substances can significantly increase the risk of schizophrenia development in the subject [118].

Several studies have reported impaired BBB in adult schizophrenia patients. CSF: serum albumin ratio (QAlb) is the gold standard cerebrospinal fluid (CSF) test for evaluating the permeability of BBB, and it was reported to be elevated in schizophrenia patients as compared with the control group. Typically, albumin is found at a level 200 times below in CSF as compared to blood. When QAlb is elevated, it suggests that BBB is not only permeable to albumin but also many other circulating macromolecules [91]. A blood-based marker for assessing BBB permeability is S100B, which is a protein released by astrocytes, oligodendrocytes, and expressed by neuronal and ependymal cells. It is found at substantial concentrations in the brain but in negligible concentrations in blood under normal circumstances. Two meta-analyses reported elevated levels of S100B in the serum of schizophrenic patients as compared with controls confirming the impairment of BBB in the schizophrenia group [3, 110]. Also, the meta-regression analysis reported a positive association between serum S100B levels and duration of illness and clinical symptoms, particularly the score of the positive and negative syndrome scale (PANSS), in turn suggesting that BBB impairment progresses with the disease progression [110].

4.5.4 Complement System (C3 and C4)

The complement system is an essential member of the innate immune system and is composed of a group of plasma proteins. Dysregulation of the complement system or induction of autoimmunity by these proteins can lead to various CNS disorders [76].

Complement component 4 (C4) genes are implicated in the development of schizophrenia with reported higher expression of C4A mRNA in the postmortem brain of schizophrenia patients. C4 is expressed at neuronal synapses and is a critical component involved in the pruning of synapses during postnatal neurodevelopment. Hence, an exaggerated C4 response can explain the excessive elimination of synapses in the brain of schizophrenic patients [111].

One study measured the C1q levels in maternal sera of schizophrenia patients and compared them with control mothers. C1q is another complement protein that is involved in synaptic elimination during prenatal neurodevelopment, and it was found to be significantly higher in the case mothers [112]. Many studies have also directly measured the complement proteins in the blood of schizophrenia patients and reported elevated levels of C3 and C4 [5, 61, 107]. Hence, exposure to various complement components prenatally and in the early postnatal period can increase the risk of development of schizophrenia later in life. Also, elevated levels of these proteins can be involved in the pathophysiology of schizophrenia in adult patients.

4.6 Clinical Consequences in Schizophrenia

Maternal immune activation and maternal stress can lead to an increase in the level of maternal glucocorticoids, which can pass through the placenta to the fetus. This can, in turn, program the hypothalamic-pituitary-adrenal (HPA) axis of the child to be overactive. The exposure to excessive glucocorticoids in utero and hyperactivity of the HPA axis as an adult both can predispose the offspring to hypertension, diabetes, and hyperlipidemia and, in turn, increase the cardiovascular risk. This might explain the higher risk of physical comorbidities in schizophrenia patients exposed to maternal stress and infections [54].

Chronic mental illnesses such as schizophrenia are often associated with multiple physical and psychiatric comorbidities and leave a significant impact on the quality of the social and family life of the patient [113]. Multiple studies have reported increased mortality in schizophrenia patients compared with the general population [43]. Various causes are reported for this increased mortality, such as ischemic heart disease, smoking-related lung disease, diabetes mellitus, and unnatural death by suicide or violence [25, 43]. The risk of suicidal death is reported to be 12 times higher in this patient group as compared with the general population [105]. Schizophrenic patients are also described to have increased rates of abuse of alcohol and other drugs, including tobacco. The prevalence of smoking in this patient population is around 70%, whereas it is 20% in the general population, which further deteriorates their cardiovascular health [80].

Overall, an integrated approach in the care of schizophrenia patients should be used to address the multiple psychiatric and medical comorbidities better and to reduce the increased mortality in this patient population due to natural and unnatural causes.

5 Conclusions and Future Directions

As discussed in this chapter, various animal and human studies have demonstrated that MIA strongly influences the neurodevelopment of the offspring, inducing behavioral and cognitive changes, including schizophrenia later in life. The association of multiple cytokines and chemokines with psychosis-related changes in the brain has been shown in various maternal studies as well as in the postmortem studies of adult schizophrenia patients. Future research can be directed at reducing the levels of different inflammatory markers in the maternal blood and evaluate if it reduces the risk for schizophrenia in the child. It is also imperative to definitely prevent major infections during pregnancy by interventions such as vaccines and effectively treat these infections if they occur to avoid the long-lasting neurodevelopmental damages it incurs on the offspring.

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Sex and Age Influence in The Effects of Perinatal Immune Activation in Animals

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Abstract Biological sex is an important risk factor for neurodevelopmental disorders (ND), such as autism spectrum disorder (ASD) and schizophrenia. Indeed, sex influences the incidence, onset, and clinical course of ND. For example, schizophrenia is diagnosed in men at younger ages when compared to women. However, postmenopausal women diagnosed with schizophrenia present more severe symptoms and worse prognosis when compared to men. Regarding ASD, the male-to-female ratio is close to 3:1. Notably in ASD, a diagnostic gender bias seems to occur. Preclinical models based on maternal immune activation (MIA) or neonatal immune activation (NIA) were developed for a better understanding of neurobiological alterations underlying the development of schizophrenia and ASD. Importantly, MIA models relate to immune challenges on the first and second trimesters of human pregnancy, whereas NIA models to immune challenge at the end of the third trimester in humans. Despite the importance of perinatal infections for the pathogenesis of ND and for a better understanding of sex influences in the neurobiology of these disorders, preclinical studies evaluating sex-related alterations in animal models of perinatal immune activation (PIA) are still limited. This chapter summarizes the current findings on sex influences in PIA models and brings some perspectives for novel studies in this field.

Keywords Schizophrenia · Age · Sex · Maternal immune activation · Neonatal immune activation · Neurodevelopment

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Abbreviations

ASD	Autism spectrum disorder
BDNF	Brain-derived neurotrophic factor
DA	Dopamine
ED	Embryonic day
LPS	Lipopolysaccharide
MIA	Maternal immune activation
mPFC	Medial prefrontal cortex
NIA	Neonatal immune activation
PAMP	Pathogen-associated molecular pattern molecules
PIA	Perinatal immune activation
PN	Postnatal day
Poly IC	Polyinosinic–polycytidylic acid

1 Sex and Age Influence in Schizophrenia and ASD: An Overview

Evidence from the last decades points to sex differences in brain anatomy, biochemistry, and various psychological and cognitive processes. For example, males present larger brain volumes and brains optimized for intra-hemispheric communication, while female brains are optimized for inter-hemispheric communication. Besides this, males and females present 2.5% of genes differentially expressed and spliced. These genetic differences may partially explain sex differences in susceptibility, progression, symptom severity, and pathology of neurodevelopmental disorders, mainly the so-called dopamine (DA)-associated disorders, such as autism spectrum disorder (ASD) and schizophrenia ([1], for review).

1.1 Sex and Age Influence in Schizophrenia

Kraepelin [2] was the first psychiatrist to report sex-related differences in schizophrenia, by noting at that time that the disorder was more common in men and that women present a delay to first hospitalization compared to men. Notwithstanding, few research groups have devoted their efforts to the investigation of the neurobiological changes underlying sex influences in this mental disorder. Sex and age influences in schizophrenia have been recognized in several aspects, such as incidence and development, symptoms, treatment responsiveness, and risk factors. In a neurobiological perspective, sex- and age-dependent vulnerability to neuropsychiatric disorders seems to be related to complex interactions between sex hormones and to

brain region-dependent alterations in brain transcriptome, glia cell activation profile, and neuroinflammatory changes ([3], for review).

The incidence of schizophrenia in men is about 1.4 times higher than in women [4]. Men suffering from schizophrenia have a worse illness course and outcomes, possibly associated with the earlier onset of this disorder. Moreover, men present worse psychosocial and neurocognitive functioning and greater vulnerability to stressful events than women [5, 6]. On the other hand, women show a less severe illness course and a better prognosis. Also, women present better outcomes and a greater quality of life (e.g., they are more likely to stay employed, get married, and keep in touch with friends and family) [5]. These sex differences in the onset and course of schizophrenia seem to be related to the neuroprotective effects of estrogen [7]. In line with the hypothesis of estrogen protective role in schizophrenia, contrary to schizophrenic women at young ages, postmenopausal women diagnosed with this disorder present more severe symptoms and worse prognosis when compared with men [5].

Schizophrenia has a typical onset in late adolescence, which is considered a critical period in brain development [8]. There is a statistically significant association between lower age of onset and more negative symptoms, worse social/occupational functioning, recurrences, hospitalizations, and poorer global outcome [9]. In general, men present a single incidence peak, usually starting schizophrenia between 21 and 25 years of age, while women have two peaks of incidence: one between 25 and 30 years old (3–5 years later than men) and another one after 45 years of age, corresponding to the menopause period [10, 11]. Thereby, if we consider the first half of life, the prevalence of schizophrenia is higher in men, while in the second half of life, the prevalence is higher in women [12]. However, this higher incidence in men seems to be only from the age of 17 onwards, while at younger ages there is no significant difference between the sexes [13].

Regarding schizophrenia symptoms, both sexes seem to have the same degree of positive symptoms; however negative and cognitive symptoms are more prevalent in men than in women. Clinical features such as social isolation, lack of motivation, emotional blunting, poverty of speech, cognitive deficits related to attention, reasoning, and memory deficit are more likely to be present in men [14]. On the other hand, women with schizophrenia have more affective symptoms, such as depression, anxiety, and irritability [5].

Sex also influences pharmacological treatment of schizophrenia. Men have a worse response to typical antipsychotics, requiring higher doses of these drugs due to greater liver enzymatic clearance. Apart from that, men present higher hospitalization rates, higher probability of relapses, and lower remission rates than women [15, 16]. Vis a vis, women show a better treatment response with around 50% fewer hospitalizations [17]. Despite this, women have more adverse effects on antipsychotic drugs such as hypotension, hyperprolactinemia, weight gain, and increased risk for autoimmune diseases, while men present more sexual dysfunctions and dystonia [15]. Importantly, female schizophrenic patients during postmenopausal period (usually after age 50) need higher doses of antipsychotics, probably due to decreased estrogen levels [18].

1.2 Sex and Age Influence in ASD

ASD is a neuropsychiatric disorder with strong male bias. In this regard, there are three males to every female diagnosed with ASD [19]. Furthermore, symptoms manifest prior to the age of three and are diagnosed more frequently in males than in females. Males and females also display distinct symptoms [20]. This makes ASD diagnosis more challenging and contributes to its under diagnosis among women and girls [21]. Hence, a diagnostic gender bias seems to occur, i.e., girls who meet criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis.

Regarding ASD symptoms, a large community-based study comprising 241 adolescents and adults with ASD revealed that older members (31 years and older) had fewer maladaptive behaviors and experienced improvement of repetitive behaviors over time [22]. In terms of cognition, specific problems on spatial working memory are often seen in high-functioning adolescents with ASD [23].

2 Animal Models of Perinatal Immune Activation

Epidemiological evidence suggests that infections during the prenatal or early postnatal developmental periods may increase the risk for neurodevelopmental disorders [24], including schizophrenia and ASD. Animal models of maternal immune action (MIA) and neonatal immune activation (NIA) have been developed to broaden our understanding about long-term brain changes induced by perinatal immune activation (PIA). Notably, these animal models induce behavioral alterations that resemble ASD and schizophrenia [25–27].

Animal models of PIA are based on prenatal or neonatal exposure to virus, such as human influenza [28] and Borna virus [29] as well as to pathogen-associated molecular pattern molecules (PAMPs) such as the bacterial endotoxin lipopolysaccharide (LPS) [30] and the viral mimetic particle Polyinosinic–polycytidylic acid (poly IC) [31]. In these models, prenatal challenges are conducted in distinct embryonic days (ED), for example, ED9 and ED17, respectively, representing human first and second trimester of pregnancy. There are important differences in terms of behavioral consequences of this exposure in different EDs. For example, adult offspring from dams challenged with poly IC on ED9 present more schizophrenia-like positive symptoms, whereas those challenged on ED17 present more negative and cognitive-like alterations ([32], for review). Such findings suggest that MIA during early/mid and late fetal development in animals leads to distinct behavioral and cognitive dysfunctions in adulthood that are implicated in schizophrenia and ASD [33, 34].

Regarding NIA, poly IC challenge on postnatal days (PNs) 5–7, a period related to human third trimester of pregnancy, seems to trigger schizophrenia-like positive, negative, and cognitive symptoms [35].

In relation to PIA with LPS, recent studies based on LPS prenatal challenge on ED9.5 [36] or neonatal challenge on PNs 5 and 7 [37] have associated this endotoxin perinatal exposure to the development of ASD-like alterations.

Based on the relevance of perinatal exposure to PAMPs, as a first hit, to the development of behavioral and neurobiological alterations related to schizophrenia and ASD, in this chapter, we will focus on results obtained from animal models of PIA with poly IC and LPS.

2.1 Sex and Age Influence in Animal Models of Immune Challenge with Poly IC

The first studies evaluating the influence of sex on neurodevelopmental changes induced by poly IC were conducted relatively recently. These studies have pointed out important sex-biased behavioral and neurobiological alterations.

The studies based on poly IC challenge during gestation showed that adult male offspring from dams challenged with poly IC on ED 9.5 presented pronounced differences in microglial distribution and morphology, cellular stress, and synaptic interactions in the hippocampus in relation to females. These microglial alterations were accompanied by behavioral impairment, such as sensorimotor gating deficits in males. Male animals also presented increased expression of genes related to inflammation in the cerebral cortex and hippocampus. Taken together, these findings suggest that males present increased microglial reactivity to MIA, which might influence the greater susceptibility of this sex to the development of schizophrenia [38]. In line with male susceptibility to the development of poly IC-induced behavioral and neurobiological alterations, poly IC challenge on ED12.5 caused impaired social interactions and motor deficits in adult male offspring. These behavioral alterations in males were accompanied by reduced number of Purkinje cells in the cerebellum and by reduced number of neurons in the motor cortex. Notably, these changes were not observed in females [39]. Poly IC prenatal challenge also caused sex-related memory alterations. Indeed, adult male offspring challenged with poly IC on ED15, but not females, required more trials to reach the criteria of 10 correct choices in the visual-cue discrimination test and perseverated during set-shifting. On the reversal day, male poly IC-exposed rats made fewer regressive errors. Females took more pre-training days and were slower to respond during the trials when compared to males regardless of prenatal treatment [40]. Contrary to the studies showing increased vulnerability to PIA-induced alterations only in male rodents, adult female rats exposed to poly IC on ED15 presented behavioral abnormalities related to schizophrenia and ASD, including impaired sociability, visual and cross modal memory, and oddity preference [41].

A study comparing the effects of MIA with poly IC or LPS in mid-gestation revealed that adult male offspring from poly IC-treated dams presented reduced motor activity. In the evaluation of ritualistic or repetitive behaviors by the marble

burying test, only male offspring from both LPS and poly IC-challenged mothers showed increased marble burying. These findings indicate that male offspring from mothers exposed to MIA are more vulnerable to the development of stereotyped repetitive behavior than female offspring [42].

Sex differences were also observed in the progression of clinical symptoms in animals submitted to the model of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, and exposed to MIA with poly IC [43]. Poly IC exposure on mid-gestation in EAE model increased anxiety and depression in male, but not in female offspring. This immune challenge also resulted in an earlier onset of the EAE clinical signs in male offspring and enhanced the severity of the disease in both male and female offspring.

A recent study showed the influence of sex in the development of schizophrenia or depressive-like changes in animals neonatally challenged with poly IC. In this study, an innovative protocol was conducted based on the challenge of lactating dams with 4 mg/kg poly IC on PN4 and the transmission of immune activation to the offspring through lactation. This model led to distinct sex-related behavioral abnormalities in adult offspring. While male offspring exhibited attentional, executive, and hypodopaminergic abnormalities, females exhibited hyperdopaminergia, behavioral despair, and anhedonia, mimicking the well-known sexual bias in schizophrenia and depression [44].

Our research group using rats neonatally challenged (PNs 5–7) with poly IC (one-hit) and further exposed to peripubertal unpredictable stress (two-hit model) showed that adult two-hit rats present sex-specific behavioral alterations, with females presenting more deficits in prepulse inhibition of the startle reflex and hyperlocomotion, while males showing more social withdrawal. Both sexes presented similar working memory deficits. We also observed sex influences in brain oxidative alterations in animals exposed to two-hit model [45].

In an attempt to understand the influence of estrous cycle in the manifestation of schizophrenia-like behavioral and neurobiological alterations, our research group found that male mice exposed to the two-hit model (neonatal challenge with poly IC plus peripubertal stress) present behavioral alterations related to schizophrenia positive, negative, and cognitive symptoms accompanied by hippocampal proinflammatory changes. Similarly, females in diestrus (phase of the estrous cycle with lower estrogen levels) presented schizophrenia-like behavioral alterations. However, females in proestrus (phase of the estrous cycle with higher estrogen levels) did not present any behavioral or hippocampal changes (unpublished observation). Overall, these results reinforce the protective role of estrogen in schizophrenia.

In conclusion, the results obtained from adult offspring exposed to PIA with poly IC reveals that male animals present more behavioral and proinflammatory alterations related to neurodevelopmental disorders. In females, it seems that estrogen levels are important to the manifestation of the alterations, but more studies are needed to better address this issue.

2.2 *Sex and Age Influence in Animal Models of Immune Challenge with LPS*

Studies assessing the effects of sex and age on LPS-induced neurodevelopmental changes precede the ones with poly IC [46].

The first evidence for sex influences on behavioral and neurochemical alterations induced by PIA with LPS came from the study of Kohman et al. (2008). These authors showed that neonatal challenge with LPS on PNs 4 and 5 attenuated the LPS-induced (i.e., after LPS re-exposure during adulthood) decrease in motor behavior in female, but not male, rodents. Additionally, PIA with LPS impaired avoidance learning in male, but not female, rodents in the absence of adulthood LPS re-exposure. Male mice neonatally exposed to LPS presented reduced central IL-1β gene transcription following adulthood LPS challenge. These findings indicate that perinatal endotoxin exposure may lead to sex-biased alterations in learning ability during adulthood, with male mice presenting baseline (i.e., without the need of a second challenge with LPS) impaired avoidance learning [46].

Prenatal exposure to LPS caused impairments in social behavior in both adult male and female rats [47] and hypersensitivity to acoustic startle in males, but not females, without altering prepulse inhibition [48]. On the contrary, by using the three-"hit" model (genetic load × environmental factor × sex), an elegant study observed that only mice (male) exposed to all three hits showed deficits in social behavior. In the brains of the three-hit mice, a significant interaction between corticotropin-releasing hormone receptor-1 (Crhr1) gene expression and epigenetic alterations in histone H3 N-terminal lysine 4 trimethylation (H3K4me3) over the Crhr1 promoter was found. These authors concluded that genetic and environmental factors interact to cause sex-specific effects that may help explain the male bias in ASD incidence [49].

Regarding age and sex influence, the exposure of rats to LPS on EDs 15 and 16 and evaluated at periadolescence and young adult age (PNs 40 and 60, respectively) revealed that LPS-exposed females displayed baseline hypolocomotion and decreased reactivity to amphetamine, while males exhibited spatial learning (acquisition trials) and memory impairments. Since this protocol resulted in behavioral changes in offspring during early adulthood, the authors proposed that this might be a model for schizophrenia-like, but not ASD-like, endophenotypes [50]. Still regarding age-related alterations, different results were obtained with neonatal LPS exposure on PNs 3 and 5. This neonatal exposure to LPS resulted in social impairment at adolescence (PN40), but not adulthood (PN70). On the other hand, male rats neonatally exposed to LPS exhibited intact spatial memory during periadolescence, which was impaired in later life, accompanied by reduced prefrontal cortex levels of glutathione on PN40, which was normalized in adult animals. This evidence points towards different age-related alterations induced by neonatal LPS [51].

Our research group also found important age- and sex-related alterations in mice neonatally exposed to LPS. We observed that on PN35 (periadolescence), LPS-challenged male mice presented depressive, anxiety-like, repetitive behavior, and

working memory deficits, while on PN70 (adulthood), only depressive- and anxiety-like behaviors were observed. Conversely, females presented deficits in prepulse inhibition (PPI) in both ages studied. Behavioral changes in periadolescence and adulthood were accompanied, in both sexes, by increased brain levels of interleukin (IL-4) and decreased levels of IL-6. BDNF levels were increased in both sexes during adulthood. We concluded that neonatal LPS challenge triggers sex-specific behavioral and neurochemical alterations that resemble ASD, being a relevant model for the mechanistic investigation of sex bias associated with the development of this disorder [52]. Taken together, these results indicate that the consequences of neonatal exposure to LPS are detectable even early in juvenile development, what seems to be distinct from the prenatal exposure.

Considering neurobiological alterations induced by PIA with LPS, the intraperitoneal exposure of dams on ED18 and 19 to 500 μg/kg LPS caused important sex- and age-related alterations in astroglial markers (S100B and glial fibrillary acidic protein – GFAP) in the prefrontal cortex and hippocampus. The S100B protein exhibited an age-dependent pattern of expression, being increased in the frontal cortex and hippocampus of the MIA group on PN 60 (adulthood), while at PN 30 (periadolescence), male rats presented increased S100B levels only in the frontal cortex. Furthermore, increased levels of GFAP were detected in the frontal cortex of the LPS group at PND 30, but not in the hippocampus [53]. Since the secretion of S100B is reduced by elevation of glutamate levels, this early increment of S100B in the frontal cortex of males may be associated with a frontal glutamatergic hypofunction, one core neurobiological alteration present in schizophrenia. Still regarding LPS-induced long-term glial alterations in males, prenatal LPS challenge also resulted in a significant increase in the number of spines in the granule cells of the dentate gyrus and in a reduction in hippocampal expression of the fractalkine microglial receptor (CX3CR1), involved in mediating the pruning process in the offspring, only in male progeny of the LPS-challenged dams [54]. Figure 1 summarizes the main changes observed in male and female adult rodents exposed to PIA with poly IC or LPS.

3 Conclusions and Future Perspectives

Animal models based on PIA with poly IC and LPS have provided meaningful insights for a better understanding of the influence of sex in neurodevelopmental disorders. Indeed, male rodents exposed to a PIA present distinct behavioral and neurochemical alterations when compared to females. This may help the understanding of the molecular basis underlying neurodevelopmental disorder possibly resulting in future sex-based pharmacological treatments, contributing to precision medicine in psychiatry.

Future studies need to address the time course of changes in males and females in different developmental periods. The influence of estrous cycle phases in these alterations is another important point to be addressed in future studies. Finally, it is

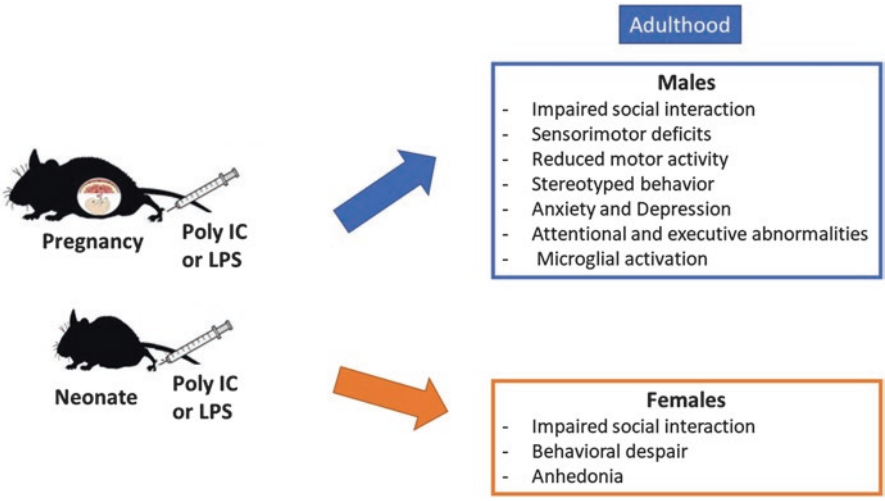

Fig. 1 Exposure to poly IC or LPS during pregnancy or neonatal life triggers sex-related behavioral and neurochemical alterations. These alterations are more prominent in male rodents demonstrating the vulnerability of male subjects to neurodevelopmental disorders

necessary to encourage the development of new and creative experimental models to understand how sex and age crosstalk, interfering with the vulnerability to neurodevelopmental disorders.

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Maternal Immune Activation and Neuropsychiatric Disorders: The Intricate Puzzle of Autism Spectrum Disorder

Mellanie Fontes-Dutra, Bruna Rabelo, Júlio Santos-Terra, Iohanna Deckmann, Gustavo Brum Schwingel, and Carmem Gottfried

Abstract Pregnancy is a complex phenomenon in which several physiological changes are orchestrated to provide appropriate fetal development. In this context, the immune system plays important roles, oscillating between many states in the spectrum of tolerance and inflammation in order to balance the maternal–fetal interface. Infections caused by different agents are capable to trigger countless alterations in immune profile, which are especially harmful during the gestational period, being already linked to important development impairments. Regarding this, numerous evidence have pointed out the relation between maternal immune activation (MIA) and neurodevelopmental disorders like schizophrenia and autism spectrum disorder (ASD). Specifically, ASD is a highly prevalent disorder that stands out as a field of study because of its extensive complexity and relatively poorly known etiological mechanisms. Several animal models of MIA already helped to understand possible pathways by which immune activation could increase ASD risk, clarifying important roles of immune-related factors in the modulation of fetal development. Therefore, the main objective of this chapter is to compile and comment evidence that may improve the knowledge between immune system and ASD in the context of MIA.

Keywords Autism spectrum disorder · Immune · Inflammation · Environmental risk factors · Neurodevelopmental disorders

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Abbreviations

APC	antigen-presenting cell
ASD	autistic spectrum disorder
BD	bipolar disorder
CC	cingulate cortex
CMV	cytomegalovirus
CNS	Central nervous system
CRS	congenital rubella syndrome
CTB	cytotrophoblast
CXCL1	(C-X-C motif) ligand 1 or keratinocyte chemoattractant (KC)
DNA	deoxyribonucleic acid
DSM-5	5th edition of Diagnostic and Statistical Manual of Mental Disorders
dsRNA	double-stranded RNA
EEG	electroencephalograms
EVT	extravillous trophoblasts
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
G-CSF	granulocyte colony-stimulating factor
GFAP	glial fibrillary acidic protein
GM-CSF	granulocyte-macrophage colony-stimulating factor
hCG	human chorionic gonadotropin
HDAC	histone deacetylase
Hip	hippocampus
HSV	herpes virus
ICAM	intercellular adhesion molecule 1 or cluster differentiation (CD54)
IFN	interferon
IL	interleukin
iNOS	inducible NOS (nitric oxide synthase)
IVS	intervillous space
JNK	c-Jun N-terminal kinases
LPS	lipopolysaccharide
M1	motor cortex
MBP	myelin-basic protein
MCMV	murine cytomegalovirus
MCP-1	monocyte chemoattractant protein 1
MD	major depression
MGE	medial ganglionic eminence
MHFD	mice born from dams fed a high-fat diet
MIA	maternal immune activation
MIP-1α	inflammatory protein 1 alpha
mPFC	medial prefrontal cortex
MRD	mice born from dams fed a regular diet
mRNA	messenger ribonucleic acid

NK cell	natural killer cell
PBMC	peripheral blood mononuclear cell
PFC	prefrontal cortex
PND	postnatal day
PNS	prenatal stress
poly(I:C)	polyinosinic:polycytidylic acid
PV	parvalbumin-positive neurons
RANTES	regulated on activation, normal T cell expressed and secreted
RLN	reelin-positive neurons
SST	somatostatin-positive neurons
SYN	syncytiotrophoblast
SZ	schizophrenia
TGF-β	transforming growth factor–β
TLR	toll-like receptor
TNF	tumor necrosis factor
TNFRI	tumor necrosis factor receptor I
TRP	transient receptor potential
V1	primary visual cortex
VCAM-1	vascular cell adhesion protein 1
VEGF	vascular endothelial growth factor
VPA	valproic acid

1 Introduction

Current knowledge has brought the immune system to a new scenario for the interplay between neurons and immune mediators, not only in disease but also in brain homeostasis. In the past, the central nervous system (CNS) was called “an immune-privileged region” with the blood–brain barrier controlling the crosstalk between the brain and the periphery. Nevertheless, recent findings had shed some light that this privilege is not due to the absence of immune modulation in brain activity and homeostasis, but rather an intimate relationship with time-dependent specific modulation in different regions during brain development.

The idea that altered neuroimmune mechanisms might play a role in neurodevelopmental disorders gained popularity in recent years. The first pieces of evidence supporting this mechanism date more than a century ago, when Karl A. Menninger revealed an association between influenza exposure and psychotic disorder in patients who were admitted to the Boston Psychopathic Hospital after the outbreak of the 1918 influenza pandemic.

This early neuroimmune hypothesis of psychotic disorder was only brought back by Torrey et al., in the 1970s, suggesting that latent viruses might be involved in the development of schizophrenia (SZ). The field has been expanding ever since and

nowadays various infectious agents are considered to play an important role in the development of SZ and related disorders.

Considering this, substantially interest has been bearing upon the possible contributions of infections in gestational life. The prenatal period seems highly sensitive to alterations induced by an immunological threat, such as infections. Indeed, infection-induced insults directed at dams can lead to not only pathophysiological changes in the fetal environment but also long-lasting consequences in postnatal life, in both the brain and the behavior. These immunological processes seem relevant for autism and other neurodevelopmental disorders, including SZ and bipolar disorder (BD), which are all believed to be associated with alterations in early developmental processes. While these associations provide a rationale for suggesting that prenatal infection might contribute to the cause of these disorders, they do not prove causation.

Therefore, the main aim of this chapter is to present an overview of the risk factors in prenatal life that may lead to neurodevelopmental disorders, considering (a) the physiology of immune system during gestational period, (b) the outcomes of prenatal immune challenge, in both the CNS and peripheral body, and (c) the relationship between maternal immune activating (MIA) and the development of autistic-like behaviors in animal models.

2 Risk Factors Associated With MIA

Pregnancy is an intricate moment regarding the functionality of immune system. Not only the risk of infections of different natures, such as bacterial, viral, parasitic sources, is elevated, but also the severity of the presented symptoms [180, 206]. The mechanisms underlying the increased susceptibility are related to the physiological adaptations assumed by the female body in order to provide an ideal environment for embryo and fetal development. The increase of cardiac rate and decrease of pulmonary residual capacity in order to provide blood supply to the fetus may contribute to the development of respiratory infections, especially by influenza virus [44]. Therefore, it is important to understand the possible outcomes of these conditions and the pathways by which they interfere in neuroimmune parameters.

Fever itself, a common symptom observed in infections, is a known risk factor for neurodevelopmental disorders like autistic spectrum disorder (ASD) [94] and SZ [63]. In ASD, specifically, some studies using large cohorts from different countries (the USA, Denmark, and Norway) [13, 34, 94, 213] demonstrated that fever episodes, in the first and, especially, in the second trimester, increased significantly the risk of autism in a time and dose-dependent manner: early febrile episodes were associated with ASD with severe intellectual disability, whereas recurrent fever was related to increased risk of ASD. Although the mechanisms of fever are relatively well known, the use of antipyretics during pregnancy demonstrated controversial results in this context: in the USA cohort, nonsteroidal anti-inflammatory drugs (NSAIDs) seemed to reduce the autism risk factor when used to mitigate fever

associated with influenza infection, but, in the Norway cohort, the use of acetaminophen demonstrated only slight protective effects.

Few clues were proposed to explain the mechanisms by which fever triggers these important outcomes. Animal models had already demonstrated that hyperthermia may be a teratogenic factor: agonists of transient receptor potential (TRP) ion channels, which are endogenously activated by temperature, induced several craniofacial alterations in neural crest from chicken and zebrafish embryos [43, 97, 189] mice and rats fetus [181, 209], as well as leading to cellular apoptosis in cerebral cortex of adult rats [104]. The animal models of maternal immune activation, regardless the induction factor, demonstrated that the increased temperature itself in critical periods of pregnancy may be involved in the mechanisms underlying the risk of developmental disorders associated with fever during pregnancy, alongside alterations in chemokine, interleukin, and immune cell profiles.

2.1 Bacterial Infections During Pregnancy

Balance is a key concept in the context of bacterial infections and their effects on human health, especially during pregnancy. On the one hand, the microbiome plays important roles regarding adaptations of the body to sustain properly the gestation. On the other hand, dysbiosis could lead to many infections—mostly with unknown influences in the development of the fetus.

Regarding ASD, some studies demonstrated that bacterial infections, regardless the pathogen source, may be particularly deleterious during pregnancy: a Taiwanese study demonstrated that bacterial infections in the third trimester increased the risk of ASD development by 24%, while genital infections, which were mostly related to bacteria, increased the risk by 34% [68]. Similar results were previously reported in a USA study that observed a twofold increased risk of ASD in children whose mothers had bacterial infections, mostly in the genitourinary tract, during the second and third trimesters of gestation [214] and in a Danish study that found similar relations in the second trimester [14]. Interestingly, the species of the pathogens themselves do not appear to be determinant of increasing risks. Nonetheless, the common immune system alterations triggered by bacteria seemed to be the key to the harms. For example, elevated levels of interleukin (IL) 4, IL-10, tumor necrosis factor (TNF) α, and TNFβ in amniotic fluid were related to increased risk of autism in a Danish cohort [2]. Beyond that, the concentrations of interferon (IFN) γ, IL-4, and IL-5 in maternal serum were associated with a 50% increased risk of ASD [82]. Moreover, this kind of alterations—specifically increase in IL-1β and IL-4—was observed in the serum of neonatal children posteriorly diagnosed with ASD [114]. However, some specificities must be considered, for example, the presence of endotoxins like lipopolysaccharide (LPS) and *staphylococcal* enterotoxin A notably elicits a stronger immune response that has, in consequence, more severe outcomes. In this case, some hypotheses have already been proposed regarding the cytokine profile alteration and other mechanisms, like the production of antibodies against LPS

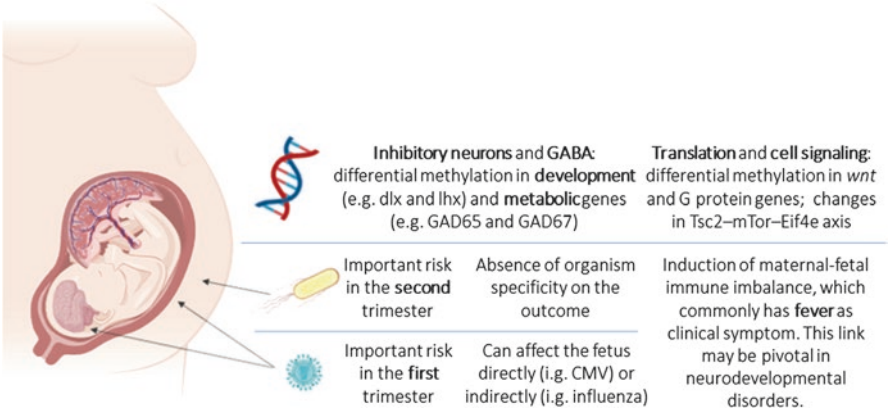

Fig. 1 Genetic and environmental factors in maternal immune activation context. on the top, the main genetic alterations identified in MIA, possibly triggered by the consequences of immune unbalance on transcription factors and methylation patterns. On the bottom, differential viral and bacterial effects during pregnancy related to increased risk of neurodevelopmental disorder and a possible path of convergence related to cytokine expression and its clinical outcome – fever. *GABA* gamma-aminobutyric acid, *GAD* glutamic acid decarboxylase, *CMV* cytomegalovirus

which could interfer in growth factors once these molecules share sialic acid modifications [152]. Nevertheless, studies using MIA animal models (see more in "*Animal models of MIA*") are crucial to bring clarity to these mechanisms (Fig. 1).

2.2 Viral Infections During Pregnancy

Vaccination schedules all around the world provide important prophylaxis against several viral infections, such as measles, rubella, influenza, and many others. However, the combination of both fake associations between vaccines and the increase in ASD development and the lack of accessibility to basic health resources in many countries is a great challenge in eradicating infections that may cause important outcomes, especially in pregnancy.

Interestingly, the early studies of a possible relationship between viral infection during pregnancy and increase in ASD risk came out in the 1970s, when it was observed that the prevalence of ASD in children with congenital rubella syndrome (CRS) was 200 times higher than the general US population [45, 46]. Other studies from that time demonstrated similar results [56], showing a major concern about the rubella outbreak in the 1960s (in 1 year, 20,000 cases of CRS were identified in the USA). Nowadays rubella infections appeared to be controlled in the USA, although it is important to note that this situation does not apply to many other countries.

The biological pathways by which rubella induces neurodevelopmental alterations combine MIA and the action of the virus itself which can trespass barriers and infect the fetus, causing direct damages. Conclusive studies evaluating biological

tissues of ASD individuals who were infected with CRS previously are unavailable, but several similarities can be observed in the 1970s studies and the recent ones with aborted fetus with CRS. Considering phenotype similarities, both CRS and ASD share higher rates of heart, ophthalmological and hearing impairments, besides behavioral alterations like absent or delayed language and sensorial hypersensitivity [98].

Little is known about the maternal immune response to rubella since the tools to perform this type of analysis were unavailable in the 1970s. Fetus infected with rubella presented elevated IFNα, proliferation of natural killer (NK) T lymphocytes (T cells) [118] and microglial activation [200] drawing a parallel with ASD, which is marked by a chronic status of inflammation with alterations in blood and CNS of several cytokines like IL-1β, IL-6, IL-8, TNFα and IFN-γ as reviewed by Deckmann et al. [53]. Although the relationship between rubella infection during pregnancy and ASD is undeniable, the immune background involved is still poorly understood.

More recently, non-classical viral infections during pregnancy also demonstrated important relations with ASD demonstrated. The critical window seems to be the first trimester of gestation [14] and the outcomes of infections are extensively diverse.

Cytomegalovirus (CMV) infection during pregnancy is capable to cause important teratogenic effects like deafness and visual impairments [193]. The relations with ASD were first described in the 1980s. Recently, studies demonstrated an increased prevalence of CMV congenital infections in ASD children, being tenfold higher than the general population [79] and a relationship between CMV infection and higher severity of ASD symptoms [57]. In addition to the classical viral mechanisms, rodents exposed to CMV increased TNFα and IL-6 secretion in fetal CNS, both molecules already associated to the ASD pathophysiology [188].

Finally, other infections with no major association with teratogenic effects have been related to the ASD triggering. Some evidence demonstrate that measles and mumps [159], herpes simplex virus (HSV) [131], and even influenza infections during pregnancy [13, 14] may induce neurodevelopmental disorders. Concerning HSV, the only evidence available shows an association between maternal antibodies against herpes simplex virus 2 (HSV-2) at mid-pregnancy and the risk of ASD in boys [131]. In addition to the epidemiological data, animal models of influenza infection demonstrated several autistic-like alterations in many levels (see more in *"Animal models of MIA"*).

Taken together, these data lead us to two major concerns about viral infections during pregnancy: fetal infection associated with teratogenicity and MIA in order to eliminate the pathogen (Fig. 1). Extensive studies are necessary to elucidate the biological pathways involved in order to promote strategies to mitigate these deleterious effects and improve health care in new epidemics, such as Zika and chikungunya infections.

2.3 Genetic Factors Related to MIA

Fetal development is marked by a highly complex and time-dependent transcription factor expression, which can be altered by environmental interferences leading to multiple outcomes. Pathogen interactome, a term to describe the protein network related to host–parasite interaction during pregnancy, is an emergent study field in MIA context.

A study using LPS-induced model of MIA demonstrated dysregulation of 3285 genes in the offspring, which also presented autistic-like behaviors. Strikingly, most of these genes are related to proteins of cell cycle processes and GABAergic neurons development [160]. Genome-wide DNA methylation study performed in mice from MIA model demonstrated altered methylation in GABA-related genes (*Dlx1*, *Lhx5*, and *Lhx8*), *wnt* pathway genes (*Wnt3*, *Wnt8a*, *Wnt7b*), and neural and synaptic development genes (e.g., *Efnb3*, *Mid1*, *Nlgn1*, *Nrxn2*) [170]. This can be combined to the evidence of altered methylation patterns in genes related to synaptic integrity, GABAergic metabolism (leading to a decrease in GAD65 and GAD67 protein expression) [117], and G-protein cell signaling [22]. Together these findings suggest that the alterations promoted by MIA in several sets of genes already related to ASD may be associated with epigenetic mechanisms. Besides, MIA can modulate maternal care and depressive-like behaviors in the offspring in a transgenerational manner, helping to sustain the epigenetics hypothesis [174].

Beyond that, another study demonstrated the "fetal programming" feature of MIA in genetic alterations related to ASD, such as the downstream pathway of FMR and CHD8 genes. In this case, the consequent alteration in Tsc2–mTor–Eif4e axis signaling, which is directly related to translation initiation, seems to be impaired in both MIA and ASD. Moreover, a study comparing bioinformatics data from several interactomes between infections and ASD observed that 206 genes related to ASD may also be modified by several types of infections [42].

Finally, a study demonstrating larger effects of MIA in BTBR T(+)tf/J mice, a genetic animal model of ASD, highlights the importance of genetic background in this context [183]. The haploinsufficiency *mpk27* gene (an animal model of MIA in mice, targeting c-Jun N-terminal kinases—JNK) elicited an altered expression of cytokines in fetal brain, bringing attention to JNK signaling during these processes [158].

The accumulated data regarding genetic factors influenced by MIA leads us to think about an integrated system in which the protein interactions in both dams and offspring in response to environmental stimuli work in a dynamic way promoting alterations at the epigenetic, translational and transcriptional levels. The expression profiles in several contexts seem to point toward known related ASD pathways; however, further studies are needed in order to improve and clarify the genetic-environmental network in MIA and ASD (Fig. 1).

3 Typical Immune Physiology and Pregnancy

3.1 Innate and Adaptive Immunity

The immune system refers to a complex interplay between cells and molecules that trigger together processes in order to protect an organism against microorganisms and other external macromolecules. These processes can be divided into two approaches (known as "lines of defense"): innate immunity and adaptive immunity [136].

3.1.1 Innate Immunity

Innate immunity is the first-line defense, acting even before the establishment of infection, due to its antigen-independent defense mechanism (non-specific), which is recruited immediately after the antigen recognition by the host. Therefore, it is well known as the immediate response against an invading pathogen [9, 136]. The innate responses do not present memory mechanisms, unlike adaptive response, regardless of previous exposure to pathogens [77].

The main components of innate immunity [9, 202] are:

(1) Anatomical/physical and chemical barriers, such as epithelium and antimicrobial agents produced on epithelial surfaces
(2) Physiological barriers, such as temperature and pH alteration
(3) Phagocytic and effector cells (neutrophils, macrophages), dendritic cells and natural killer (NK) cells and other lymphoid cells
(4) Inflammatory molecules (blood proteins or "soluble mediators"), including members of the complement system and other mediators of inflammation

3.1.2 Adaptive Immunity

Innate and adaptive immunity are distinct concepts for didactic purposes. However, they are not mutually exclusive considering the normal immunological defense of the host, acting in a "synergic manner" in order to covering failures in both systems. Unlike the innate immunity, adaptive immunity is antigen-dependent and -specific, taking more time from pathogen exposure to the response be triggered. The major difference from innate immunity is the ability of the adaptive immunity to "memorize," through different regulatory mechanisms, the pathogens when the first exposure occurs in order to make immunological responses to subsequent exposures to the same pathogen more rapid and efficient [29].

In this way, the adaptive immune has a coordinated repertoire to recognize the self- and nonself-antigens [29, 136], to generate responses toward specific immunological pathways for the elimination of pathogens or cells infected by them and to

develop immunological memory to optimize the response to a subsequent threat [29]. The adaptive immune cells are tightly regulated by each other, including antigen-presenting cells (APCs) and T and B lymphocytes [29, 136].

3.2 Placental Barrier

The placenta is an organ considered a barrier that protects the fetus against the invasion of external pathogens in maternal body [165]. During pregnancy, several immunologic alterations and adaptations occur in which placenta has a pivotal participation in order to ensure the fetal development, such as redistribution of nutrients and oxygen [58, 113]. The placenta is formed after the blastocyst implantation in maternal endometrium which becomes the decidua, a specialized tissue playing important roles, such as being a maternal interface. During decidua formation, the maternal blood surrounds the placenta in order to promote the adequate exchange of nutrients through both maternal and fetal circulation, remodeling the spiral arteries. These vascular modifications occur by means of NK cells and macrophages, allowing higher maternal blood bathing the placenta [7].

The fetal interface is represented by two layers of trophoblast: an inner formed by cytotrophoblast (CTB) and an outer composed by syncytiotrophoblast (SYN). In this way, this interface is formed by a continuous barrier that physically separates the mother from the fetus, despite allowing the selective passage of soluble molecules [7, 37].

A set of villi composes human placenta. A single layer of SYN coats the outermost surface, forming the main cellular barrier between the fetus and the maternal blood. The CTBs are progenitor trophoblast cells, subjacent to SYN, and they can differentiate into mononucleated extravillous trophoblasts (EVTs) which are located at the edge of the villi. The SYN transports nutrients, gases, and waste, in addition to the production of human chorionic gonadotropin (hCG) and progesterone during the first 8 weeks of gestation, having an endocrine function until the placenta is able to produce progesterone by itself. EVTs are a physical anchor to the human placenta in the decidua. In the transition from the first to second trimester, EVTs allow the direct contact of maternal blood with placenta in intervillous space (IVS), facilitating the efficient exchange, separating the early and later stages of pregnancy. In the first trimester of pregnancy, the IVS is bathed with uterine gland secretions which contain growth factors that regulate placental development, including epidermal growth factor, vascular endothelial growth factor (VEGF), and transforming growth factor–β (TGF-β) [7].

Thus, the placenta is a pivotal maternal–fetal interface. In this way, despite of not every infection leads to miscarriage, placental infection triggers the production of inflammatory cytokines which can activate not only the maternal immune system and leading to placental damage, but also that of the fetus. This immunological activation may lead to inadequate neurodevelopment, including diseases in the offspring in adulthood stage [113] (Fig. 2).

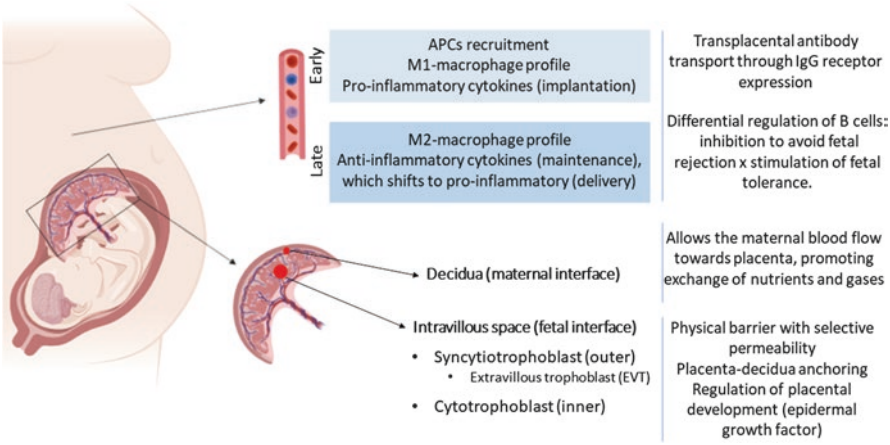

Fig. 2 Maternal physiology during pregnancy. On the top, time-related shift in expression of soluble inflammatory markers and immune cells during early and late pregnancy. On the bottom, the maternal-fetal interface and the main functions of these transitory tissues (placenta, decidua, syncytiotrophoblast and cytotrophoblast). *M1* macrophage subtype 1, *M2* macrophage subtype 2, *APCs* antigen-presenting cells

3.3 Immunological System Influence in Pregnancy and Neurodevelopment

Pregnancy is a unique condition in maternal body that ensures fetus growth and development (protecting them from pathogens), whereas maintaining immunological response to the mother against infections, environmental stressors, and even the presence of the fetus itself in the uterus (not recognizing them as a "foreign body"). Thus, this specific switch in maternal immunity guarantees fetal development and preserves the gestation [187]. Modifications in maternal physiology include: changes in cardiac output in order to redistribute the maternal blood in placental circulation; maternal hyperventilation toward an adequate exchange of respiratory gases across the placental barrier, and insulin resistance in the third semester of pregnancy which directs the flows of glucose, amino acids, and lipids to the fetus in the stage when fetus growth is more accentuated [58, 113].

The immune system evolved in the sense to protect organisms against pathogen threats. The uterus, for example, is capable to release IL-15 to promote NK cells maturation; NK cells induce a decidua remodeling by means the secretion of cytokines, such as IFNγ, VEGF, and TNFα, whereas Treg cells modulate the activities of APCs cells. Beyond that, it seems to be necessary a refined balance in memory T cells to maintain the delicate stability of pregnancy; thus, this mechanism works together allowing maternal tolerance to the fetus [7, 106, 137].

Despite the immune tolerance in pregnancy, inflammatory events occur in several stages, like implantation, which is characterized by increased levels of pro-inflammatory chemokines, cytokines, and growth factors. In the first phase of preg-

nancy, the immune system recruits a set of APCs, including mast cells, dendritic cells, monocytes, and macrophages. During placental development, M1-macrophages pattern is dominant, shifting to M2 in the second and third trimester (with anti-inflammatory profile), which is crucial to fetus development [31, 172]. Moreover, the placenta is able to transport antibodies to the fetus via expression of the immunoglobulin G (IgG) receptors, creating, a transplacental via of maternal humoral immunity [172].

Furthermore, the Th2 and Treg cells participate in the maintenance of pregnancy, inhibiting the fetal rejection (mediated by T helper type 1 (Th1) and Th17 responses) by production not only IL-4 and IL-10, but also TGF-β. Another mechanism is the negative regulation of a specific B cells population, avoiding autoimmunity against the fetus, while stimulate other B cells subset responsible for antibodies production against pathogens [31, 172] (Fig. 2).

4 Central and Peripheral Alterations in MIA Offspring

4.1 Central Markers

4.1.1 Neuronal Abnormalities and Cortical Disorganization

The neurodevelopment covers a complex organization of processes under genetic, environmental and immune regulation, being vulnerable to a variety of insults in critical biological windows. For example, GABAergic neuronal populations might be differentially altered during MIA. Studies have demonstrated an increase in density of somatostatin-positive neurons (SST) in white matter corpus callosum [62], while parvalbumin (PV) and reelin-positive (RLN) neurons are decreased in hippocampus and cerebral cortex [24, 210, 215]. This neuronal population decrease is differentially observed in a time-dependent manner according to the time precursor neurons migrate from the medial ganglionic eminence (MGE) to the early cerebral cortex [39, 144, 146, 210]. In adult life, rodents exposed to MIA protocols present an increase in the number of PV neurons in prefrontal cortex (PFC), such as medial prefrontal cortex (mPFC) [28]. Several markers of GABAergic phenotype are altered in offspring of rats exposed to MIA, such as a decrease in the relative expression of mRNA from GAD_{67} and a shifted pattern of chloride channels (NKCC1 and KCC2) involved with GABA receptor activity during development, pointing to immature GABAergic phenotype related to MIA exposure [186].

Similar to PV neurons, time-dependent embryonic exposure during MIA in rodents affects cell content, resulting in decreased cerebellar density of Purkinje cells in lobule VII [154], and increased cerebellum size and number of Purkinje cells after the mitosis phase [1].

Alterations in pyramidal neurons and cortical organization are seen in MIA animal models as well. Studies have demonstrated that after MIA induction with Poly(I:C) [47] or LPS [210], respectively, a loss in specific neuronal populations is seen, reflecting in altered layer-specific neuronal markers, such as TBR1. These

altered number and localization of neurons reflect in patches of cortical disorganization in MIA offspring, described in the primary somatosensory cortex, secondary motor cortex, and temporal association cortex [24, 186]. These patches were sensitive to the time of MIA and the size of patches in the primary somatosensory cortex was correlated with behaviors characteristic of MIA offspring, possibly affecting neuronal migration. Moreover, prenatal human influenza viral infection in embryonic day 9 (E9) of pregnancy by a neurotropic strain of influenza A virus (H1N1) led to abnormal corticogenesis by decreasing Reelin expression, as well as inducing a reduction in cerebral cortex thickness in the brains of neonatal offspring [70].

These neuronal alterations in MIA models might be key for underlying alterations in synchronicity and brain oscillations. Significant reductions were seen in electroencephalograms (EEG) coherence from MIA-induced by Poly(I:C) animals, especially in mPFC and in hippocampus, with changes in synchrony occurred within delta (2–4 Hz), theta (4–12 Hz), beta (12–30 Hz), and low-gamma (30–48 Hz) frequency bands [59, 60]. These alterations were correlated to behavioral abnormalities, such as decreased prepulse inhibition of startle [60] (Fig. 3).

4.1.2 Glial Cell Activation

Many psychiatric disorders, such as SZ [72, 100, 197], BD [88, 92, 151], major depression (MD) [198], and ASD [128, 153, 162], present inflammatory responses accompanied by microglial activation in the central nervous system. Therefore, it has been proposed that changes in microglia phenotype can be an important aspect of prenatal immune activation, leading to altered course in the developing brain and behavioral and neuronal deficits detected in MIA models in postnatal life [192] (Fig. 3).

4.1.2.1 Microglia

Microglial cells are immune-derived cells resident in the CNS playing important roles in modulating cell maturation and establishing proper neuronal connection during development and promoting tissue repair and homeostasis. Once in postnatal period, microglial cells can alter their gene expression profile and shape in response to minor pathological perturbations in the CNS environment, changing their status from “resting” to “activated” [54, 115]. Since microglial cells are never inactive and show highly dynamic surveillance functions in the CNS, many authors suggest that this surveillance state of the microglial cells should be renamed “surveying microglia” instead of “resting microglia” [119, 155, 208].

In order to investigate the role of microglia in MIA processes, many authors proposed to analyze the pattern of microglial markers related to their activity. Nonetheless, in a recent review [192], the authors pointed divergences among these studies. Poly(I:C) models found out a significant increase in cellular density of microglia in hippocampus [102, 120, 217], striatum [102, 217] and prefrontal and

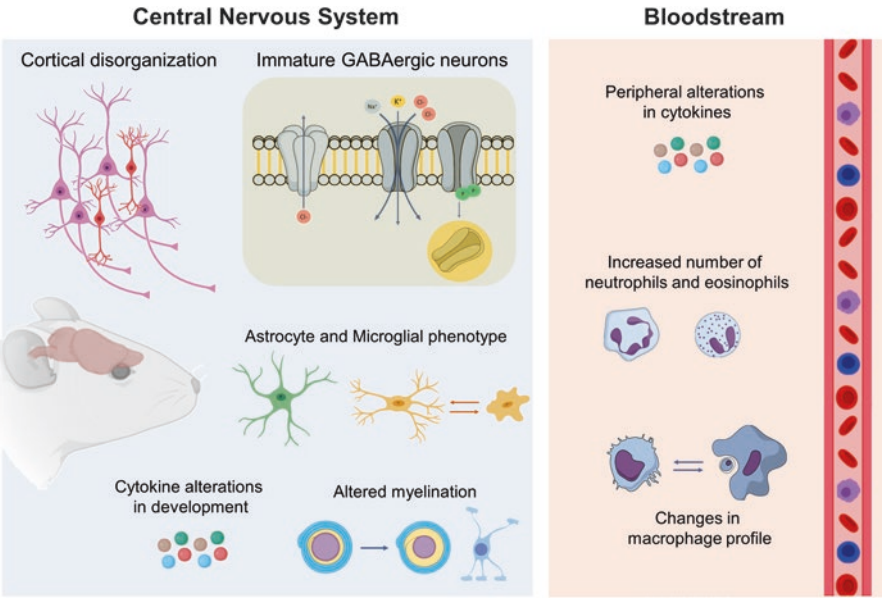

Fig. 3 Central and peripheral alterations in offspring exposed by maternal immune activation during gestation. In blue box, the main alterations in central nervous system in MIA models: (1) cortical disorganization, in purple, pyramidal neurons, in red, inhibitory interneurons, (2) Immature GABAergic neurons and their ion channel distribution: in left to right, ionic chloride channel function, NKCC1 channel presenting Na^+ K^+ and Cl^- influx, and KCC2 phosphorylation, leading to channel internalization, (3) Astrocyte and Microglial phenotype, in green, astrocytes, in yellow, the shift of microglial phenotype, from a surveillance state with ramified shape (left) to a phagocytic state with ameboid (right) shape, (4) cytokine alterations in development and (5) altered myelination, with normal (left) and altered thin (right) myelin sheaths. In red box, the main alterations in bloodstream: (1) peripheral alterations in cytokines, (2) increased number of neutrophils and eosinophils and (3) changes in macrophage profile, shifting to M1/proinflammatory (right) profile, presenting an ameboid/phagocytic phenotype

primary visual (V1) and motor (M1) cortex [217]. Besides, classic microglial activation markers [30, 204, 217] are found in both LPS and Poly(I:C) models, as well as in the shifting to less arborized microglial [102]. However, other studies did not find any significant alterations [76, 80, 81]. This controversy of MIA effects on the offspring of rodents exposed to similar MIA protocols might be a consequence of considering only one parameter for microglia activation, that is, density or morphology or expression of specific markers or cytokines, as well as the technical limitations regarding the sensitivity to detect these alterations and particularities of protocols to induce MIA [192].

4.1.2.2 Astrocytes

Astrocytes also play important roles in propagating and regulating neuroinflammation [69, 126, 156] by releasing inflammatory mediators and cytokines, including IL-1β [41, 101]. Activated astrocytes produce many regulatory factors that may influence CNS immunity and provide negative feedback to activated microglia [147]. Brain inflammation involving astrogliosis (characterized by overexpression of glial fibrillary acidic protein (GFAP) and/or astrocyte hypertrophy) has been observed in the offspring of MIA models in IL-6 or LPS-treated mothers [90, 179]. Taken together data indicate that astroglial changes induced by MIA are dependent on sex and brain region and that these changes could reflect astroglial dysfunction. The S100B protein exhibited an age-dependent pattern of expression, being increased in the frontal cortex and hippocampus of the MIA group at postnatal day (PND) 60, while at PND 30, male rats presented increased S100B levels only in the frontal cortex [52]. Furthermore, a significantly increased number of activated astrocytes, characterized by a rounded shape with large cellular body and fewer processes, were observed in the white matter and amygdala of the offspring exposed to LPS [99, 150].

4.1.2.3 Oligodendrocytes

Numerous evidence have indicated the participation of oligodendrocytes after MIA induction. Histological studies targeting myelin-basic protein (MBP) have shown that loss of myelination in polyinosinic:polycytidylic acid (poly(I:C)) mice is not accompanied by loss of oligodendrocytes [132]. In fact, axonal diameters were significantly smaller in juvenile poly(I:C) mice with reversion of this pattern in adult life in the same study. Moreover, changes in oligodendrocytes population are also seen in embryonic rat spinal cord following MIA [139].

4.1.3 Cytokine Expression

Alterations in maternal serum and fetal brain cytokines are evidenced in animal models exposed to MIA during the gestational period (M. L. [65, 67]). After a few hours of exposure, alterations in fetal brain cytokine expression can be observed, specifically increase of several pro-inflammatory cytokines in Poly(I:C) model, such as IL-1β, IL-6, and TNFα [144–146]. Besides that, increases in maternal IL-17a lead to elevations in fetal neuronal IL-17 receptor expression which is related to social and repetitive behavioral alterations in postnatal life [47, 65].

Studies have investigated the E12.5 Poly(I:C) effects of cytokine profiles in different time points of neurodevelopment in brain regions, such as frontal cortex, hippocampus, cingulate cortex (CC) [76]. After birth and in adulthood PND 7 to PND 30), four cytokines were significantly higher in the frontal cortex: IL-1β, IL-10, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF),

while IL-1α, IL-6, IL-9, and IL-10 in adult life. Conversely, many cytokines are significantly decreased in the frontal cortex in animals exposed to Poly(I:C) at PND7, a critical period of synaptic remodeling in rodents, such as IL-2, IL-4, IL-5, IL-10, and IL-12. In CC, IFNγ, IL-12, and monocyte chemoattractant protein 1 (MCP-1) are significantly increased at birth, but only IFNγ and IL-10 remain increased in adulthood. In the frontal cortex from PND 7 MIA animals, five cytokines are lower, including IL-2, IL-5, IL-6, IL-10, and eotaxin, while IL-17 is higher in CC. At birth, when analyzing hippocampus, MIA exposure leads to altered cytokine levels of IL-6, while IL-1β, IL-2, IL-4, keratinocyte chemoattractant (KC or (C-X-C motif) ligand 1 - CXCL1), MCP-1, and macrophage inflammatory protein (MIP-1α) are lower. In synaptic remodeling period (PND 7), IL-4 remains lower, while KC and MIP-1α reverse their pattern, being elevated. In addition to these cytokines, IL-3, IL-5, and IL-10 are decreased, while IL-9 is increased in the same brain region. In adult life, only IL-6 and MIP-1α are altered in hippocampus from MIA exposed animals [76].

A recent report analyzing the genetic expression of cytokine receptors indicates: (a) an overall increase in cytokine signaling at PND 7, (b) a dramatic decrease at PND 14 during periods of postnatal synaptic remodeling, and (c) an increase during periods of plasticity (PND 30) and early adulthood (PND 60) in the frontal cortex from Poly(I:C) offspring [65].

Changes of cytokine and chemokine profile are also seen in cerebellum and persist throughout the development. As demonstrated previously, analyzing tissues from cerebellum from the MIA model induced by Poly(I:C), at first day of life (PND 1), the levels of Fas (CD95) ligand (Fas-L) and IL-6 are increased, while only a downward trend is seen in basic fibroblast growth factor (bFGF). After the first week of life (PND 7), the levels of IL-2, IL-3, and TNF receptor I (TNFRI) are increased, while eotaxin-2 was decreased. At the peak in synaptogenesis (P14), a significant increase in the levels of MIP-1γ, TNFRI and its ligand TNFα is observed, while the levels of Intercellular Adhesion Molecule 1 (ICAM-1 or CD54) and IL-10 are decreased in MIA offspring. At early adult life (PND 30), the levels of MIP-1γ are increased, while the levels of IFNγ and IL-17 are decreased [164].

4.2 Peripheral Markers

4.2.1 Peripheral Blood Cells

Numerous evidence have indicated immune dysfunction in individuals with neurodevelopmental disorders, but a relationship between in utero MIA exposure and long-term immune dysfunction has not been well established yet. Macrophages play a key role as first responders to infection as phagocytes and orchestrators of adaptive responses. Studies sampling macrophages from MIA offspring's bone marrow, a source for circulating macrophages, showed a shift of macrophage profile to M1 pro-inflammatory phenotype [157], indicating a potential relationship

between long-term outcomes in utero MIA and macrophage function in the offspring.

Furthermore, LPS models of MIA during fetal development presented significantly increased levels of peripheral Gr-1+ CD11b + neutrophilic and monocytic cells in adult offspring [95, 175]. Curiously, MIA during pregnancy demonstrated no effect on neutrophil activity as measured by the production of reactive oxygen species (oxidative burst) and phagocytosis of *S. aureus*, indicating that this manipulation has no or minor impact on neutrophil-mediated innate immunity [212]. However, other aspects of the innate immunity such as monocyte/macrophage activity were not analyzed in the same study (Fig. 3).

4.2.2 Cytokines and Proteins Related to Immune Response

There are many studies investigating the effect of MIA on cytokine levels from the serum of pregnant rodents, shedding some light on the intricate relationship between cytokine levels of MIA-dams and behavioral phenotypes in MIA-exposed offspring [16, 123, 124, 162]. As pointed by Beumer et al., both LPS- and poly I:C-induced MIA models in rat and mouse have been associated with elevated protein circulating levels of TNFα, IL1β, IL-6, inducible NOS (nitric oxide synthase - iNOS), IL10, MCP1, and both protein and mRNA levels of VEGF [10, 25, 27, 38, 83, 127, 163, 203].

Many important cytokines have already been detected in fetal brain and the serum of MIA offspring after the first postnatal week. According to a study performed by Garay et al., IL-12 and "regulated on activation, normal T cell expressed and secreted" (RANTES) are increased at birth (PND 0), while the levels of IL-3, GM-CSF, and MIPα are decreased. After the first week of postnatal life (P7), the levels of IL-1β, IL-3, IL-6, IL-12, granulocyte colony-stimulating factor (G-CSF), IFNγ, KC, RANTES, and TNFα are all higher in the serum, while IL-1α, IL-2, and IL-12 are in lower levels at the same age. Strikingly, at PND 14, a period related to synaptic remodeling, only MIP-1β remains significantly higher. In early adult life (PND 30), IL-1β, IL-6, and IL-9 are higher (1.2-fold), while IL-3 is lower in the serum from MIA offspring. In adult life (PND 60), no alterations in cytokine levels were found between MIA and control offspring [76].

The course of cytokines oscillation in periphery does not reflect the pattern observed in brain regions (frontal, CC, and hippocampus), indicating that both processes might have different pathways and cellular components to maintain these differential patterns. Only six cytokines presented a constant level in the serum throughout development (PND 0 - PND 60), such as TNFα, IL-2, −5, −9, −12, −17, which were not observed in any brain region analyzed [76] (Fig. 3).

5 Maternal Immune Activation and ASD

5.1 Autistic Spectrum Disorder

Autistic spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a behavioral dyad consisting in social and communication deficits and stereotyped behaviors with restricted activities and interests [8]. ASD is a high prevalent disorder, affecting 1:59 children, causing a great impact in different ways, such as economic costs for both families and society [35]. The neuropediatric/psychiatric diagnosis is established when the child presents social deficits around the third year of life, commonly due to the exposure to new contexts that demands complex social behavior [15]. Another factor in ASD is the heterogeneity of the symptoms, which implies a spectrum formed by not only the variety of behavioral manifestations, but also the severity of the alterations.

There is no biomarker that could be used for early diagnosis of ASD yet [96]. Even though there are many well-accepted surveys for behavioral diagnosis, ASD is a highly complex and heterogeneous disorder [75, 168], and this heterogeneity could be potentially explained by the individual's background, for example, the particularities of immune system.

In the last decades, the research community credited to Leo Kanner and Hans Asperger the first descriptions of ASD-like behaviors in the early 1930s. Recently, many studies have pointed out that the first description of ASD-like behavioral alterations was described by Grunya Sukhareva, a Soviet child psychiatrist who was the first to publish a detailed description of autistic symptoms in 1925. The description included many abnormalities in social behavior and sensory deficits in six boys. The original description was in Russian followed by the publication in German a year later, being translated to English only in 1996.

5.2 Sensory Alterations in ASD

The sensory alterations manifest early in neurodevelopment and contribute to the diagnostic criteria of autism. These abnormalities could be clinically observed in the first 6 months of life [20]. Those symptoms could be assessed from 6 months of life through 6 years of life using questionnaires like Sensory Experiences Questionnaire and with a behavior-observing tool like Sensory Processing Assessment [19, 125].

The cortical and subcortical alterations in excitability commonly seen in autistic patients affect the process of neural adaptation, being related to a sensory hypersensitivity or a hyposensitivity [195]. Decreased olfactory cortex activity is associated with impaired odor perception [111] and may help elucidating some cases of sensory perturbation in ASD children [19, 20]. Thus, the sensory impairment precedes the behavioral alterations of autism and could be helpful to an early intervention

[64]. Furthermore, sensory-related behavioral alterations were reported in ASD animal models like impairment in tactile response and olfactory behavior related to nest recognition [74, 182] in sensorimotor gating [135] and nociceptive response [21]. Recently, strategies using prenatal interventions with antioxidant and anti-inflammatory molecules were performed in ASD animal models, being a reliable tool to investigate the molecular mechanisms involved in cortical organization of both excitatory and inhibitory cells that might be related to the behavioral alterations seen in ASD animal models [74].

5.3 Cytokines Alterations in Neurodevelopmental Disorders

Alterations in the immunological environment during the gestational period may lead to several abnormalities in the offspring behavior, as seen in disorders like ASD and SZ. Here we summarize some alterations in relevant cytokines which imbalance affects pathways and mechanisms substantial to the typical brain machinery.

IL-1β is an important cytokine that promotes inflammation by activating macrophages and enhancing lymphocyte function. It also has the capacity to support the infiltration of the inflammatory cells into peripheral tissues, increasing the production of adhesion molecules like vascular cell adhesion protein 1 (VCAM-1) and ICAM-1 [61, 85]. Findings of IL-1β in ASD patients include both increasing and decreasing in their levels, demonstrating that perturbations in this cytokine may contribute to a vast range of alterations [134, 194]. In an animal model of ASD, LPS exposure induced higher levels of IL-1β in hippocampus [129], and the same pattern of alteration was also related to stereotypy, a core symptom of ASD (Paul [11]).

IL-2 is a cytokine secreted by CD8+ and CD4+ T cells, and controls the survival of mature and immature T cells [103, 133]. Few studies evaluated IL-2 in ASD, but one showed a decreased level in neonatal dried blood samples [3].

Produced by T cells, IL-4 is the main cytokine of the Th2 response, contributing to proliferation of B cells and cytotoxic T cells, and stimulating IgG and IgE production [201]. Data in ASD subjects showed reduced levels of IL-4 in neonatal dried blood samples [3], while the levels in the amniotic fluid were increased [2].

IL-5 is produced by T cells and plays important roles in activating eosinophils [86]. This cytokine promotes the proliferation and maturation of eosinophils and also stimulates the production of IgA and IgM [201]. Data in ASD showed decreased levels in neonatal dried blood samples and increased levels in plasma [3, 194].

IL-6 is mainly produced by the T helper cells, macrophages and fibroblasts, activating plasma cells and B cells and stimulating them to produce IgG [201]. IL-6 has a dual effect, pro- and anti-inflammatory [61], and it has been largely studied in ASD, being related to both the development of core symptoms of ASD and the pro-inflammatory response in MIA models of autism [190].

IL-8 is produced mostly by macrophages, targeting neutrophils and activating them [26]. Therefore, this cytokine has a chemotactic role and pro-inflammatory activities [201]. Data have associated higher levels of IL-8 with stereotypy and

hyperactivity, symptoms commonly seen in neurodevelopmental disorders [11]. In ASD subjects, scientists found elevated levels of IL-8 in plasma [194], cerebrospinal fluid [205], and the frontal cortex [121].

IL-10 has a primary anti-inflammatory activity, being produced by many cells types, including macrophages, NK cells, eosinophils, neutrophils, mast cells, and B cells [130]. It also regulates the differentiation and the growth of B cells, NK cells, Th cells, mast cells, granulocytes, and keratinocytes [130, 201]. Hence, this cytokine plays a central role in controlling the immune response when the organism faces pathogens, acting in order to maintain the homeostasis [130]. Many studies have reported an increased level of IL-10 in ASD subjects in the anterior cingulate gyrus and in the amniotic fluid [201, 205], while decreased levels were found in peripheral blood mononuclear cells (PBMCs) (P. [12]).

IL-12 is produced by T cells and plays roles in the activation of naive T cells and NK cells [201], also inducing IFN-γ production, Th1 cell profile [78]. Higher levels of IL-12 were found in plasma, PBMC, and the serum of ASD subjects [169, 194]. Those higher levels were also associated with lethargy and stereotypy in ASD subjects [12].

IL-13 is produced by T cells, basophils, eosinophils, and NK cells. Synergistically with IL-4, IL-13 participates in the type 2 immunity [18]. However, little is known about the role of IL-13 in ASD; there is only one study showing increased plasma levels of IL-13 [194].

IL-17 is produced by NK cells and innate lymphoid cells, presenting a key role in the immunity against pathogens in both intra- and extracellular compartments. Moreover, IL-17 also plays a significant role in inflammation-associated diseases, like tumors and infections [116, 216]. Few studies have shown elevated levels of IL-17 in the serum and plasma in ASD subjects [6, 194].

IL-23 is produced by macrophages, keratinocytes, and antigen presenting cells after a pathogen is recognized, being significantly important to autoimmune disease responses [73, 199, 218]. Increased levels of IL-23 were reported in the serum of ASD patients [169].

6 Animal Models of MIA

Preclinical studies using animal models have explored the relationship between MIA and neurodevelopment by inducing inflammation in pregnant mice, rats, and nonhuman primates. It is well known that the maternal immune response, but not a specific pathogen, increases the risk factor for neuropsychiatric disorders including SZ, ASD, MD, and BD [32, 33, 67, 89]. These models provide an opportunity to uncover pathogenic mechanisms and explore potential therapeutic interventions against MIA-induced neurodevelopmental disorders [40, 91, 140, 143]. Thus, different agents have been used to induce maternal immune response during gestation in animal models [140] (Fig. 4).

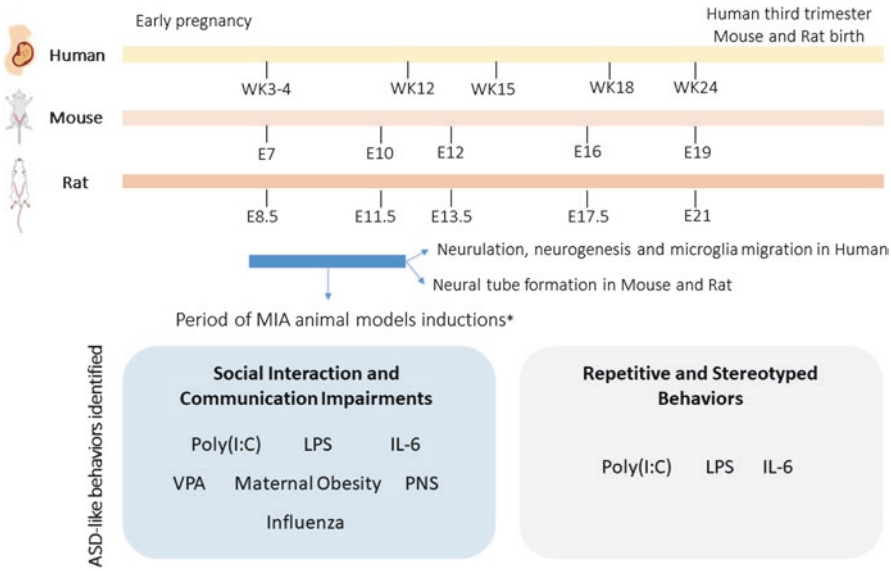

Fig. 4 Neurodevelopment stages in rodents and humans. (**a**) The timing of neurodevelopmental processes differs between mice, rats and humans. These processes include formation of a neural tube, neurogenesis and microglia migration from approximately embryonic day (E)7.5–11.85 in mouse/rats and 3–4 weeks gestation age in humans. These period of time are critical for the MIA animal models inductions. (**b**) Mechanisms by which prenatal maternal immune perturbation influences animal ASD-like behavior

6.1 Induced by Biological Compounds

The most commonly used agents are poly(I:C), LPS and IL-6.

6.1.1 Poly(I:C)

Poly(I:C) is a commercially available synthetic analog of double-stranded RNA (dsRNA), which is generated during viral infection as a replication intermediate for single-stranded RNA or as a by-product of symmetrical transcription in DNA viruses [5]. It is recognized as foreign by the mammalian immune system through the transmembrane protein toll-like receptor 3 (TLR3) [5]. During pregnancy, Poly(I:C) is given systemically at a specific gestational stage, accurately mimicking the acute phase response to viral infection [108] and leads to significant inflammatory responses in the fetal brain. The mechanisms of these responses involves the production and release of many pro-inflammatory cytokines, including IL-1β, IL-6, and TNFα [49], as well as induces the production of type 1 IFNs, such as IFNα and IFNβ [108].

Many neurochemical and brain morphological alterations have been detected in adult mice and rats after maternal gestational exposure to Poly(I:C) (Urs [141–143]). A great number of rodent studies further provided robust evidence for the emergence of behavioral, cognitive and pharmacological dysfunctions after prenatal Poly(I:C)-induced immune activation [140]. This treatment protocol has been shown to induce several cognitive and social features of ASD (Urs [140]), such as abnormal vocalization, deficits in social interaction, and communication [164]. Furthermore, since their initial establishment, animal models induced with Poly(I:C) have repeatedly documented structural and functional phenotypes that are implicated in SZ and related psychotic disorders [67, 140, 141].

One intriguing feature of the prenatal Poly(I:C) model is that the full spectrum of behavioral, cognitive and pharmacological abnormalities only appears after the offspring has reached late adolescence or early adulthood [161, 166, 207, 219]. This maturational delay is indicative of progression of pathological symptoms from pubescence to adulthood, which is consistent with the post-pubertal onset of full-blown psychotic behavior in SZ and related disorders [196]. Compared to live pathogens like influenza virus, the use of Poly(I:C) mimics the immune activation while conferring control over time course and dose of immunogen exposure. This allows to design a protocol with precise time of maternal immune response according to specific periods of fetal development [27].

6.1.2 LPS

Maternal administration of the bacterial endotoxin LPS is a widely used model system to mimic an innate acute phase response to bacterial infection in the absence of live bacteria exposure [140]. LPS is a gram-negative bacterial cell wall component, which is recognized mainly by the pathogen recognition receptor transmembrane protein TLR4 [5]. Binding to TLR4, LPS stimulates the expression of a wide range of innate immune responses that include the synthesis and release of various pro-inflammatory cytokines [5].

There are some notable similarities between the responses triggered by LPS and poly(I:C) [5, 107]; therefore, the prenatal LPS treatment also triggers several behavioral and neurochemical changes relevant to neuropsychiatric disorders, such as ASD [140]. Despite the similarities between LPS and Poly(I:C)-induced effects, there are also some differences between the two models related to the nature of the brain and behavioral changes. Such differences in the long-term outcomes between prenatal exposures to bacterial-like and viral/viral-like immunogens might support the idea that different pathogens can induce a distinct set of neuroimmune abnormalities across brain development [140]. As in the Poly(I:C) model, in LPS, the immunological threat is given to the pregnant animals at a critical gestational stage and also allows the time and intensity of MIA to be more precisely controlled [143]. The most remarkable methodological disadvantage of LPS is marked fetal losses due to spontaneous abortion in higher doses [140].

6.1.3 IL-6

During pregnancy, infection or immune responses induce cytokine release, influencing fetal neurodevelopment and leading to neurological conditions in adulthood [179]. Smith et al. have examined several pro-inflammatory cytokines as potential mediators of the effects of MIA on fetal brain development. They identified IL-6 as a key immunological mediator of the link between maternal immune activation and altered brain development (S. E. P. [190]). When IL-6 is administered to pregnant animals, it induces long-lasting functional and structural alterations in the adult offspring, some of these abnormalities are highly comparable to those induced by prenatal exposure to Poly(I:C) and LPS [179, 190]. Strikingly, the offspring of pregnant mice treated with IL-6 during midgestation also demonstrated core behavioral features associated with ASD including impaired social interaction, decreased communication, and more repetitive behavior [148].

Interestingly, if IL-6 is eliminated from the maternal immune response by genetic interventions or if IL-6 blocking antibodies are used, the maternal immune challenge by Poly(I:C) is no longer efficient in inducing behavioral changes as well as brain alterations in the resulting offspring [140]. Studies showed that blocking IL-6 prevents >90% of the changes seen in offspring of Poly(I:C)-injected females [190].

6.2 Induced by Pharmacological Drugs

6.2.1 Valproic Acid

Valproic acid (VPA) is a fatty acid and widely used as anticonvulsant and mood stabilizer in the treatment of epilepsy and BD [167, 176]. Clinical studies over the years have shown that intrauterine exposure to VPA is associated with birth defects, cognitive impairments, and an increased risk of autism [176]. Based on these observations, a prenatal injection of VPA has been used to induce autistic-like features in animal models in rodents [17, 182].

A single administration of VPA in utero during a critical immunological window leads to developmental delays and lifelong deficits in motor performance, social behavior, and anxiety-like behavior in rat offspring [17, 112, 182]. In addition to the behavioral alterations, molecular [84, 177], morphological [55, 71, 84, 173] and electrophysiological autistic-like features [51, 135, 171] were also seen in this model.

Even though the mechanism underlying the teratogenicity of this drug is still unknown, histone deacetylase (HDAC) inhibition by VPA and changes in gene expression may explain part of the immunological alterations as well as the outcomes in psychiatric disorders [54, 84].

6.3 Non-infectious Models

6.3.1 Maternal Obesity

Maternal obesity during pregnancy has been associated with a low-grade inflammation from chronic activation of the innate immune system [23, 48, 50]. It is also a risk factor for chronic behavioral and neurodevelopmental disorders in the offspring, including ASD [149]. Studies that have examined behavioral changes in mice born from dams fed with a high-fat diet (MHFD) compared to dams fed with a regular diet (MRD) have shown that MHFD induces a shift in microbial ecology that negatively impacts offspring social behavior. Thus, offspring of MHFD dams had fewer social interactions, no preference for social novelty and impaired sociability compared to MRD controls [36].

6.3.2 Prenatal Stress (PNS)

Similar to MIA, PNS also contributes to psychiatric risk and aberrant offspring behavior. Prenatal stress exposure has been identified as a risk factor for the development of neuropsychiatric disorders in offspring including ASD [93, 105, 109]. In animal models, research has linked PNS to heightened levels of anxiety, decreased sociability, and deficits in cognitive and motor function [4, 178]. The mechanisms underlying these outcomes are still not clear. Offspring microglia and the pro-inflammatory cytokine IL-6, known to influence microglia, may serve as common a mechanism between PNS and MIA. Delay in GABAergic progenitor migration is also seen in PNS models. Behavioral effects of prenatal stress in offspring, including increased anxiety-like behavior, decreased sociability, and locomotor inhibition, may be related to these GABAergic delays [87].

6.4 Others

6.4.1 Influenza

Strains of influenza have also been used to induce MIA phenotypes, with the main advantage of eliciting a full spectrum of immune responses [140, 191]. In this model, the dams received intranasal infusion with a sublethal dose of a mouse-adapted human influenza strain [140]. A pioneering study in 2003 showed that the offspring of virus-infected dams exhibited highly significant changes in exploratory behavior, social interaction, and sensorimotor tests [184]. These alterations in behavior are observed in several mental illnesses, including ASD [138]. The striking behavioral changes in mice born from infected dams suggest that brain development was altered by this perturbation of the fetal environment [184]. By exposing pregnant dams to influenza virus at different gestational stages, the prenatal influenza

model has also been used to explore the impact of the precise prenatal timing [110]. It is important to note that in these experiments, maternal viral infection acts through the maternal inflammatory response to alter fetal brain development. However, viral RNAs are not detectable in fetal brains from infected dams the exposed offspring display striking behavioral and histological abnormalities [185].

6.4.2 CMV

Many pieces of evidence suggest that maternal CMV infection may be associated with neurodevelopmental disorders in the offspring, including ASD (M. L. [66, 211]). To further understand the mechanisms underlying these viral infections, an animal model was created to investigate whether murine CMV (MCMV) infection causes alterations in placental IL-6/10 and TLR2/4 levels and also to determine if this infection could be associated with the neurodevelopmental disorders in progeny [122]. Unlike human CMV, MCMV does note cross mouse placenta to infect the embryo. Thus, it can be used as a model to naturally exclude the direct impact of MCMV-related MIA on the offspring [122]. The study demonstrated that an MCVM infection can lead to a significant reduction in the weight of placenta and fetal brain. The increased gene expression of placental TLR2 and TLR4 in the MCMV group might be involved in placental inflammation and production of pro-inflammatory cytokine IL-6. Unbalanced expression (either increase or decrease) of IL-6 in placenta might be associated with the neurodevelopmental disorders in offspring [122].

7 Final Considerations

The evidence and discussions brought up in this chapter demonstrated the high level of complexity involving MIA and consequent neurodevelopmental alterations in the offspring. It is important to note that the underlying mechanisms of maternal–fetal interactions are still beginning to be understood, although the hypothesis of long-term postnatal effects associated with MIA goes back to the 1970s. Several epidemiological studies demonstrated time-dependent and, sometimes, pathogen-dependent relations regarding MIA and the increased risk of neurodevelopmental disorders, besides interesting genetic factors, which can provide more insights about maternal–fetal interaction and the possible impaired outcomes provided by an imbalance in this relation.

Pregnancy is a condition characterized by a diverse expression of soluble markers of inflammation and differential immune cell pattern. This immune profile shift is essential to assure the natural physiology of the process. However, immune challenges during pregnancy may confer a susceptible factor regarding neuropsychiatric diseases due to the interactions of immune response with maternal–fetal features.

Fetal impairments following MIA can be observed at several levels: cytokine alterations in both the serum and the CNS; microglial and astrocyte activation and

increased risk of postnatal psychiatric disorders onset. In order to clarify these mechanisms in the context of neurodevelopmental alterations, several animal models with different approaches emerged. Especially for ASD, those models were very useful to elucidate key mediators in this context, as the pivotal role of IL-6 and TLR receptors, besides neuroglial and immune pattern modifications already related to the classic set of behaviors identified in ASD.

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Zika virus Infection and Potential Mechanisms Implicated in Neuropsychiatric Complications

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Abstract *Zika virus* (ZIKV) emerged as a global health threat due to its association with severe outcomes in humans, including microcephaly and other neurological complications. ZIKV replication and induction of neuronal death are considered key factors for severe ZIKV-induced disease. Understanding the pathogenic mechanisms induced by ZIKV infection is crucial to identify potential therapeutic targets that may prevent or at least minimize the consequences in early phases of disease and adulthood. This chapter will discuss how ZIKV emerged in the past few years, will describe some aspects of the infection and, finally, will focus on the evidence of neuropathological mechanisms of the disease in humans and experimental models and its potential neuropsychiatric outcomes. The mechanisms explored are: (i) infection and virus replication, activation and apoptosis of neural progenitor cells, mature neurons and glial cells with concomitant induction of neuroinflammation; (ii) induction of neuronal excitotoxicity; and (iii) autophagy modulation during ZIKV infection.

Keywords *Zika virus* (ZIKV) · Neuroinflammation · Congenital zika syndrome (CZS) · Neuronal cell death · Glutamate · Neuronal excitotoxicity · Autophagy

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1 Introduction

1.1 Zika Virus

Zika virus (ZIKV) is an arbovirus that emerged as a global health threat due to its association with severe outcomes, such as Guillain–Barré syndrome (GBS) in adults and birth defects associated with congenital infection. It was initially isolated from sentinel rhesus macaques in Zika Forest, Uganda, in April 1947 [1], and first reported in humans in Nigeria, in 1954 [2]. The first epidemic episode occurred in 2007 when over 70% of the population of Yap Island (Micronesia) got infected, although no hospitalization or death related to ZIKV-infection was registered [3, 4]. Later, an epidemic in French Polynesia between October 2013 and April 2014 resulted in almost 32,000 infections with ZIKV and an unexpected 20-fold increase in GBS incidence, suggesting an association between ZIKV infection and GBS [5–9]. Then, ZIKV emerged in Brazil on March 2015 [10] causing a major epidemic that led to 440,000–1,300,000 infections [11] followed by a huge increase in microcephaly and GBS incidence [12].

ZIKV belongs to *Flaviviridae* family, *Flavivirus* genus, Riboviria realm, which includes other public health relevant pathogens, such as *Dengue virus* (DENV), *Yellow fever virus* (YFV), *West Nile virus* (WNV), *Japanese encephalitis virus* (JEV), among others [13]. Although there are two lineages described so far, African and Asian [14], all viral samples isolated during epidemics in the Americas and Pacific regions belong to the latter lineage [15]. There are two natural viral transmission cycles: an enzootic cycle between nonhuman primates and sylvatic species of *Aedes* spp. and an urban cycle in which the virus is transmitted between humans and peridomestic *Aedes* spp., mainly the prevalent species *Aedes aegypti* [16]. In addition to the spread through infected *Aedes* mosquitoes, other relevant routes of ZIKV infection are blood transfusion, sexual and vertical transmission in humans [17, 18].

ZIKV transmission was registered in more than 80 countries and territories between 2015 and 2017 [19]. Even though the majority of countries in the Americas and the Caribbean experienced a decline in Zika cases since later 2017, virus reintroduction and exposure to naïve population may occur, especially in areas with arthropod vector circulation [20].

1.2 Clinical Presentation and Its Underlying Physiopathology

Almost 80% of ZIKV cases in humans are asymptomatic. Acute symptomatic cases present clinical signs similar to other arboviruses of medical relevance, such as Chikungunya virus (CHIKV) and DENV, making the diagnosis challenging in endemic countries with circulation of multiple arboviruses. Some clinical and laboratory variables may help in the accurate diagnosis of the infection (Table 1) [21].

Table 1 Clinical signs of ZIKV, DENV, and CHIKV

Clinical manifestations	Zika virus	Dengue virus	Chikungunya virus
Fever	Mild	High	High
Rash	High	Low	Low
Arthralgia	Low	Low	High
Hemorrhage	No	High	No
Guillain– Barré syndrome	Low	Very low	Very low
Microcephaly	High	Absent	Absent

Modified from Karkhah et al. [25]

A hallmark of ZIKV infection in humans is the associated neurological complications: congenital microcephaly, GBS, myelitis and meningoencephalitis [5, 22–24]. After transmission to the human host, ZIKV incubation period lasts around 3–10 days, triggering symptoms with different levels of severity including fever, rash, arthritis or arthralgia, myalgia, headache, and conjunctivitis. Some nonspecific clinical manifestations, such as cough, sore throat, vomiting, and nausea, can be observed in a few cases [25].

Regarding the neurological outcomes induced by ZIKV infection, an unexpected increase in GBS cases (42 cases, representing a 20-fold increase in the incidence) occurred in the French Polynesia population during the epidemic of 2013–2014 [6]. Increased numbers of neurological manifestations in adults (manifested as GBS) and in infants born to infected mothers (microcephaly) also occurred in Brazil. According to the Pan American Health Organization alert [26], 76 patients with neurological syndromes and a recent history of ZIKV infection were identified, 42 of whom were diagnosed as GBS [26]. In the reported cases associated with ZIKV, it was suggested that GBS had an electrophysiological pattern compatible with acute motor axonal neuropathy (not necessarily related to neuronal cell death), resulting in generalized muscular weakness, with gait impairment and signs of facial paralysis [9, 22].

In 2016, the causal link between ZIKV infection and birth defects was confirmed [17, 27, 28] and the World Health Organization (WHO) called Zika as a global health emergency [29] that ended in November 2016 [30]. ZIKV identification in fetal brain samples from infected mothers provided evidence that ZIKV is able to break through the biological placental barrier to infect developing neural cells [28], leading to neuronal death and consequently reduction of the occipital-frontal head circumference of the newborn below the average of its gestational age, gender, and race, a condition known as microcephaly [31, 32]. Then, the WHO adopted additional diagnostic criteria for ZIKV infection beyond head circumference measurement in newborns. These include evaluation of the presence of ophthalmological and auditory complications, and changes in bone and joint formation, suggesting that severe microcephaly is only the "tip of the iceberg." This scenario is even more worrying since many children who were born in Brazil from the recent epidemic in 2015 and considered healthy at the time, may develop important consequences in the future [17, 33]. The risk of microcephaly may range from 0.88% to 13.2% if ZIKV

infection occurs in the first trimester of pregnancy. However, little is known about the neurological and psychiatric consequences in the long term. Ongoing follow-up studies with children affected by ZIKV during the recent epidemic in Brazil will help to address these questions. Accordingly, Satterfield-Nash et al. [41] showed that among 19 children with the diagnosis of microcephaly, who were followed from birth until 24 months of age, the majority presented severe motor dysfunction, visual and auditory abnormalities, epilepsy, and sleep problems. Migration, organization, and neuronal myelination may be impaired by central nervous system (CNS) infection, leading to different conditions, such as brain malformations and "functional" neuropsychiatric syndromes, including intellectual disability and autism.

According to Moore et al. [34], five important features differentiate congenital Zika syndrome from other congenital infections: severe microcephaly with the partially collapsed skull, thin cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, and also marked early hypertonia with symptoms of extrapyramidal involvement.

Microcephaly may develop during the gestational period or after the birth of the neonate [8, 35, 36]. The first is usually caused by changes in neurogenesis or death of neuronal progenitor cells (NPCs) [8]. Experimental evidence has shown that the regulation of NPC numbers and subtypes is essential for controlling brain size and morphology. For example, significant reduction in the number of these cells due to cell death, cell cycle arrest, or premature neuronal differentiation can reduce the size of the developing brain and, consequently, induce microcephaly [28, 37–39]. Microcephaly seems to be the worst scenario, but neonates born to ZIKV-infected mothers presented other neurological and fetal development manifestations defined as congenital Zika syndrome [40]. Experimental models corroborate this. Nem de Oliveira Souza and colleagues [42], using Swiss mice inoculated with ZIKV at day three after natural birth, showed the occurrence of postnatal microcephaly and behavioral changes during adulthood, as demonstrated by the increase in incidence of seizures, motor, and cognitive dysfunctions in the offspring [42]. ZIKV maternal infection of mice lacking type I and II Interferon (IFN) receptors resulted in transient hearing loss as well as a restriction of offspring growth, although no motor or cognitive deficits were observed in adulthood [43]. In a model of maternal infection during fetal development, DENV-specific antibodies in pregnant mice infected with ZIKV increased vertical transmission of ZIKV and led to a phenotype consistent with microcephaly which was dependent on the neonatal Fc receptor, FcRN [35]. Camargos and colleagues [36] have recently shown that congenital ZIKV infection induced several congenital deficiencies in immunocompetent mice, from embryonic phase to adulthood, such as decreased total brain volume, ophthalmologic abnormalities, changes in testicular morphology, and rupture in bone microarchitecture. Moreover, treatment with an antiviral amphipathic α-helical (AH) peptide during the early stages of pregnancy seems beneficial during early maternal infection by ZIKV.

Although ZIKV presents tropism to several body tissues and fluids, including brain, eyes, testes, female genital tract, placenta, spleen, liver, saliva, tears, semen, and urine [44], it is the nervous system tropism that accounts for most of its clinical relevance. ZIKV can infect almost all cells of the brain, from neurons and glial cells

to endothelial cells and pericytes [45]. Such tropism potentially impairs brain growth and results in microcephaly and other neurological conditions [44, 46]. The mechanism by which ZIKV exerts these effects has been recently investigated and involves: (i) induction of neuronal excitotoxicity [45]; (ii) infection, activation, and apoptosis of neural progenitor cells, mature neurons, and glial cells with concomitant inflammation [46–48]; (iii) and neuronal autophagy [49]. In the following sections, we will describe these mechanisms.

2 Neuronal Death Induced by ZIKV

2.1 ZIKV-Induced Excitotoxicity

ZIKV exhibits high neurotropism and can cause a massive neuronal damage, especially to NPCs [46, 50]. The CNS utilizes glutamate as the major excitatory neurotransmitter. In homeostatic conditions, glutamate plays a key role in neural development, synaptic plasticity, learning, and memory [51]. Once released, glutamate exerts its effects via activation of different ionotropic and metabotropic receptors. The metabotropic receptors are G-coupled protein receptors named mGluR, and based on sequence homology, second messenger coupling, and pharmacology, they are categorized into three groups: group I (mGluR 1 and 5), group II (mGluR 2 and 3), and group III (mGluR 4, 6, 7, 8). The ionotropic receptors are voltage-dependent ionic channels, and the three main ionotropic receptors are N-methyl-d-aspartate (NMDAR), α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor (AMPAR), and kainate receptor (KAR) [52, 53].

NMDAR-mediated cell signaling pathways located at synaptic sites are involved in neuronal survival as well as in neuroplasticity [54]. NMDARs are calcium-permeable cation channels widely distributed in neurons, inducing different intracellular responses [55]. They are composed of four subunits derived from three families: GluN1, GluN2, and GluN3, forming a heteromeric structure. GluN1 interacts with the GluN2 or GluN3 subunits to form a functional receptor. Classically, NMDAR requires two GluN1 subunits, which bind to glycine, and two GluN2 subunits that bind to glutamate. The activation of the NMDA receptor requires two molecules of glutamate and two molecules of glycine. Glutamate binding and activation of NMDA receptors open the cation channel within the receptor resulting in neuronal depolarization by triggering NMDAR signaling dependent on intracellular Ca^{2+}. The activation of synaptic NMDARs stimulates the induction of genes related to plasticity and maintenance of neuronal homeostasis. However, an overactivation of NMDA receptors can deregulate cell homeostasis, leading to neuronal death, a phenomenon called excitotoxicity. Actually, excitotoxicity is an induced neuronal death process in response to different insults, such as ischemia, traumatic brain injury, viral infections, and neurodegenerative conditions [56, 57].

Glutamate-induced excitotoxicity and neuronal damage is mediated mainly by NMDA receptors. Indeed, the use of NMDAR antagonists is capable of modulating

receptor activity negatively and preventing neuronal death both in vivo and in vitro. In the context of ZIKV infection, the blockade of NMDAR by an FDA approved allosteric antagonist used to treat Alzheimer's disease, Memantine, prevented the increase of intraocular pressure, and reduced microglial activation and neurodegeneration induced by ZIKV in the brain of type I interferon (α/β) receptor ($IFNAR^{-/-}$) deficient mice [45]. In vitro studies confirmed these findings and showed that ZIKV actively replicates in primary neurons triggering excitotoxicity and leading to massive decrease of synapses and neuronal cell death [45, 58]. Olmo et al. [59] also demonstrated that ZIKV induces cellular apoptosis through a nonautonomous mechanism dependent on increased levels of extracellular glutamate and production of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1β. Together these factors induced NMDAR's overactivation by promoting excitotoxicity and, consequently, neuronal cell death. Interestingly, the single blockade of TNF-α or IL-1β with etanercept or IL-1RA, respectively, resulted in partial amelioration of Ca^{2+} intake and neuronal cell death. Similarly, treatment with Ifenprodil, a GluN2B specific-subunit NMDAR, was able to decrease intracellular Ca^{2+} levels and increase the activation of the pathways involved in cell survival, including Extracellular signal-regulated kinases (ERK) and cAMP response element-binding protein (CREB).

In sum, NMDAR blockade by Memantine prevented ZIKV-induced cell death in vivo and in vitro without affecting the ability of the virus to replicate in these systems. Meanwhile, viral replication in target cells seems to be important to neuronal cell death induction [60, 61]. Jackman et al. [62] have shown that the therapeutic administration of brain-penetrating antiviral peptide (AH-D) to ZIKV-infected mice protected against mortality and markedly reduced clinical symptoms, suppressed efficiently viral load and neuroinflammation, mitigating neurodegeneration, and brain damage. Furthermore, AH peptide protected against lethal ZIKV infection in primary neuronal cells and exhibited antiviral activity in vitro [60–65] and in vivo, in both adult and offspring of ZIKV-infected dams [36, 60].

It is important to evaluate whether the combination of neuroprotective drugs, such as Memantine, and antiviral drugs could be an effective strategy against ZIKV infection and related complications. Future approaches must also target other mechanisms of neuronal cell damage resulting from ZIKV infection. The use of these drugs might open new perspectives for the treatment of ZIKV infection, especially for patients at risk of complications, such as pregnant women during the early stages of pregnancy.

2.2 ZIKV-Induced Neuronal Death Is Associated With Microgliosis and Astrogliosis

Along with the mechanisms depicted above, nonneuronal cells can contribute to ZIKV-induced neuronal death. Although ZIKV is characterized by neurotropism and neurovirulence, the virus can infect nonneuronal cells of the CNS, including microglia and astrocytes [47, 48, 66, 67].

Microglia cells are the brain's resident macrophages that deal with tissue insults. In homeostatic conditions, microglia are characterized by a small cell body and high numbers of ramifications actively "looking for" signs of pathogens and damage. When challenged, these cells become activated: their processes retract completely, the cell body changes into a round shape so they can move, release mediators, and phagocyte more efficiently [68]. Astrocytes are the other abundant glial cell type of the CNS. They provide neuronal support in homeostatic conditions, but also become immunologically active after neural insults. Astrocytes keep healthy the chemical environment and uptake neurotransmitters in order to allow an optimal function of neurons. In response to challenges, such as viral infections, these cells can increase in number and change their morphology and function. This is known as astrogliosis, a phenomenon quite relevant in the brain's active response to potential damages [69]. Both microglia and astrocytes synthesize a plethora of mediators, including IL-1β, TNF-α, glutamate, nitric oxide (NO), and others, that can trigger neuronal death after ZIKV infection [45, 48, 59, 67, 70–72].

Microglia activation and astrogliosis have already been detected in the ZIKV-infected nervous tissue. The brain tissues of microcephalic ZIKV-positive neonates with fatal fate exhibited high numbers of $S100^+$-astrocytes and $CD68^+$ or $CD163^+$-microglia/macrophages among the inflammatory cells of parenchyma [48]. Similarly, ZIKV-infected microglia-like and astrocyte-like cells were frequently observed in the brain of newborns with microcephalia [71]. Noteworthy, these cells were found especially in cortical areas with neuronal depopulation. Murine experimental data mimicked this human evidence [45, 59]. Intracerebral inoculation of embryonic mice with ZIKV triggered extensive microglial activation and astrogliosis as detected by IBA-1^+ and $GFAP^+$ immunostaining, respectively. Such phenotype was associated with significant death of NPC and neurons in the developing brains. ZIKV infection culminated in increased caspase-3 and TUNEL staining of NPC and neurons, which are classical apoptotic markers [73, 74].

Besides direct ZIKV-induced neuronal damage, apoptosis can result from mediators released by the activated microglia. There is strong evidence supporting the role of proinflammatory cytokines in neuronal death in vivo and in vitro. However, it is still debatable whether the cause of neuronal death is mainly due to direct neurotoxicity or secondary to the activation of microglia and astrocytes.

ZIKV-infected neurons express high levels of TNF-α, IL-1β, and glutamate which, in turn, trigger cell death of uninfected neurons [45, 59]. Regarding glia activation, in vitro data clearly show that ZIKV induces inflammasome activation in glial cells which finally results in the release of IL-1β [67, 70, 72]. Similarly, inflammasome activation and IL-1β, IL-18, IL-33 expression were detected in the neural parenchyma of fetal ZIKV-induced microcephaly cases [71]. Azevedo et al. [48] also observed increased expression of IL-1β and TNF-α in the ZIKV-infected brain samples concurrent with apoptotic neuronal events. These cytokines released by glial cells, especially TNF-α and IL-1β, can induce neuronal apoptosis by activating caspase-8 and necroptosis when RIP1, RIP3, and MLKL, but not caspase-8, are activated [75]. Accordingly, the blockade of TNF-α or IL-1β with etanercept and IL-1RA, respectively, resulted in partial amelioration of Ca^{2+} intake and neuronal

cell death [59]. Other mechanisms may include release of Fas ligand and/or cathepsin B by activated glial cells that can be neurotoxic and trigger neuronal apoptosis [76, 77].

Aside from proinflammatory cytokines, the mononuclear inflammatory infiltrate, also containing glial cells, was positive for the expression of iNOS and arginase 1 in the neural parenchyma of ZIKV-infected brains [48, 71]. The expression of these enzymes was intense in areas containing dead neurons, including necrotic, apoptotic, and vacuolated neurons. Usually, iNOS expression is not constitutive in the brain. It is the challenge associated with ZIKV infection (and other stressing agents) that raises iNOS expression by microglia and astrocytes and, consequently, increases their potential neurotoxicity. In a plethora of cells, increasing iNOS and NO release can trigger necrosis of surrounding cells via inhibition of mitochondrial cytochrome oxidase and glycolysis, or via inducing mitochondrial permeability transition. High NO levels can activate p53 oxidation, induce p38 MAPK pathway or stress the endoplasmic reticulum, triggering neuronal apoptosis [78]. Also, increased NO levels associated with microglial NADPH oxidase activation may result in neuronal apoptosis mediated by peroxynitrite. Moreover, NO can induce astrocytes to release glutamate, so excitotoxicity mechanisms can be activated [72, 79].

In addition to these potential mechanisms of ZIKV-induced neuronal death by nonneural cells, activated microglia can also phagocyte stressed-but-viable neurons, resulting in neuronal depopulation. The stress associated with the proinflammatory mediators released by glial cells may induce phosphatidylserine exposition by neurons, which, in turn, trigger their phagocytosis by active microglia. Peroxynitrite and glutamate, mediators already detected in ZIKV-infected brain tissues, can induce neurons to expose phosphatidylserine at least transiently, and this is a classical “eat-me” signal [80]. Therefore, besides the direct damage induced by ZIKV in the CNS, neuronal death can also occur indirectly via activated glial cells.

3 Autophagy Regulation During ZIKV Infection

Autophagy is a highly conserved intracellular process among eukaryotic organisms that involves cargo transportation from cytoplasm to lysosomes for subsequent degradation via double-membrane autophagosomes, contributing to the maintenance of cellular homeostasis [81]. This process occurs physiologically in almost all cells of an organism, though it has greater importance in specific cell types. Autophagy can also contribute to cell death when excessively induced [82]. In neurons, there are several molecules that are produced and degraded to maintain their dynamic functions. Due to its normally nondividing nature, tight control of autophagy is essential to sustain cell homeostasis and, as consequence, nervous system development, neuronal activity, and survival. Hence, defects in autophagy pathway are related to the development of several neurodegenerative diseases [83, 84].

The degradation-targeted content includes bulk cytoplasm, organelles, aggregate-prone proteins involved in neurodegenerative process and several pathogens [85].

There are three types of autophagy: (i) microautophagy, in which the cytoplasmic cargo is transported directly into lysosome for degradation mediated by acidic hydrolases; (ii) chaperone-mediated autophagy, in which unique proteins containing specific targeting motif are recognized and carried to lysosome by a chaperone complex; and (iii) macroautophagy, in which cytosolic material is degraded after sequestration into autophagosomes that subsequentially fuses with lysosomes. The latter is the most investigated and will be referred here as autophagy [86, 87]. Autophagy can also be classified according to its specificity: the canonical or bulk autophagy as described above, which sequestrates random components of cytosol for degradation, and the selective autophagy, which involves specialized autophagosomes confining substrates in a selective mode [88]. So far, studies have demonstrated a possible dual role for autophagy in terms of promotion and inhibition of viral replication.

Some studies have shown that ZIKV infection in vitro increases autophagy induction. Although autophagy can restrict viral replication by mediating viral protein degradation, it can be subverted by some viruses that use components of autophagy pathway to promote their own replication [89]. Liu et al. [90] investigated a transcription profile of *Drosophila* flies infected with model virus *Drosophila* C (DCV) and identified several induced genes related to "defense response to bacterium," including *CG1667*, which is an important innate regulator gene and the fly ortholog of Stimulator of Interferon Gene (STING). ZIKV was also able to induce *d*STING expression, which resulted in induced autophagy in the fly brain upon ZIKV-infection. Increased autophagosome formation was also observed in different cell types, such as primary skin human fibroblasts [89], human fetal neural stem cells (fNSC), mouse embryonic fibroblasts (MEFs), HeLa [91], human neural progenitor cells [92], human cytotrophoblasts JEG-3 [93], and human umbilical vein endothelial cells (HUVEC) [94]. Liang and colleagues [91] showed that ZIKV replication is reduced in cell lines lacking different autophagy proteins (Atg). Moreover, autophagy induction by rapamycin resulted in increased ZIKV replication in fNSCs and HeLa cells, while the inhibition of this process occurred upon 3-MA or chloroquine treatments and led to reduced ZIKV replication [91]. Liang and colleagues [91] showed that autophagy induction is mediated by viral NS4A and NS4B proteins which inhibit Akt-mTOR signaling pathway and contribute to neurogenesis impairment in fNSC [91]. In addition, Cao et al. [93] showed that autophagy is activated during ZIKV-infection of mouse placenta. Finally, ZIKV infection was reduced in placentas, but not in maternal serum or spleen, in mice lacking Atg16L1, a key gene in autophagy process. This resulted in decreased placental damage, fetal growth restriction, and viral loads [93]. These results suggest that ZIKV-induced autophagy contributes to viral replication and possibly to the pathogenesis of ZIKV infection.

On the other hand, the autophagy response during infection might result in different outcomes depending on the type of the target cell. Some studies have shown that autophagy can have protective effects upon ZIKV infection. Liu and collaborators [90] showed that ZIKV infection in *Drosophila* brains activates Immune Deficiency pathway (IMD) but not Toll pathway, followed by NF-κB activation,

which was associated with limitation of viral replication. Viral restriction was associated with *d*STING-mediated autophagy activation upon ZIKV infection. Autophagy inhibition led to increased ZIKV RNA levels in whole flies and heads, culminating in fly death. When the specific autophagy cargo receptors Ref (2)P (p62 ortholog) and Bchs (ALFY ortholog) were depleted, increased ZIKV infection in whole flies and heads were observed only upon Ref (2)P blockade. Indeed, these results were confirmed when flies were fed with rapamycin, a potent activator of autophagy, which resulted in protection against ZIKV infection [90].

Finally, some studies have shown that, during flavivirus infection, there is a growth and expansion of endoplasmic reticulum (ER) membranes which is essential to viral replication complex formation [86, 95]. Lennemann and Coyne [96] showed that ZIKV is able to prevent ER degradation by antagonizing reticulophagy, a specific autophagy of ER. This inhibition is caused by viral protease NS3-mediated cleavage of reticulophagy regulator 1 (FAM134B), which blocks the reticulophagy-specific autophagosomes formation. Accordingly, increased viral replication was observed when FAM134B is downregulated by interference RNA (iRNA) in human brain microvascular endothelial cells. These findings suggest that ZIKV specifically target this pathway to promote viral replication [96]. Altogether, while bulk autophagy is upregulated to promote early ZIKV infection, the viral proteins act later to prevent reticulophagy in order to support viral replication [49, 86]. Nonetheless, these contradicting results highlight the importance of investigating tissue-specific responses during viral infection to define an appropriate therapeutic strategy against ZIKV infection.

4 Conclusion

ZIKV has emerged as a public health problem worldwide, especially due to its association with increased neurological conditions, such as microcephaly, GBS, and CSZ. ZIKV has remarkable tropism to the nervous system, infecting CNS cells, such as neuronal and glial cells. Some consequences of the infection involve massive neuronal damage and neurodegeneration, as well as astrogliosis and microgliosis. Mechanisms by which ZIKV induces cell death include the release of inflammatory mediators, such as TNF-α, IL-1β, glutamate, and NO. Such inflammatory scenario culminates in massive intracellular Ca^{2+} influx and deregulated cell homeostasis, leading to neuronal excitotoxicity mediated by activation of nonneuronal cells. ZIKV replication by itself may induce neurodegeneration and glial cell activation. Finally, autophagy seems to play a dual role during ZIKV infection and neurodegeneration induction. These proposed mechanisms involved in ZIKV-induced neuronal death are illustrated in Fig. 1. Overall, it is important to continue investigating the mechanisms by which ZIKV induces neuronal death and whether the combination of neuroprotective and antiviral drugs could be an ideal treatment for ZIKV infection.

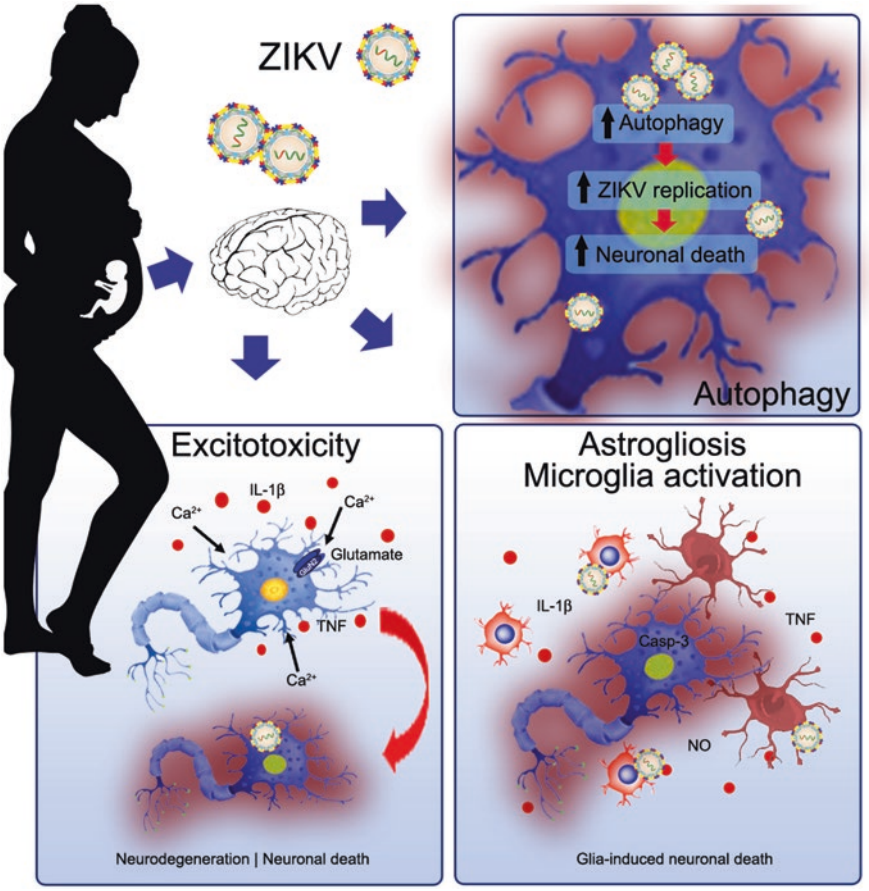

Fig. 1 Mechanisms involved in ZIKV-induced neuronal death. ZIKV infects neurons that release inflammatory mediators, including TNF-α, IL-1β, nitric oxide, and glutamate, which lead to neuronal excitotoxicity. Glial cells can also be infected by ZIKV and trigger inflammatory-mediated neuronal death of infected and noninfected neurons via caspase-3 apoptosis. ZIKV increases neuronal autophagy which, in turn, favors ZIKV replication and, consequently, enhances neuronal death

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The Immune Responses at the Fetomaternal Interface

Moisés Evandro Bauer and Priscila Vianna

Abstract During gestation, the maternal immune system is in direct contact with the fetus, with genetic material not only from the mother but also from the father. To prevent the fetus from being identified as a "foreign body," the maternal immune system must adapt to this new challenge, inducing changes that maintain the gestation until a successful outcome: the birth of the baby. We describe here the several mechanisms that work together to protect the fetus from immunological recognition and rejection. These alterations are developed to create a tolerogenic niche in which the semiallogeneic fetus can develop. More specifically, this chapter focuses on the cellular and molecular changes related to innate and adaptive immunity that occur at the fetomaternal interface. The understanding of the fetomaternal immune cross talk is helpful in getting insights into the pathogenesis of pregnancy complications as well as poor postnatal health.

Keywords Fetomaternal immunity · Lymphocytes · Inflammation · Cytokines · HLA-G · Pregnancy

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1 Introduction

The progression of the gestation, the birth of the baby, and milk production encompass well-planned sequential biological steps aimed to welcome the new-born. The immunological cross talk between mother and child occurs throughout the gestational period and is maintained during breastfeeding. Breastfeeding transfers antibodies (IgA and IgG) from the mother to the child, and this passive immunity is of paramount importance to protect the child from infections.

During pregnancy, the female body undergoes several hormonal and physical changes, as well as changes in the maternal immune system. The maternal immune system needs to tolerate the fetus, which is considered a semiallogeneic tissue because of 50% of paternal genetic material. In 1953, the Brazilian-born British immunologist Peter Medawar (1915–1987) and Nobel Prize winner of Physiology and Medicine in 1960 was the first to propose that the embryo behaves in the maternal organism as a transplant and, therefore, is subjected to rejection or immunological tolerance. Why is the fetus not rejected by the mother? In this chapter, we describe the main tolerogenic mechanisms involved in the establishment of successful pregnancies that initiate at the fetomaternal interface.

2 Placenta: The Fetomaternal Interface

Increasing evidence suggests that fetal immune tolerance is established at the placenta, a transient organ consisting of fetal trophoblasts and the maternal decidua developing from the uterine mucosa. The decidua harbors several maternal immune cells, and all of them interact intensively with fetal-derived trophoblasts and up to 40% of decidual cells are leukocytes. The fetomaternal interface is composed of the maternally derived decidua and the placenta, derived from the fetus (Fig. 1).

During fetal implantation, invading trophoblasts attach the blastocyst to the decidua (uterine epithelium) where the placentation takes place. During pregnancy, the placenta is the main tissue for all nutrient, gas, and waste exchange between the fetus and mother. During the formation of the decidua, there is a remodeling of spiral arteries mediated by fetal and maternal mechanisms; therefore, the placenta becomes bathed in maternal blood, facilitating exchange of nutrients, gases, and waste. After embryo implantation, the endothelial lining of the spiral arteries is eroded (as seen in decidual stromal cells), producing a fibrinoid wall surrounded with invading fetal placental trophoblasts [4]. The maternal macrophages and natural killer (NK) cells have been implicated in this remodeling process. These coordinated mechanisms result in the vasodilation of the spiral arteries, decreasing the force and maximizing the volume of the maternal blood bathing the placenta.

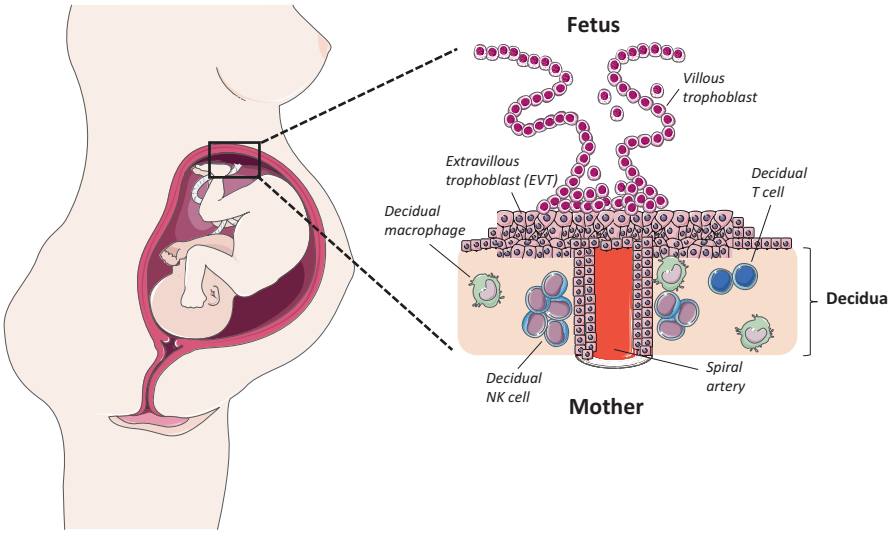

Fig. 1 The cellular composition at the fetomaternal interface. The human placenta has an external layer composed of extravillous trophoblasts (EVT), which are HLA-G+ cells, and floating villi containing MHC-negative villous trophoblasts. The EVT are produced in cell columns and invade the decidua, mediating the placental attachment of the fetus. The decidual NK cells are the most numerous leukocytes at the fetomaternal interface, and play roles including the control of viral infections in the placenta as well as promoting the development of spiral arteries and trophoblast invasion. Other important decidual leukocytes are macrophages, dendritic cells, and T cells—all of them importantly engaged in establishing tolerance to the semiallogeneic fetus [18]

3 The Innate Immune Responses at the Fetomaternal Interface

The maternal immune responses in healthy pregnancy have been conceptualized as anti-inflammatory (or Th2-type) since inflammation has been mainly associated with negative pregnancy outcomes. However, this is an oversimplified view. Actually, the first trimester of pregnancy is marked by an inflammatory profile favoring the embryo implantation and angiogenesis [7]. During the early embryo implantation, there are high levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-15) and chemokines (e.g., CCL2, CXCL8, and CXCL10) at this niche.

Following this critical period, the inflammatory maternal immune responses must be continuously suppressed until the last weeks of gestation when inflammation is triggered again to induce labor (Fig. 2). Therefore, a successful pregnancy depends on the capacity of the maternal immune responses to change and adapt to each specific developmental stage.

In this section, we discuss the regulatory roles of major innate immune cells at the fetomaternal interface.

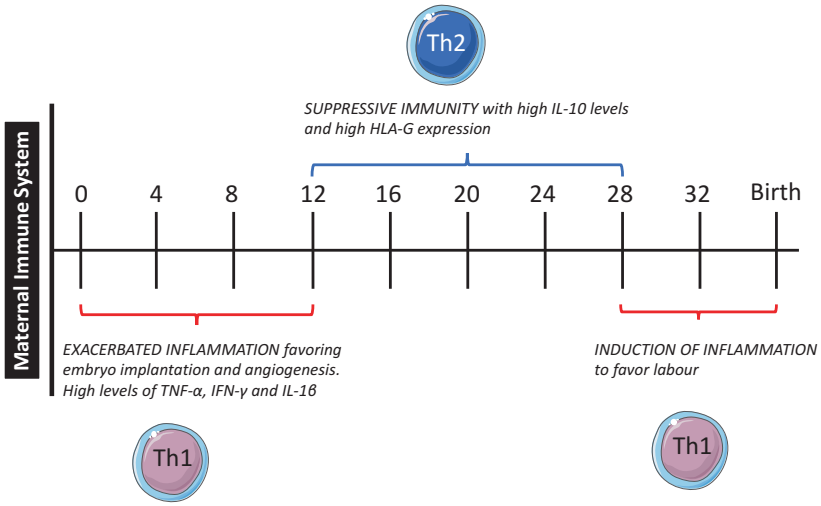

Fig. 2 Normal development of maternal immune responses during pregnancy. The maternal immune system adopts proinflammatory and anti-inflammatory characteristics at the different trimesters of pregnancy, promoting fetal survival and development

3.1 Decidual NK Cells

In the first trimester, at the site of fetal implantation and trophoblast invasion, the decidual NK (dNK) cells represent up to 70% of immune cells, followed by macrophages (20–25%) and T cells (3–10%) [30]. These immune cells are recruited by the chemokines produced by decidual stromal cells and trophoblasts.

The dNK cells of pregnancy differ from the circulating NK cells. They are highly granulated and can be phenotyped as $CD56^{brigh}CD16^{dim}$. The dNK cells secrete several growth factors, cytokines, and angiogenic factors that help remodel the decidua and spiral arteries, promoting the trophoblast invasion and increasing the supply of maternal blood at the fetal implantation. The secretion of interferon (IFN)-γ leads to dilation of spiral arteries in mice, whereas the production of IL-8 and CXCL10 by dNK cells has been implicated in inducing the implantation of extravillous trophoblasts (EVTs) into the placental bed [21]. The dNK cells accumulate around spiral arteries and may lead to the disruption of the vascular wall by the secretion of matrix metalloproteinases (MMPs) that break down the vascular endothelium [22]. The dNK cells interact with fetal trophoblasts through several cell-surface receptors (Fig. 3). Of note, the dNK cells have been shown to express killer immunoglobulin receptor (KIR), CD94/NKG2A, and ILT2, which are receptors to HLA-C, HLA-E, and HLA-G, respectively, expressed by trophoblasts [30]. These receptors play important roles in inhibiting dNK cells in close contact with fetal tissues.

Unlike most cells, the EVT cells do not express HLA-A and HLA-B, which are highly polymorphic receptors dedicated to antigen presentation to $CD8^+$ T cells. The expression of HLA-C and the nonclassical low-polymorphic HLA-E and

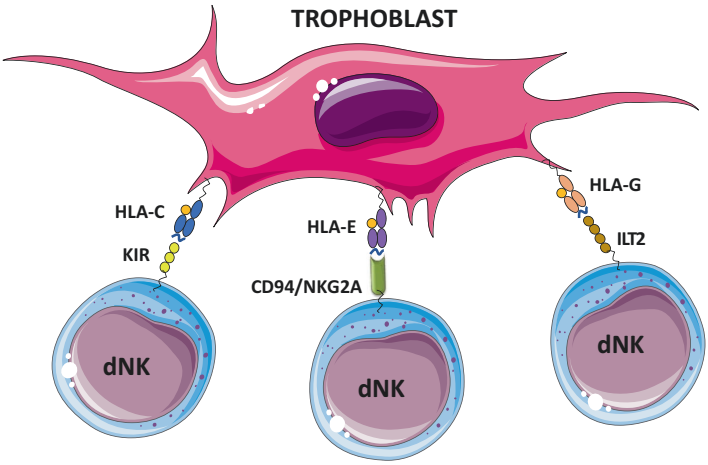

Fig. 3 Decidual NK cells (dNK) bind to trophoblasts expressing HLA class I molecules. The dNK cells interact with fetal trophoblasts through several cell-surface receptors. These receptors play important roles in inhibiting dNK cells in close contact with fetal tissues [30]

HLA-G by EVT cells is an important strategy to limit cellular recognition and destruction by maternal cytotoxic T lymphocytes.

In the absence of classical HLA class I molecules, as observed in many tumors, the NK cells could be easily activated. KIRs are highly expressed by dNK cells as compared to circulatory NK cells, indicating that most dNK cells are involved with HLA-C recognition in the decidua. The engagement of these inhibitory receptors is known to protect fetal trophoblasts from NK-mediated cytolysis and, therefore, is pivotal for the induction of maternal tolerance to the semiallogeneic fetus.

The lack of dNK cells during pregnancy in mice is associated with decreased fetal viability and anatomical alterations in the decidua and spiral arteries at the site of fetal implantation. The specific deletion of dNK cells leads to poor endometrial vascularity and impedes trophoblast invasion [21]. Similarly, there are significantly fewer dNK cells in the endometrial tissue in patients with inexplicable infertility than in fertile women [28]. The specific deletion of decidual DCs results in decidual malformation and poor vascularization of endometrium, impairing the blastocyst implantation [39]. Therefore, the immune infiltrates are required for successful pregnancies, further suggesting that immune cells are not solely recruited to the decidua as a response to "semiallogeneic" fetus, but also actively recruited to facilitate proper implantation and to promote a successful pregnancy [33].

The amounts of dNK cells at the fetomaternal interface are maintained by several local factors, including cues provided by other immune cells. For instance, it has been shown that myeloid-derived suppressor cells (MDSCs) depletion causes pregnancy loss in mice via upregulating the cytotoxicity of dNK cells [42]. The release of vasoactive intestinal peptide (VIP) by EVTs contributed to the EVT outgrowth, and increased the IL-10 release, whereas it decreased the production of pro-inflammatory cytokines by EVTs and dNK cells [37]. Therefore, a more profound

understanding of the biological changes in early pregnancy is of paramount importance for the diagnosis, prevention, and treatment of fertility/pregnancy issues in women.

3.2 Macrophages and Dendritic Cells

The decidual macrophages ($CD14^+$) constitute the most important antigen presenting cells (APCs) at the fetomaternal interface during the first trimester of gestation. Macrophages are usually grouped into two categories: classically pro-inflammatory macrophages (M1) and alternatively regulatory macrophages (M2). These two subsets can be discriminated by differential aspects concerning their effector functions, expression of cell surface markers, and cytokine secretion. The M1 macrophages are engaged in inflammatory responses by producing TNF-α, IL-12, IL-23, and reactive oxygen species, and being involved in Th1-mediated immune responses, whereas M2 macrophages have regulatory and suppressive properties by participating in tissue remodeling and promoting the Th2-type response [34].

The polarization of decidual macrophages is skewed toward M1 at the embryo implantation after which they begin to transition to a mixed M1/M2 profile when the trophoblasts attach to the endometrial lining and invade the uterine stroma [30]. Similarly to dNK cells, following the implantation period, the uterine macrophages are phenotypically characterized as M2 phenotype with homeostatic and anti-inflammatory properties [4]. This phenotype is largely influenced by local trophoblasts which secrete important cytokines involved in promoting this regulatory type of macrophage (e.g., IL-10 and macrophage colony-stimulating factor, M-CSF). The decidua macrophages play several roles during the pregnancy, including remodeling the spiral arteries and trophoblast invasion [43], promotion of angiogenesis [22], and induction of tolerance of the semiallogeneic fetus. The latter seems to be mediated by the expression of indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan and induces regulatory T cells [55]. The decidua macrophages may also play important scavenger roles at the fetomaternal interface through the phagocytosis of apoptotic trophoblasts, preventing the release of paternal antigens that could trigger a maternal immune response against the fetus [2].

Dendritic cells (DCs) are very important APCs extensively found in both mouse and human decidua. Myeloid DCs, the major blood subset, are engaged in promoting Th1 polarization and generation of inflammatory responses, whereas the plasmacytoid can generate Th2 responses [1]. During healthy pregnancies, the circulating myeloid DCs are highly tolerogenic and undergo partial inactivation with decreasing numbers during the third trimester [30]. DCs play a pivotal role in the maintenance of fetal tolerance. These cells have dual (and opposite) functions during pregnancy as they either prime the activation of T cells as mature APCs or induce tolerance by the induction of T-cell apoptosis and expansion of regulatory T cells (Treg, $CD4^+CD25^+FoxP3^+$) [52]. It has been shown that anti-paternal HLA antibodies are produced via presentation of fetal antigens by APCs at the fetomaternal

interface [17]. Conversely, in healthy pregnancies in mice and humans, the DCs are usually in a tolerogenic state (tDCs) with limited antigen presentation, reduced expression of co-stimulatory molecules, and higher IL-10 production [12]. The tolerogenic actions of DCs are mediated by galectin-1 [12], glucocorticoids (whose levels increase during gestation), and vitamin D [5].

4 The Adaptive Immune Responses at the Fetomaternal Interface

The adaptive immune system is composed by antigen-specific lymphocytes (T and B cells) and secreted antibodies. The adaptive immune system is fully integrated with the innate immune system, receiving important activation cues as well as providing regulatory mechanisms to avoid overshooting of inflammatory responses. The adaptive immune responses are generated in the secondary lymphoid organs, including the lymph nodes, spleen, and mucosa-associated lymphoid tissue. There are two major subpopulations of T cells, namely $CD4^+$ and $CD8^+$ (cytotoxic) T cells. In accordance to environmental cues provided by interactions with antigens and/or tissues, the $CD4^+$ T cells are differentiated into effector subtypes: type 1 (Th1) helper T cells, secreting TNF, IL-2, and interferon (IFN)-γ; type 2 (Th2) helper T cells, which secrete IL-4, -5, -6, and 10; and type 17 (Th17), secreting IL-17 and IL-22 [1].

Decidual T cells comprise around 5–15% of placental leukocytes during the first trimester of gestation, reaching up to 70% at term pregnancy [18]. In this section, we will discuss the role of major effector T cells at the fetomaternal interface.

4.1 $CD4^+$ T Cells

All major $CD4^+$ subsets are involved in healthy and pathological pregnancies. Th1 cells can produce TNF-α, which promotes inflammation. Consequently, these cells have been involved in pregnancy pathologies threatening fetal survival. Indeed, early studies demonstrated that spontaneous abortions are associated with increased decidual Th1/Th2 ratios [38]. In addition, peripheral blood mononuclear cells from women with unexplained recurrent abortions produce more Th1-type cytokines in vitro following culture with trophoblast antigens as compared to normal parous women [24]. Therefore, healthy pregnancies involve a bias toward Th2 responses at the fetomaternal interface as well as in the peripheral tissues of the mother, minimizing the action of Th1 cells. However, it should be noted that a second pro-inflammatory stage (Th1) is responsible for parturition [33]. In other words, a successful pregnancy depends on the ability of the maternal immune system to change and adapt to each specific developmental stage.

Th17 cells may also be involved in pathological pregnancies because of their pro-inflammatory actions. In mouse models, IL-17 induces fetal loss and anti-IL-17 antibody prevented fetal loss [61]. Patients with pre-eclampsia (PE) had higher serum levels of IL-17 than healthy pregnant women [32]. The timing in assessing cytokines associated with pathological pregnancies may be crucial as a recent study from our group reported low IL-17 levels in the peripheral blood of women just after spontaneous abortion [27]. Previous studies have investigated potential circulatory mechanisms involved in driving Th17 responses during pathological pregnancies. Th17 cells are differentiated from naïve $CD4^+$ T cells under influence of high levels of IL-6 and low levels of TGF-β [10]. Increased serum IL-6 levels found in PE may contribute to the differentiation of Th17 cells [48]. In addition, the high levels of serum TGF-β glycoprotein receptor found in PE could reduce the TGFβ signaling necessary for driving Th17 cell differentiation [29].

Regulatory T (Treg) cells play an important role in healthy pregnancies as they have suppressive properties involved in immune tolerance to self and foreign antigens [60]. Increased number of Treg cells on the day of embryo transfer was associated with higher embryo implantation rates [58]. Moreover, several studies demonstrated that the frequency of decidual Treg cells increases during pregnancy in mice and humans [31, 53, 62].

Two major subsets of Treg cells ($CD4^+CD25^+FoxP3^+$) can be identified: natural Treg (nTreg), generated in the thymus from T-cell precursors, and induced Treg (iTreg), generated in secondary lymphoid organs from naive $CD4^+$ T cells [1]. A recent study showed that the frequency of nTreg cells in the decidua was over 90%, that is, much higher than the percentage in the peripheral blood [26]. These cells were found significantly reduced in miscarriage cases. Experimental studies performed in mice have also demonstrated the important roles of Treg cells at the feto-maternal interface. A depletion of $CD25^+$ Treg cells led to gestation failure in mice, confirming the role of Treg cells in tolerization against fetal antigens [3]. Another study observed that Treg cells play a crucial role in mediating maternal tolerance to allogeneic fetuses in the implantation phase and early pregnancy but not late pregnancy in allogeneic mice [49]. Effects of iTreg depletion on PE, fetal growth restriction, and premature birth remain to be tested.

Human studies supporting the role of Treg cells in maintaining fetomaternal immune tolerance have also been described in cases of spontaneous abortion. Women with spontaneous abortion had 33% reduction in peripheral $CD4^+CD25^+$ Treg cells as compared with uncomplicated pregnancies [46]. The proportion of Treg cells in peripheral blood and decidua was found significantly reduced in patients with PE [45]. In addition to the quantitative changes in Treg cells, previous studies have proposed that a lower suppressive capacity of maternal Treg cells may contribute to recurrent pregnancy losses since the production of IL-10 and TGFβ significantly reduced as compared with healthy controls [8]. Taken together, these data highlight the protective roles for Treg cells in maintaining fetal tolerance.

What are the factors driving the expansion and maintenance of Treg cells during healthy pregnancies? Successful pregnancy has been associated with the cross talk between hormones and the immune system. A previous study described a role for

the human chorionic gonadotrophin (HCG) hormone in this process [47]. The administration of HCG to mice increased the numbers and the suppressive phenotype of Treg cells. Of note, HCG treatment prevented fetal loss in abortion-prone mice. Interestingly, HCG has been suggested to improve pregnancy outcomes in patients undergoing in vitro fertilization (IVF) therapy, indicating that the positive effects of HCG on IVF might be due to the ability of this hormone to boost Treg cell activity.

Steroid hormones such as progesterone and endogenous glucocorticoids (GCs) increase during pregnancy and are essential for pregnancy maintenance as low levels of progesterone have been associated with spontaneous miscarriage and preterm labor [6]. Progesterone can shift the cytokine balance of immune responses toward an anti-inflammatory profile and may induce the expansion of $CD4^+$ and $CD8^+$ Treg cells at the fetomaternal interface [23]. A recent study indicated that high levels of progesterone during pregnancy induce a selective T-cell death by binding the glucocorticoid receptor [23]. $CD4^+$ Treg cells were refractory toward progesterone-induced cell death, resulting in a preferential enrichment of $CD4^+$ Treg cells.

Previous studies demonstrated the pivotal role of galectins, endogenous glycan-binding proteins, in promoting immune tolerance at the fetomaternal interface [12, 41]. Galectin-1 (Gal1) is synthesized by trophoblasts, stromal cells, and by maternal immune cells. Its expression is regulated by several factors including progesterone and HCG. Women with recurrent pregnancy loss showed considerably lower levels of circulating Gal1 [41] and Gal-1-deficient mice had higher rates of fetal loss compared to wild-type mice [12]. Treatment with recombinant Gal-1 prevented fetal loss and restored tolerance through multiple mechanisms, including the induction of tolerogenic dendritic cells and Treg cells in vivo. Through extracellular mechanisms, this lectin also signals apoptosis of Th1 and Th17 cells and suppresses pro-inflammatory cytokine production [11]. Therefore, Gal-1 is a pivotal regulator of fetomaternal tolerance that has potential therapeutic implications in at-risk pregnancies.

4.2 $CD8^+$ T Cells and B Cells

Notwithstanding considerably less research compared to $CD4^+$ Treg cells, the regulatory $CD8^+$ T cells are also implicated in fetal tolerance. The $CD8^+CD28^-$ Treg cells have similar suppressive actions as compared to nTregs or iTregs. There is a steady increased in $CD8^+CD28^-$ Treg cells during gestation [54], reaching higher levels in the last trimester, which coincides with the increased detection of fetal antigens systemically [35].

Functionally, the $CD8^+CD28^-$ Treg cells may dampen antibody production by B cells, and the frequency of B cells is low in human decidua [44]. This gestational dampening of B cells may contribute to fetal tolerance by protecting the placenta from the potential deleterious placenta-specific antibody-mediated effects [5]. The lack of $CD8^+CD28^-$ Treg cells may be associated with pregnancy complications, as

women with PE had significant lower frequency of these cells in the peripheral blood [57].

5 The Regulatory Actions of HLA-G at the Fetomaternal Interface

The HLA-G, a non-classical class I MHC molecule, plays important regulatory roles during pregnancy. The HLA-G is highly expressed at the fetomaternal interface (trophoblasts, amniotic membrane, and endothelium of chorionic vessels) and is also expressed by some subsets of monocytes, $CD4^+$ and $CD8^+$ T cells [18], being sometimes acquired by transfer of membrane-bound forms (a process known as trogocytosis).

The tolerogenic properties of this molecule are related to an immunosuppressive action (e.g., IL-10 production), inhibition of effector T cells, induction of Treg cell proliferation, and via inhibition of the cytotoxic activity of NK cells. The HLA-G also inhibits the function of cytotoxic T $CD8^+$ cells and DC maturation [13, 51]. Higher serum HLA-G levels were observed in successful pregnancies when compared with women with PE [19, 20].

6 Impaired Maternal Immunoregulation and Pregnancy Complications

A failure in adapting the maternal immunity during the developmental stages of the fetus may not necessarily affect the pregnancy, but can still interfere with fetal development. Indeed, dysregulated maternal immune responses have been involved in the pathogenesis of pregnancy complications, including low birth weight, preterm birth, and PE.

PE is the leading cause of both maternal/fetal complications and mortality, taking place in 5–10% of all pregnancies. It is a major cause of preterm births and restriction of intrauterine growth. PE is characterized by high blood pressure, proteinuria, and edema associated with organ damage and prematurity [50]. In addition, PE has been associated with poor placentation and angiogenesis, exacerbated maternal inflammatory responses, endothelial dysfunction, and placental hypoxia, although its etiology is largely obscure [57]. We have previously observed that women with PE had high levels of the pro-inflammatory cytokines IL-17, IL-2, and TNF-α, as well as IL-4 and IL-10, and an increased proliferative cell activation profile [57]. Although the frequency of natural Tregs ($CD4^+CD25^{high}FoxP3^+$) did not differ between healthy and PE pregnancies, patients with PE had low proportions of regulatory $CD8^+CD28^-$ T cells. These data corroborate the "immune system

maladaptation theory" that proposes that PE may occur when the maternal immune system does not adapt properly to the semiallogeneic fetus [16].

Pregnancy has been frequently associated with significant psychosocial stress. Of note, complicated pregnancies, such as PE, are commonly associated with mood disorders and anxiety. Several studies have shown that depression, anxiety, and neuropsychiatric conditions during pregnancy are important risk factors for fetal loss, premature birth, and low birth weight [25, 36]. Around 10% of pregnant women fulfill the criteria for major depressive disorder [59]. It has been shown that there is a positive association between maternal anxiety and depression and the development of PE [40]. In addition, PE increased nearly threefold the odds for developing postpartum depression compared to healthy women [14]. Higher levels of pro-inflammatory cytokines (TNF-α and IL-6) in maternal serum were associated with depressive symptoms during pregnancy [15]. These data may indicate that stress conditions contribute to the development of pregnancy complications including PE. The underlying mechanisms of stress-related PE are largely unknown. However, we have hypothesized that distress conditions (e.g., depression, anxiety) observed during pregnancy may induce PE by further increasing cortisol levels and reducing lymphocyte sensitivity to glucocorticoids [56]. This acquired (partial) steroid resistance could be associated with inflammation and activated immune responses reported in PE. High cortisol levels observed during stress conditions could also induce hypertension and endothelial dysfunction, features reported in PE [9].

7 Conclusions

To maintain the successful gestation, the maternal immune system must continuously adapt to the semiallogeneic fetus. It was thought initially that the maternal immune system should be suppressed during all gestational stages. This was supported by observations linking inflammation with negative pregnancy outcomes. This oversimplified interpretation has changed. The inflammation observed in the first trimester of gestation is of pivotal importance for embryo implantation and angiogenesis. Following this critical period, the maternal immunity is suppressed (both systemically and at the fetomaternal interface) until the last weeks of gestation when inflammation is triggered again to induce labor. These dynamic changes in the maternal immune system are necessary for a successful pregnancy until the birth of the baby.

Most dynamic changes of the maternal immune system take place at the fetomaternal interface. At this special site, the decidua immune cells (derived from the mother) are in close contact with fetal antigens and cells. During the first trimester, dNK cells and macrophages (M1 profile) are necessary for embryo implantation and the formation of spiral arteries. During this period, the dNK cells constitute up to 70% of the leukocytes found at the fetomaternal interface. However, following this critical period, these cells become highly tolerogenic following continuous contact with fetal antigens and macrophages polarized to M2 profile (with suppressive

features). The maternal adaptive immune system also adapts to the developing fetus and healthy pregnancies involve a bias toward Th2 responses and active Treg cells at the fetomaternal interface.

It was also discussed that non-classical MHC class I molecules (e.g., HLA-G) play important regulatory roles during pregnancy, including the induction of tolerance in maternal T cells. Dysregulations of these tolerogenic features are involved with pregnancy complications, such as PE. Psychosocial stress may lead to pregnancy complications, including PE, premature birth, and low birth weight. It is thought that these stress-related changes are due to a switch toward inflammatory responses during gestational stages when the maternal immune system should be suppressed.

The understanding of the fetomaternal immune cross talk may be helpful in getting insight into the pathogenesis of pregnancy complications as well as poor postnatal health.

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Placenta and Cord Blood as Source of Immune Markers of Offspring Neurodevelopment and Psychopathology

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Abstract Classically, the placenta is considered the interface between the fetus and the mother. Furthermore, it is also a major transient endocrine organ that plays a key role in the interactions between the mother and the fetus during the pregnancy. The placenta also supports fetal development by means of adaptive responses to the maternal environment and protection against environmental insults. The prenatal environment has been increasingly implicated in general health outcomes during the lifespan, especially regarding the outcomes on neurodevelopment and mental health. There is strong evidence that the placenta and cord blood may be biological sources of several biomarkers of offspring neurodevelopment and psychopathology, both in animal and human studies. These biomarkers influence in utero development and, as a consequence, the later occurrence of abnormal neurodevelopment and psychopathology in the offspring. In this chapter, we discuss the role of placenta and cord blood as sources of immune markers and the potential pathways related to neurodevelopment and psychiatric diseases later in life.

Keywords Placenta · Cord blood · Immune markers · Neurodevelopment · Psychopathology

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1 Introduction

Classically, the placenta is described as the interface between the fetus and the mother. The placenta allows the passage of nutrients to enable fetal nourishing and blocks harmful substances. This selective permeability is responsible for optimal fetal growth and development. Currently, it has been considered that placental function goes far beyond ensuring nutrition and growth during pregnancy. Among its multiple roles, the placenta mediates the bidirectional relationship between the maternal and fetal immune systems, which interact with the developing central nervous system (CNS). This unique role has led to the nomination of the placenta as "the third brain" in pregnancy [1], and a growing acknowledgment of its role in what is called the "developmental origins of health and disease hypothesis" [2].

Factors influencing the intrauterine environment may significantly affect fetal neurodevelopmental stages with consequences that may persist later in life [3–5]. The adaptation of the mother's organism to fetal development includes modifications in her immune system, which, in turn, affects the formation of the fetal immune system. This delicate interaction is an example of how these systems influence each other continuously in a multidirectional way. In addition, interactions between the maternal and fetal immune systems may modulate the processes of multiplication, differentiation, migration, maturation, and functioning of the cells that will form the fetal CNS, as well as synapsis formation and pruning [6].

Some conditions may interfere in this delicate balance. Maternal exposure to infection during pregnancy has been classically associated with adverse psychiatric outcomes in the offspring. Even when viral/bacterial/parasite pathogens do not cross the placenta, they might still be able to trigger an exacerbated inflammatory response in both the placenta and the fetus. Also, maternal nutrition, diseases, stress, and psychiatric morbidity alter the systemic circulation of immune cells and inflammatory mediators, which influence placental function, structure, and permeability, allowing immune cells and cytokines to reach fetal circulation. This process affects neural cellular multiplication, migration, and differentiation [7–9].

The prenatal environment has been increasingly implicated in general health outcomes during the lifespan, especially regarding the outcomes on neurodevelopment and mental health [3, 10]. Events affecting the fetus may increase the risk of neurodevelopmental disorders and later the occurrence of psychiatric and other chronic diseases. Since the concept of "early life programming" has emerged, the interest in lifelong effects of in utero conditions over phenotype characteristics has risen. The increased risk of chronic diseases has been identified in both animal and humans. Most studies focused on epigenetic and inflammatory mechanisms, which may interfere with early life programming [3, 10]. One important aim of these studies is to identify potential pathways for therapeutic interventions in the future [3].

The term "two hit model" was initially proposed for cancer, then extended to the understanding of schizophrenia and, subsequently, to other neurodevelopmental and neuropsychiatric disorders [11]. As shown in Fig. 1, this model considers that an early exposure to inflammatory molecules would stimulate or prepare neural,

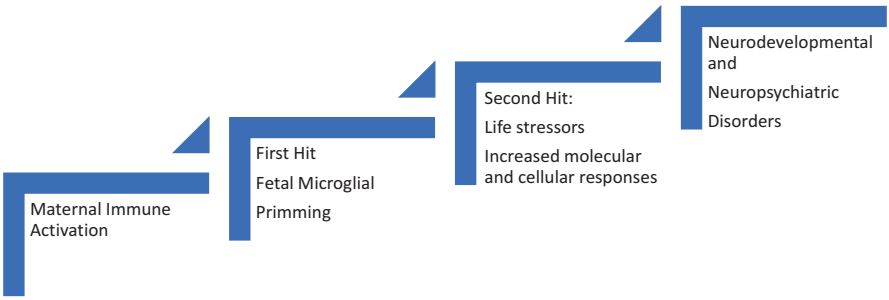

Fig. 1 The two hit hypothesis – This hypothetic model would suggest that insults in the CNS during the prenatal genetic or environmental produce a vulnerability to the disorder (First Hit). However, the onset of symptoms in a vulnerable brain would be triggered by later environmental factors (Second Hit). This model raises the hypothesis that molecular and cellular disruptions in intra-utero environment may leave some neuronal circuits vulnerable to disruptions in the signaling events that occur in the mature CNS, resulting in neurodevelopmental and/or neuropsychiatric disorders

immune, and endocrine systems to react against novel or stressful situations. This would be the first hit, potentially disrupting aspects of brain development, and establishing increased vulnerability to a second hit that may occur later in life. When the child or adult is exposed to new situations or stressors, these primed systems react with enhanced cortisol secretion and intense release of inflammatory mediators. This exaggerated response, termed as the second hit, may lead to neuropsychiatric symptoms and disorders, among other chronic conditions [11]. More recently, a "three-hit" theory of predisposition to neurodevelopmental abnormalities, especially autism spectrum disorders (ASD), was proposed, as neurodevelopmental disorders are much more frequent in males. This theory includes male fetal sex as the third hit risk factor for the adverse response to genetic load and environmental issues [12]. Sex-dependent differences have been observed to include the size of different brain regions, and the timing and magnitude of critical developmental processes in the brain like cell apoptosis and synaptic pruning [12]. However, interactions among perinatal inflammation, sex, and behavior are complex and might bring implications for neuropsychiatric disorders during lifetime [6, 11–13] (Fig. 1).

In this chapter, we discuss the role of placenta and cord blood as sources of immune markers and the potential pathways that link in utero changes to neurodevelopment and psychiatric diseases later in life.

2 Placenta As a Biological Matrix

The placenta is the first complex mammalian organ to be formed and is required for a successful development of all viviparous species [3]. It is a unique endocrine and metabolic organ that mediates transmission of environmental signals, nutrition, endocrine stimulus, immune response, and gas exchange between the mother and the fetus. It also supports fetal development by means of adaptive responses to the maternal environment and protection against environmental insults [3, 5]. The placenta clearly plays a crucial role in modulating fetal exposure to maternal factors [4, 14], and presumably in preparing the fetus for future environmental exposures [4]. Alterations of the proper function of placenta may predispose to brain injury and/or neurodevelopment complications both in the preterm and term neonates through epigenetic processes [3, 5, 15]. Among these conditions, we highlight cerebral palsy, cognitive delay [15], neuropsychiatric disorders, including schizophrenia, depression, bipolar disorder, attention deficit hyperactivity disorder (ADHD), and ASD [3, 5, 15].

Histopathological changes in the placenta affect fetal growth and development. These alterations include (i) greater number of infarctions, (ii) increased syncytial knotting, (iii) intervillous fibrin deposition, (iv) accumulation of extravillous trophoblasts in the placental membranes, and (v) accelerated villous maturation with impaired utero-placental blood flow or insufficient perfusion [15, 16]. In addition, maternal infections and systemic inflammatory diseases may also alter the placenta structure and function, causing placental dysfunction [15, 17].

Placental insufficiency or dysfunction is a critical condition during pregnancy. It is characterized by insufficient blood flow and inadequate supply of oxygen and nutrients to support normal growth and development of the fetus [18, 19]. It results in a chronic hypoxic environment that modifies fetal metabolism, hormonal, hematologic, immunology, and cardiovascular functions, leading to altered fetal growth and brain development [18].

Physiologically, the placenta synthesizes hormones and other molecules for pregnancy maintenance and actively transports a range of substrates to the fetus for growth and development [20]. These molecules act as maturational and nutritional signals controlling tissue development and differentiation and closely interacting with the in-utero environment [21]. Moreover, the placental demands change during pregnancy, according to the growth and the stage of gestation [20].

There is a controlled systemic inflammatory response in which cytokines promote trophoblast cells infiltration of the spiral arteries in normal pregnancies [22]. When there are changes in the placental structure and function, this inflammatory response becomes uncontrolled. Thus, there is abnormal activation of monocytes, neutrophils, and the endothelium, resulting in oxidative stress, release of reactive oxygen species (ROS) into the blood, and placental ischemic microenvironment [22].

The innate immune system exerts protective action during pregnancy. It encompasses neutrophils, dendritic cells, and macrophages. In pathological conditions,

these immune cells are activated as an attempt to protect the mother and the fetus. Therefore, neutrophils express a number of toll-like receptors (TLRs), including TLR9, and secrete several molecules including ROS, matrix metalloproteinase-8 (MMP-8), calprotectin, myeloperoxidase (MPO), and the pro-inflammatory chemokine Interleukin-8 (CXCL-8/IL-8). TLR9 can recognize conserved sequences known as pathogen-associated molecular patterns (PAMPs), and also responds to endogenous molecular structures termed damage-associated molecular patterns (DAMPs). This response occurs via unmethylated CpG dinucleotide motifs of mitochondrial DNA. TLRs constitute the first line of defense against many pathogens and play a crucial role in the function of the innate immune system by activating NF-κB. The activation of TLR9 involves an intracytoplasmic signaling cascade that leads to the up-regulation of transcription factors and subsequent release of pro-inflammatory cytokines [22]. This inflammatory response results in irregular support of oxygen and glucose to the fetus, impacting fetal development [18, 22].

Regarding placental angiogenesis, trophoblast cells express both vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Several reports indicate that disruption of VEGF/PLGF balance during pregnancy may be pathogenic. Altered VEGF/PLGF expression in the placenta may predict placental vascular pathologies and fetal neurological disturbances [23].

Many conditions like maternal mood, psychological stress, glucocorticoid excess, and nutrient restriction may result in excessive activation of maternal immunity. It has been described as a key pathway to predispose long-term altered patterns of neural, cognitive, and behavioral development for the baby [4, 24]. There is growing evidence of maternal prenatal distress and epigenetic changes in the placenta influencing newborn neurologic behavior [25]. Some of the proposed pathways are as follows: (i) plasma and amniotic cortisol levels may affect the offspring's outcomes via epigenetic regulation of glucocorticoid pathway genes in the placenta; (ii) downregulation of placental mRNA for the gene encoding 11β–hydroxysteroid dehydrogenase type 2 increased DNA methylation of placental HSD11B2; (iii) greater placental DNA methylation of NR3C1, the gene encoding the glucocorticoid receptor, predicted poorer self-regulation, lower muscle tone, and more lethargy in neonates; (iv) placental DNA methylation of FKBP5 was associated with an increased likelihood of high arousal in newborns; and (v) glucocorticoids upregulated placental HSD11B2 expression [3, 25].

Growing evidence highlights the placental role in physiological and pathological processes influencing neurodevelopmental outcomes, including (i) epigenetic influences in genes related to glucocorticoids, (ii) modifications in the hypothalamic-pituitary-adrenal (HPA) axis with placental gene regulation and fetal behavior, and (iii) immunomodulatory response to pro- and anti-inflammatory molecules [15, 25]. Cord blood might also offer significant information about these cellular and molecular mechanisms [26], supporting the hypothesis of an in-utero programming of the offspring's future mental health.

Due to its role as an interface between maternal and fetal circulations, the placenta is constantly exposed to endogenous and exogenous influences, through contact with diverse molecules, which act as signaling of infection, disturbances, or

inflammation. It is important to notice that the placenta is also a major transient endocrine organ, playing a key role in enabling or impeding many of these complex interactions [27]. These exposures might leave molecular marks on the placenta [27], making this organ a biological source for biomarkers of offspring neurodevelopment and psychopathology. In this sense, cord blood is also an easily available way to evaluate maternal circulating biomarkers [28, 29].

3 Pre-clinical Evidence for the Role of Placenta and Cord Blood on Long-Term Outcomes

There is strong evidence that the maternal mood during pregnancy can alter the development of the fetus and the child, with an increased risk for later psychopathology in the offspring. Several underlying mechanisms including the role of the placenta, gene-environment interactions, epigenetics, and specific systems, including the HPA axis and cytokines, may provide an adverse intrauterine environment, influencing the neuroendocrine and neurobehavioral functioning of the offspring [1, 4, 26].

The majority of adverse pregnancy outcomes may originate in the placenta. Animal models of these mechanisms have helped us to understand the placental alterations and the development of neuropathology and/or in psychopathology [3, 4, 18]. Animal models also supported that exacerbated inflammatory response with increased levels of IL-6, CXCL-8/IL-8, TLR9, and ROS predicts worse neurological development [22]. However, the time of occurrence of this inflammatory response may result in different outcomes, impacting fetal neurodevelopment at diverse stages and leading to altered animal offspring phenotypes [26, 30]. Studies with rodents showed an association between inflammatory response at the first trimester of pregnancy with sensorimotor gating and associative learning difficulties. These deficits may be related to alterations in the dopaminergic system. On the other hand, if the inflammatory response occurs at or after the second trimester, there is an association with deficits in social interactions, perseverative behaviors, cognitive inflexibility, and characteristics of ASD [30].

Preclinical studies with sheep and rodent models associated placental insufficiency with the development of neurological alterations [18]. Placental insufficiency can cause chronic hypoxia in utero, leading to adverse effects in brain gray matter development, white matter, and cerebellum [18]. Besides that, it has been associated with neurodevelopment deficits and neuropsychiatric disorders [18, 30].

Accordingly, some studies showed that the hypoxic environment is characterized by elevated concentrations of specific molecules in the cord blood and placenta, including leptin and CXCL-8/IL-8. Leptin is in the same protein family of inflammatory molecules as interleukin 6 (IL-6) [31]. Exacerbated levels of leptin and CXCL-8/IL-8 during pregnancy mediate intercellular signals and are predictors of worse impulse control via differential cortex, amygdala hippocampus, and thalamus

[30, 31]. In addition, these molecules may inhibit serotonin synthesis, which is also considered a possible mechanism responsible for mental health disorders [32].

Animal models have identified fetal sex as a key determinant of lifelong outcomes [32–34]. Many studies have shown that fetuses of male gender are more sensitive to prenatal insults, including gestational stress, maternal infection/inflammation, and placental dysfunction [33]. A male offspring is at greater risk of detrimental outcomes following in utero perturbations and is more vulnerable to prenatal insults than a female offspring [31, 32]. Male fetuses are especially at risk to develop ADHD and ASD later in life [30]. The mechanisms responsible for sex-specific programming remain unclear [32–34]. One hypothetical mechanism refers to insulin dysfunction. Insulin deficiency has been shown in placental tissue in some disease conditions related to pregnancy, including gestational diabetes, preeclampsia, and inflammation. Thus, signaling and dysfunction of insulin in placental tissue may contribute to psychopathology in the offspring by altering the neurodevelopmental programming [34]. Another hypothetical mechanism associated with high risk for male sex is that the X-linked metabolic and epigenetic placental enzyme, O-linked *N*-acetylglucosamine transferase (OGT), acts as a defense against gestational perturbations in females, in part via its regulation of the broad transcriptional repressive mark, H3K27me3, and transcriptomic placental programs [32]. In addition, female trophoblast gene expression, at baseline, is epigenetically organized differently than male trophoblast gene expression. Placental OGT-mediated epigenomic programing promotes greater baseline homogeneity in female trophoblast gene expression relative to males. Whereas repressive transcriptional regulation is reduced in females, male-like transcriptional variability is induced, possibly underlying environmental risk for neurodevelopmental vulnerability [32]. Furthermore, maternal mood seems to influence the offspring development. A mouse model of prenatal stress results in male offspring with a phenotype of neuroendocrine dysregulation, including hyperactive HPA stress axis sensitivity and metabolic dysfunction [33].

In short, studies have shown that mother and fetus are in close connection during pregnancy. This process is bidirectional, being regulated by induced and modulated signaling molecules [17–27, 30, 31]. Changes in concentrations of specific signaling molecules in maternal serum at different moments and adverse environmental factors may affect fetal development [26, 27, 30, 35]. Moreover, these changes can lead to long-term impact on later health and disease [30, 35]. Preclinical studies have shown the placental and cord blood importance for the identification of risk factors for developmental outcomes. Evaluation of molecular changes in placenta and cord blood may become helpful for diagnosis, prevention, and treatment of fetuses and neonates in the near future.

4 Human Studies

Mental health problems are a leading cause of disability with long-lasting effects throughout life [4]. Environmental risk factors in early childhood are known to modify neurodevelopment and also influence the genesis of mental disorders in the childhood and/or adulthood [4, 36]. Recently, adverse fetal exposures have been receiving closer attention due to their role in the pathogenesis of chronic diseases later in life.

As previously addressed, poor maternal diet and smoking, as well as maternal mood disorders, including prenatal depression or anxiety, increase the risk of psychopathology in the offspring [4, 36]. The mechanisms proposed are modifications in the placental structure or function, and also alterations of reactive systems, including HPA axis, cytokines, and serotonin, as well as epigenetics mechanisms [4].

Maternal economic and social disadvantage was associated with an altered transcriptional profile in both cord blood and placenta of 79 women followed during pregnancy to full-term. In the same study, a sample of 20 women were submitted to psychosocial intervention during pregnancy, and compared with traditional prenatal care. In this subsample, genes that were associated with disadvantage were upregulated in the group submitted to the intervention, reinforcing the potential of the defense factors in reducing detrimental programming [24].

In another study, methylation of glucocorticoid pathway genes was analyzed in term placentas of 67 women, and was associated with higher mother distress, as well as reduced fetal coupling of heart rate and movements [25]. The response of the maternal HPA axis to psychological distress alters circulating cortisol levels, to which the fetus is exposed, and might lead to an altered programming of the fetal HPA axis.

Prospective longitudinal analyses suggest that changes in placenta and levels of cytokines in the cord blood might significantly affect the development resulting in clinical problems of public health relevance [4]. In a large American cohort, 537 newborns were assessed using the Neonatal Intensive Care Unit Network Neurobehavioral Scales after 24 hours of birth, and a pattern of altered methylation in glucocorticoid genes in the placenta was associated with different behavior profiles [37].

For a better understanding on pre- and perinatal aspects that may influence neurological outcome as well as psychiatric disorders, some studies have considered placenta and cord blood as key sources of biomarkers, reflecting their role in the physiology of pregnancy. Some measures of abnormal placental function including fetal and/or placental cell inflammatory response, gene expression, gene-environment interaction, and placental morphology have been associated with adverse neurological outcomes and psychiatric disorders [38, 39].

For instance, an altered profile of gene activation was observed in the transcriptome analysis of umbilical cord blood samples after birth from mothers with psychiatric morbidity, as posttraumatic stress disorder (PTSD) and depression, when compared with controls. There were altered profiles in genes involved in axon guid-

ing and RNA stability in depressed mothers, whereas, in PTSD, the profile indicated altered TNF-signaling and cellular response to stress. There was also an overlay with genes previously associated with higher risk of ASD and schizophrenia, reinforcing the relationship between maternal distress and epigenetic mechanisms in neurodevelopment diseases [40].

In contrast, in a cohort of 125 pregnant adolescents (ages 14–19), the presence of maternal negative mood (anger, frustration, irritation, stress) was associated with accelerated fetal development and higher levels of fetal coupling. However, there was also observed a sex-gradient in response to the mother's mood variations, cortisol and physical activity levels, with female fetuses being apparently more susceptible to the changes [41].

In a large cohort of 737 pregnant women and later their children, higher levels of CXCL8/IL-8 during the first trimester were associated with an increased risk of externalizing symptoms, including agitation and aggression, while the higher IL-1 receptor antagonist in the second trimester was related to internalizing symptoms (anxiety, sadness, social withdrawal), with potential differences between sexes [42].

In another prospective study, in which participants were followed for more than 40 years, 88 cases of schizophrenia and affective psychoses were compared to 100 healthy controls. Prenatal IL-6 levels were higher among males with schizophrenia, while lower TNF levels were detected among females with the same disease in comparison to controls [43].

Other aspects as the placental chorionic surface vascular network (PCSVN), variant shapes, cord insertion sites, and placental disk thickness have been associated with reduced placental efficiency. A typical placenta is described as round or oval, but it is also rare to have perfectly round placentas with central umbilical cord insertion. It can have various shapes and thus placental shape variability may be the norm. Abnormal placental angiogenesis has been linked to low birth weight, fetal growth restriction, preterm birth, preeclampsia, and other pregnancy complications [38, 39]. These conditions have been associated with neuropsychiatric disorders that occur in childhood, as ASD [38, 39] and ADHD, but also to schizophrenia and depression, which usually happen later in life [46].

Several adverse events during the perinatal period, including stress, infection/inflammation, and abnormal placenta sets, have also been associated with neuropsychiatric disorders. Recent studies raise the possibility that both acute and chronic placental dysfunctions are linked to adverse life-long neurological injury and psychiatric disorders [44]. The placenta and cord blood reflect the prenatal environment of the fetus. The prenatal phase is a critical period in which the CNS can be programmed for conditions that will occur during the lifetime [44]. Table 1 summarizes main findings of human studies associating immune markers and pathways that link changes in placental structure and function with neurodevelopment and psychiatric diseases later in life.

Table 1 Human studies that associated immune markers and the potential pathways that link changes in placental structure and function with neurodevelopment and psychiatric diseases later in life

Author	Analyzed material	Assay technique	Neurodevelopment outcome
Miller et al. 2017 [24]	Placental biopsy and umbilical blood	PCR-clean, RNAse-free	Maternal disadvantage was associated with a transcriptional profile indicative of higher immune activation and slower fetal maturation, particularly in pathways related to brain, heart, and immune development. Cord blood cells of disadvantaged newborns also showed indications of immaturity, as reflected in down-regulation of pathways that coordinate myeloid cell development.
Monk et al. 2016 [25]	Placental biopsy and salivary cortisol	PCR; ultraperformance liquid chromatography-tandem mass spectrometry assay	Alteration in placenta DNA methylation can be a biological mediator of prenatal maternal mood effects on the future child. Genetic variation can significantly alter gene regulation, and it is possible that maternal and/or fetal genes may predispose to psychopathology.
Garay et al. 2019 [34]	Placental weight and salivary cortisol	Human tissue authority licensed Salimetrics	Environmental risk factors in early childhood are known to modify neurodevelopment and also influence the genesis of mental disorders in the childhood and/or adulthood.
Paquette et al. 2015 [35]	Placental parenchyma	PCR	Methylation patterning of glucocorticoid response genes results in a degree of inability to adapt to the stresses in the postnatal environment among healthy populations of infants exposed to low-to-moderate prenatal stress.
Park et al. 2018 [36]	Placenta morphology	Pathological protocol: Placental shape, umbilical cord displacement and disk thickness	Gross morphological differences can provide an initial indication to ASD. Morphological changes could be mechanistically important in ASD etiology if reduced compensatory capacity leaves the fetus more vulnerable to other stressors.
Chang et al. 2017 [37]	Placenta morphology	Variations in the PCSVN structure pathology evaluation	Variations in the PCSVN structure are associated with a high risk for ASD.
Breen et al. 2018 [38]	Umbilical Coord blood	WGCNA	Molecular aspects of maternal psychological distress can change neuroimmune UCB gene expression profiles.
Doyle et al. 2015 [39]	Salivary cortisol, plasma	ELISA	Maternal psychobiological status influences fetal development and neuro-behavioral outcomes. This study did not find association of IL-6 and CRP with development outcome.

(continued)

Table 1 (continued)

Author	Analyzed material	Assay technique	Neurodevelopment outcome
Giollabhui et al. 2019 [40]	Plasma	ELISA	Elevated maternal inflammation during pregnancy is associated with the emergence of separate psychological phenotypes and that timing of exposure and fetal sex matter for offspring outcomes.
Goldstein et al. 2014 [41]	Serum	Multiplex	Prenatal immune disturbances in the early third trimester significantly increased the risk for psychoses in a sex-dependent manner more than 40 years later. Male offspring were most strongly affected by maternal IL-6 elevations; female offspring were affected when maternal TNF levels were lower.

ASD Autism Spectro Disorders, *CRP* C-reactive Protein, *IL* Interleukin, *PCR* Polymerase Chain Reaction, *PCSVN* Placental Chorionic Surface Vascular Network, *TNF* Tumor Necroses Factor, *UCB* Umbilical Cord Blood, *WGCNA* Weighted gene co-expression network analysis

5 Concluding Remarks

In summary, the effects of environmental stressors in neural embryogenesis are able to modulate CNS functioning by means of epigenetic mechanisms and alterations in immune and endocrine systems homeostasis. Stress chronically increases the levels of cortisol, which signals immune system cells, both peripherally and in the CNS. In addition, maternal immune system activation enhances the production of systemic cytokines and provokes microglial activation in the fetal CNS, thus altering the proliferation, migration, and myelinization of neural cells. This process also leads to cell apoptosis and reduced synaptogenesis at fetal CNS. These events may result in impaired fetal brain development, altered regulation of gene expression, and increased CNS vulnerability to developmental and neuropsychiatric disorders throughout life [45].

The identification of molecular and developmental factors responsible for neuropsychiatric disorders later in life is extremely important in elucidating the etiology, and in predicting the severity and associated symptomology. The developing brain is especially sensitive to environmentally derived perturbations in placental function. Consequently, the placental activity and responses to insults may contribute to increased risk to neurodevelopmental and psychiatric disorders [33]. Studies examining exposure to environmental insults in utero, developmental outcomes, and maternal emotional disorders have found a range of detrimental effects on neurological development and behavior [46, 47]. Further studies can help understanding how placental mechanisms and cord blood markers might impact in the epigenomic landscape responsible for health in utero development or for psychopathy in the offspring.

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Cytokine Model of Cognition in Relation to Mental Disorders During Neurodevelopment

Célia Fourrier and Bernhard T. Baune

Abstract Cognitive dysfunctions are current across psychiatric disorders and negatively impair patients' quality of life and normal daily functioning and reduce clinical recovery. It is therefore important to understand the biological mechanisms underlying these cognitive impairments in order to develop new therapeutic strategies targeting these symptoms. Previous findings provided evidence for a cytokine model of cognition, in which immune cells and inflammatory cytokines can regulate cognitive processes in both physiological conditions and psychiatric disorders. There is now mounting evidence that genetic markers and perinatal environmental stressors contribute to abnormal development of both the immune system and the central nervous system and increase vulnerability to psychiatric disorders. However, whether cognitive alterations in psychiatric patients may also be a consequence of immune system dysregulations during development remains unclear. Hence, we review in this chapter the current knowledge suggesting that cognitive function in adult psychiatric patients may be influenced by long-lasting effect of immune system alterations during neurodevelopment. A better understanding of the complex influence of the developing immune system on brain structure and function may therefore help in identifying vulnerable individuals and develop preventive and therapeutic strategies to reduce the detrimental impact of cognitive impairments on psychiatric patients.

Keywords Neurodevelopment · Brain development · Cognition · Psychiatric disorders · Cytokines · Neuroinflammation · Immune activation · Immune system

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1 Introduction

Psychiatric disorders are often accompanied by cognitive impairments. The range of cognitive deficits across those disorders is broad and complex, as it includes various cognitive domains such as attention, memory, executive function, processing speed, social cognition and language [1]. Although impairments in specific cognitive domains are reported across distinct psychiatric conditions, other cognitive domains are affected transdiagnostically. For example, attention is impaired in most psychiatric disorders, including attention deficit hyperactivity disorder, post-traumatic stress disorder, panic disorder, obsessive compulsive disorder and autism spectrum disorder [1]. Importantly, cognitive deficits across psychiatric disorders do not only aggravate the course of the diseases but also have a deleterious effect on patient's occupational, social and daily functioning and quality of life [2]. They can predict future development and severity of the symptoms, suggesting that they may participate in the development of the diseases [3]. In addition, cognitive symptoms impair recovery and remission in psychiatric patients, and they often persist after recovery, representing a risk factor for relapse [4–6]. Therefore, there is a strong need for improving management and treatment of cognitive dysfunction across psychiatric conditions. A better knowledge of the biological mechanisms underlying these cognitive impairments is essential, as they could represent therapeutic targets to improve cognition in psychiatric patients.

It is now recognised that both genetic and pre- and postnatal environmental factors can contribute to abnormal brain development and therefore to the vulnerability of an individual to psychiatric disorders [7–9]. Although there is evidence showing that gene- and environment-induced immune system dysregulations during development increase the risk of adult-onset psychiatric disorders, it is still unclear whether they could partially explain the cognitive impairments associated with these mental conditions. Hence, this chapter reviews the current knowledge suggesting that cognitive function in adult psychiatric patients could be influenced by long-lasting effect of alterations of the developing immune system.

2 Cytokine Model of Cognitive Function in Psychiatric Disorders

Epidemiological, clinical and pre-clinical studies have suggested that inflammatory processes might be central to the development and progression of psychiatric disorders, at least in a significant subpopulation of patients [10]. By altering brain structure and function, inflammatory mediators such as cytokines can trigger the development of transient 'sickness behaviour', characterized by behavioural changes including reduced appetite, fatigue and lassitude [11]. However, sustained production of peripheral and brain cytokines (i.e. chronic low-grade inflammation) is associated with the induction of chronic neuropsychiatric symptoms [12, 13], suggesting that they could participate in the development of such symptoms in psychiatric con-

ditions. Elevated peripheral levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF- α) have often been reported in psychiatric conditions such as major depressive disorder, bipolar disorder, and schizophrenia [10, 14, 15]. Moreover, a role of central inflammation in the aetiology of psychiatric disorders has also been suggested, although the evidence mostly comes from pre-clinical models of the diseases [12, 13, 16, 17]. Changes in immune system regulation may therefore affect diagnosis, prognosis and treatment outcomes across disorders.

Immune cells and inflammatory mediators can also regulate cognitive processes in both physiological conditions and psychiatric disorders [18–20]. Previous findings provided evidence for a cytokine model of cognition: in physiological conditions, the immune system is able to positively modulate cognitive function through its effect on underlying brain processes such as neuronal plasticity, neurogenesis and neuromodulation [18, 20]. Although immune cells can directly modulate cognition [21, 22], inflammatory mediators are also required for the physiological regulation of memory processes. Among other cytokines, IL-1β, IL-6 and TNF-α have been the most studied for their facilitating role in learning and memory processes. Exogenous administration of low doses of IL-1β or TNF-α potentiated learning and memory in rodents [23, 24], whereas pharmacological or genetic blockade of IL-1β or TNF-α signalling impaired their cognitive functions [23–25]. Importantly, the role of cytokines in cognitive regulation relies on a delicate balance since overexpression of IL-6, IL-1β or TNF-α disrupted normal learning and memory in rodents [26, 27].

Dysregulations of the immune system as observed in psychiatric disorders could therefore participate in the cognitive impairments reported across these conditions [19]. Elevated levels of inflammatory cytokines in major depressive disorder, bipolar disorder and schizophrenia patients indeed correlate with the severity of cognitive impairments in these individuals (for review, [19]). Raised inflammatory processes, such as activated microglia cells and elevated levels of inflammatory cytokines can disrupt neurobiological processes underlying cognitive function, which may lead to the induction of the cognitive impairments displayed by psychiatric patients.

3 Genetic and Early-Life Environmental Factors Associated with Cognitive Impairments in Adult Psychiatric Disorders

3.1 Immune System Gene Polymorphisms Are Associated with Adult-Onset Cognitive Impairments in Psychiatric Disorders

Genetic predisposition could be an important aetiological factor for cognitive dysfunction across psychiatric conditions. In particular, there might be a role of cytokine gene polymorphisms in cognitive changes in various pathological conditions, including psychiatric disorders [28]. Single-nucleotide polymorphisms (SNPs) are a common type of genetic variation, which represents a difference in a single nucle-

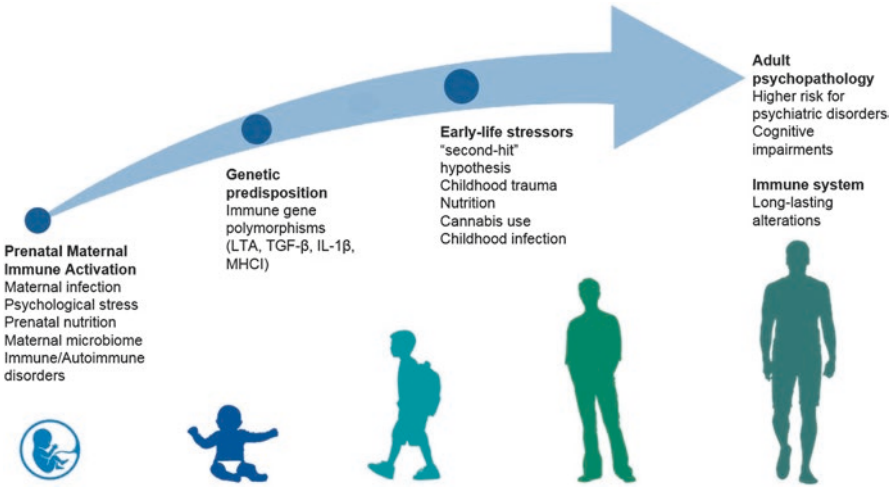

Fig. 1 Immune gene polymorphisms and perinatal environmental stressors influence cognitive outcomes in adult psychiatric patients. (*LTA* lymphotoxin alpha, *TGF-β* transforming growth factor beta, *IL-1 β* interleukin-1 beta, *MHCI* major histocompatibility complex class I)

otide and can affect the gene's function. Cytokine production is under strong genetic control, and cytokine SNPs are well known to affect cytokine gene expression or the functional activity of the encoded proteins [29]. Genetic background predisposing to higher pro-inflammatory profile could therefore increase the risk for cognitive impairments in psychiatric patients (Fig. 1).

Functional polymorphisms in lymphotoxin alpha (LTA), a member of the tumour necrosis factor family, have been associated with an increased risk of schizophrenia in a Caucasian population [30]. A significant association was found between the rs2857713 polymorphism of the LTA gene and cognitive function in adult schizophrenia patients, with individuals with the A/A genotype displaying the lowest cognitive function and individuals with the C/C genotype having the highest cognitive function. The rs2857713 polymorphism was associated with attention in particular, considered as a core cognitive deficit of schizophrenia, but not with other cognitive domains. This was specific to schizophrenia as no association was found in bipolar disorder patients and healthy controls [31]. A similar association was reported between TGF-β polymorphisms and cognition in schizophrenia patients. The TGF-β polymorphism rs1800470 was associated with schizophrenia susceptibility with the carriers of the T allele (TT and TC genotypes) being more likely to develop the disease, particularly in females [32]. Among female schizophrenia patients, the T allele carriers scored significantly lower in processing speed, as measured by the digit symbol coding task [33]. Although no direct relationship has been reported between IL-1β SNPs and cognitive function in psychiatric patients, a study suggests that hypoactivity of the dorsolateral prefrontal cortex during cognitive tasks, which is a consistent finding in schizophrenia, could be partially explained by IL-1β SNPs. The rs16944 T allele of the IL-1β gene (reflecting greater expression of

the gene that regulates IL-1β production) was associated with decreased metabolic activity in the left dorsolateral prefrontal cortex of schizophrenia patients during an attention task [34]. Although this association has only been reported in schizophrenia patients, the rs16944 SNP has been associated with bipolar disorder [35] and depression [36]. Finally, genome-wide association studies were performed to investigate whether some genetic variants were associated with cognitive impairments in schizophrenia patients. They determined that the immune function network *via* major histocompatibility complex class I (MHCI) (53 genes immune system related to MHCI) was connected to cognitive impairments in schizophrenia [37].

3.2 Perinatal Environmental May Predispose the Individual to Adult-Onset Psychiatric Disorders and Associated Cognitive Symptoms

Although immune system SNPs emerge as an important risk factor for psychiatric disorders, an environmental contribution is also likely to be implicated. Clinical and preclinical evidence has reported perinatal stress to be associated with adult-onset psychiatric disorders [38]. During pregnancy, maternal immune activation induced by an environmental challenge can compromise the integrity of the placental barrier and therefore expose the foetal brain to maternally derived cytokines [39]. Maternal infection (i.e. by viruses and bacteria), autoimmune disorders, psychological stress, microbiome changes and poor prenatal nutrition have been implicated in the pathophysiology of psychiatric conditions, including schizophrenia, anxiety disorders and mood disorders [40] (Fig. 1).

It has been hypothesised that maternal pro-inflammatory cytokine response to a biological or a psychological challenge is transmitted to the foetus via the maternal serum, placenta and amniotic fluid [41, 42] and can exert a major impact on brain development and contribute to the pathogenesis of psychiatric disorders [40]. It is however noteworthy that most triggers of maternal immune activation do not lead to psychiatric symptoms later in life. Hence, it is thought that maternal immune activation may act as a "primer" or a first hit, predisposing the offspring to increased vulnerability for psychiatric disorders when they are exposed to a second hit later in life. Indeed, childhood and adolescence adversity similarly increase the risk for psychiatric disorders at adulthood [43] (Fig. 1). Such environmental challenges include, among others, malnutrition, childhood infection, childhood trauma and adolescence cannabis use. Childhood adversity and adolescent cannabis use are also associated with immune activation and increased peripheral levels of CRP, IL-6 and TNF-α [44, 45]. Environmental exposures during neurodevelopment, from pregnancy to adolescence, could therefore play an important role in the vulnerability to psychiatry disorders at adulthood. Cognitive impairments in psychiatric patients may similarly arise as a result of environmental challenge-induced immune activation.

4 Immune System and the Development of Neural Pathways Underlying Cognitive Function

Numerous studies have demonstrated that interactions between the immune system and the brain can shape the brain and influence neurobiological mechanisms and behaviour later in life. Although the brain has long been considered as an immune-privileged organ protected by the blood-brain barrier, peripheral circulating cytokines can reach the brain through a number of different pathways [46] and influence its functioning. Once within the CNS, cytokines activate microglia, leading to the subsequent production of inflammatory mediators within the brain. In this section, we review findings suggesting that immune-mediated mechanisms during development could contribute to cognitive impairments that are common across psychiatric disorders.

4.1 Microglia and the Development of Brain Pathways Regulating Cognitive Function

Microglia play an important role in the formation of the brain. They regulate structural plasticity, by mediating the formation and elimination of new synaptic elements [47, 48]. Exposure to environmental factors such as malnutrition, psychological stress and immune challenge during critical windows of development can lead to abnormal microglial development and have long-lasting effects on brain function during development and beyond [49].

During development, microglia proliferate and accumulate to facilitate neuronal turnover (i.e. neuronal death and survival) [47]. Maternal immune activation during pregnancy disrupts microglia numbers and activation, therefore affecting neuronal death and survival and proper CNS development. Microglia also modulate neurogenesis during pre- and postnatal development and are a main contributor of synaptic pruning, the process of elimination of overproduced synapses that occurs during development in various brain areas including the hippocampus [50]. Hence, alterations of microglia number and function during neurodevelopment could impair neuronal function, connectivity and plasticity and have direct consequences on cognition later in life, particularly when those changes occur in brain areas that are crucial for the regulation of cognitive processes [51] (Fig. 2).

4.2 Cytokines and the Development of Brain Pathways Regulating Cognitive Function

Cytokines are of particular importance for the development and function of the brain, at all stages of neurodevelopment [52]. Importantly, several studies have shown that physiological levels of cytokines are crucial for the normal development of brain pathways regulating cognition, particularly in the hippocampus. Cytokine

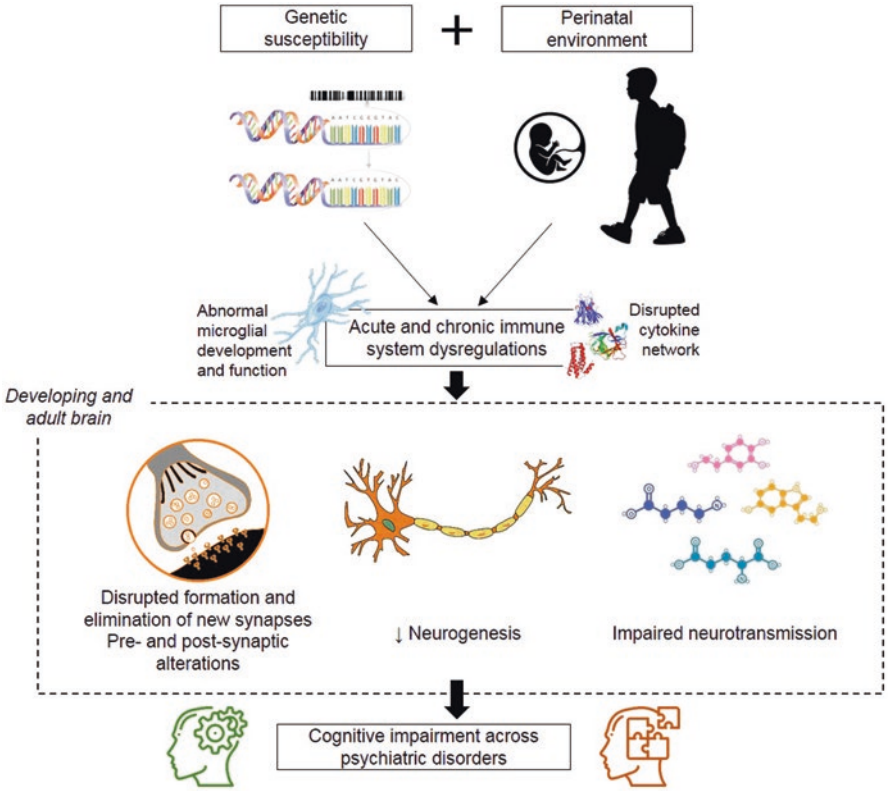

Fig. 2 Immune system and development of neural pathways underlying cognitive function

receptors are expressed ubiquitously throughout the CNS, but it is noteworthy that the highest density of cytokine receptors within the brain is in the hippocampus, a critical brain region for learning and memory, which is sensitive to damage throughout life [53].

During neurodevelopment, TNF-α and IL-9 are involved in the survival of neurons that acquire proper connections and in the elimination of those that fail to properly integrate neuronal networks [52]. TNF-α is also a key mediator of developmental synapse formation. It modulates synaptic strength in the hippocampus through a process called synaptic scaling, which involves changes of AMPA receptors surface expression and is meant to provide stability to neuronal networks within the hippocampus and other brain areas [54]. Similarly to TNF-α, other cytokines such as TGF-β and IFN-γ and proteins of the complement system have critical effects on synaptogenesis and synapse elimination and in the development of brain neuronal networks [52].

Research has suggested that the disruption of the balance between pro and anti-inflammatory cytokines induced by early-life immune activation may be a key mechanism in the disruption of the neurobiological pathways regulating cognition, particularly when these changes happen in the hippocampus. Two possible mecha-

nisms could explain how cytokine network alterations during development can be associated to cognitive impairments later in life [55]: (1) early-life immune activation could impair the development of brain pathways regulating cognition and therefore induce long-lasting cognitive impairments, or (2) early-life immune activation could prime the adult immune system, which would respond inappropriately to an immune challenge at adulthood. The subsequent exaggerated immune response would therefore alter brain pathways regulating cognition and result in cognitive dysfunction.

4.2.1 Early-Life Immune System Dysfunction and Disruption of Neurobiological Pathways Underlying Cognition

Maternal immune activation leads to long-lasting, age-specific and region-specific changes in brain cytokine content in offspring, which may mediate long-lasting changes in brain development and adult behaviour [56]. Numerous pre-clinical studies have demonstrated that an inflammatory challenge early in life impairs the development of brain pathways underlying cognitive regulation at adulthood (Fig. 2). At the neurochemical level, prenatal viral infection with polyribocytidylic acid (PolyI:C) in mice increased the levels of dopamine and its metabolites in the adult prefrontal cortex, an important brain structure for cognitive functions such as decision making and planning complex behaviours. It also decreased serotonin and its metabolites in the hippocampus of these mice [57]. Similarly, prenatal infection induced modifications of GABAergic [58, 59], glutamatergic [60] and endocannabinoid neurotransmission [61] in the hippocampus, which were associated with working memory alterations. In addition, immune activation induced by prenatal stress induced long-lasting changes in neurotransmission since it altered the expression of glutamatergic and serotoninergic receptors in the frontal cortex of adult mice [62].

Early-life immune activation rodent models showed that prenatal infection does not only alter neurotransmitter systems but also induces synaptic alterations in adult offspring, in particular in the hippocampus. Prenatal PolyI:C exposure induced adult onset presynaptic deficits in the mouse hippocampus [63]. Adult, but not pubescent, offspring displayed a decreased density of the presynaptic proteins synaptophysin and bassoon. In addition, the density of the postsynaptic protein PSD95 was decreased in the hippocampus of PolyI:C offspring from pubescence, suggesting that early-life immune activation impaired expression of both pre- and postsynaptic synaptic proteins in the hippocampus. These observations were associated with increased hippocampal IL-1β in adult mice, although the role of IL-1β in the synaptic alterations observed remains to be elucidated. The observations reported by Giovanoli and collaborators' study suggest that adult onset of presynaptic deficits may be important for the onset of neuropsychiatric disorders. The synaptic changes observed in the hippocampus may disrupt neuronal activity, thereby contributing to cognitive impairments frequently observed in psychiatric patients. Consistent with this hypothesis, the work from Vignes and others confirmed that prenatal immune activation (induced by stress or LPS administration) disturbed hip-

pocampal synaptic transmission and plasticity throughout development and at adulthood [64–66], possibly contributing to the cognitive impairments that are associated with early-life immune system activation.

4.2.2 Early-Life Immune Activation, Sensitisation of the Adult Immune System and Cognitive Impairments

An immune challenge early in life could also indirectly alter cognition in psychiatric patients [44]. The immune system could be "primed" or sensitised to produce an inappropriate response to a second hit later in life, thereby affecting the processes that support cognitive function. In the last few years, Bilbo and collaborators designed a set of pre-clinical experiments to determine whether a prenatal *E. coli* infection permanently impaired hippocampus-dependent memory or impaired the adult immune response to a second challenge and subsequently impaired cognition [67]. They reported that the prenatal infection affected memory and concomitantly increased hippocampal IL-1β transcription only when the offspring was submitted to an inflammatory challenge at adulthood. These data therefore support this second hypothesis and are in agreement with the "two-hit hypothesis" reported in the human literature, suggesting that a combination of early-life and later-life challenges activating the immune system is required for the manifestation of psychiatric disorders and associated cognitive symptoms [68, 69]. It is however unlikely that only one of these two hypotheses is valid in the context of cognitive impairments induced by early-life inflammatory alterations. Indeed, the pre-clinical evidence reported above suggests that perinatal inflammatory challenges lead to adult-onset cognitive deficits both with and without a second hit at adulthood. To date, there is no data suggesting that the nature or the timing of the early-life immune activation could be associated with one or the other hypothesis.

5 Discussion

The early-life environment of an individual is critical in shaping the development of the immune system and the brain. We reported in this chapter that both genetic and early-life environmental factors can have significant consequences for brain and cognition throughout the remainder of the lifespan. Although there is mounting evidence showing that perinatal and particularly prenatal immune activation increases the vulnerability of an individual to develop psychiatric disorders later in life, to date, very little research has been directed at understanding how it can contribute to cognitive impairments across disorders. There is therefore a strong need to integrate how the immune system influences the maturation of neurobiological systems modulating cognitive function to help advance understanding of cognitive impairments in adult psychopathology.

It is noteworthy that the strongest evidence for a developmental origin of cognitive impairment in psychiatric disorders is between early-life environmental challenges and the later development of schizophrenia. There is however indication that perinatal immune activation, during pregnancy or during later stages of neurodevelopment, is associated with a much wider range of psychiatric disorders. Maternal immune activation has recently also been linked to anxiety disorders, major depressive disorder and bipolar disorder [70–72]. Cognitive impairments are common across schizophrenia and these disorders, suggesting that immune dysregulation early in life may impair common pathways and similarly contribute to adult-onset cognitive impairments in various psychiatric disorders.

Determining when these pathways are disrupted still remains unclear. Most early-life challenges do not lead to adult-onset psychiatric and cognitive symptoms, suggesting that the timing of the challenge may be critical in determining cognitive outcomes at adulthood [67]. Most studies testing this hypothesis have been conducted in rodents, using various models of maternal immune activation. It appears that the time of the stressor exposure matters because it impacts the developmental time course of both the immune system and the central nervous system [73]. Elevated levels of particular cytokines, such as IL-1β, IL-6, TNF-α and IL-11, and cytokine receptors coincide with important processes of brain development [73]. Therefore, altering homeostatic or physiological levels of cytokines during these stages of development may disrupt normal brain structure and function throughout life. The timing of brain colonisation by microglia may also be a sensitive period for long-term cognitive impairments, since an early immune challenge could change their function not only at the time of the challenge, which could be a critical period for brain network development, but also throughout life, which would promote an exaggerated immune response to a second hit later in life [73].

Another factor that may determine how immune system dysfunctions during neurodevelopment influence the vulnerability to cognitive impairments later in life is the sex. Sex differences occur in the field of psychiatry, with depression and anxiety disorders being more common in women. On the other hand, there are no marked sex differences in the prevalence of bipolar disorder and schizophrenia [74]. Sex has also been associated with differences in age of onset, course of the disorders but also symptom profile and severity, with, for example, women with major depressive disorder being more likely to experience steeper declines in memory or more severe cognitive symptoms [75]. It was recently demonstrated that maternal inflammatory response during gestation in mice induced transcriptomic changes and behavioural abnormalities (i.e. anxiety-like behaviour, social behaviour) at adulthood in a sex-specific manner, although short-term memory was not impaired [76]. This suggests that different molecular responses to an early-life immune challenge may contribute to sex difference in the vulnerability to psychiatric disorders and in the behavioural impairments displayed by males and females. This hypothesis is supported by evidence showing that postnatal LPS permanently increased the number of microglia in the dorsal and ventral hippocampus in adult rat females more than in males, although this was not associated with differences in TNF-α levels at adulthood [77]. Oestrogen is known to increase the immune response, and females may therefore

have more pronounced response to an immune challenge, changing their vulnerability to adult-onset psychiatric disorders [78].

A promising direction for future work in the field is the study of gene-environment interplay. Environmental factors in genetically vulnerable individuals may be necessary for the expression of cognitive impairments in psychiatric patients. This has already been suggested for the expression of the disorders themselves, in particular for schizophrenia [79], but to our knowledge, it is still unknown for cognitive impairments. The effect of an environmental exposure would be greater in the presence of a susceptibility gene. This also suggests that it might be more difficult to detect susceptibility gene if the presence of an environmental stressor is required. Strategies to identify immune candidate genes that interact with environmental stressors could therefore lead to preventive strategies, since eliminating exposure to the environmental stressors in genetically susceptible individuals could prevent the expression of cognitive impairments at adulthood. In addition, if the environmental exposure cannot be prevented, identification of genetically susceptible individuals may help to detect cognitive impairments in the early stages of the disorder and therefore allow early intervention strategies, using psychological, physical or pharmacological treatment aiming at improving cognitive dysfunction in psychiatric patients [80].

To conclude, we believe that the data discussed in this chapter are small pieces of a much bigger picture in which the immune system throughout life is critically involved in the development of maintenance of normal brain and pathological function and cognition. More research is necessary on the complex influence of immune cells and inflammatory mediators, particularly cytokines, on cognition, in order to identify vulnerable individuals and develop preventive and therapeutic strategies to reduce the detrimental impact of cognitive impairments on psychiatric patients.

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