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Review

Perinatal inflammation and adult psychopathology: From preclinical models to humans

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ABSTRACT

Perinatal environment plays a crucial role in brain development and determines its function through life. Epidemiological studies and clinical reports link perinatal exposure to infection and/or immune activation to various psychiatric disorders. In addition, accumulating evidence from animal models shows that perinatal inflammation can affect various behaviors relevant to psychiatric disorders such as schizophrenia, autism, anxiety and depression. Remarkably, the effects on behavior and brain function do not always depend on the type of inflammatory stimulus or the perinatal age targeted, so diverse inflammatory events can have similar consequences on the brain. Moreover, other perinatal environmental factors that affect behavior (e.g. diet and stress) also elicit inflammatory responses. Understanding the interplay between perinatal environment and inflammation on brain development is required to identify the mechanisms through which perinatal inflammation affect brain function in the adult animal. Evidence for the role of the peripheral immune system and glia on perinatal programming of behavior is discussed in this review, along with recent evidence for the role of epigenetic mechanisms affecting gene expression in the brain.

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1. Introduction

Adult brain function is the result of a genetic developmental program and its interaction with the external environment throughout life. Many lines of research seek to understand how psychiatric disorders emerge both from the genome and its environment. Although many psychiatric disorders such as schizophrenia and autism have a big genetic contribution [1,2], the environment is emerging as a key determinant of brain health and malfunction. The perinatal environment in particular has been identified as a key factor that impacts brain development and has long-term consequences on its function [3].

Perinatal programming refers to the ability of an environmental event to affect the normal course of development, resulting in an adult animal whose physiology and/or behavior has been significantly impaired [4]. Many environmental factors are known to affect neurodevelopment and result in long-term alterations in brain physiology. Examples are toxins [5], stress [6], infection [7], drugs [8], and alcohol [9]. Moreover, changes in normal perinatal stimuli such as maternal care or diet can have profound, lasting effects on adult behavior [10]. As many environmental factors affect similar brain functions and behaviors, current studies are aimed at understanding how these factors converge in the developing brain. Inflammatory responses and peripheral immune system function are prime candidates as critical components of perinatal programming, as most adverse early events appear to elicit immune or inflammatory responses in the host. Here I will review the effects of perinatal inflammation on adult behavior, the links between environmental factors and inflammation, and the mechanisms proposed to underlie perinatal programming.

Studies on animal models are consistent with clinical studies in showing an increased risk for psychiatric disorders in individuals perinatally exposed to infection or to other inflammatory stimuli. For example, children prenatally exposed to influenza, rubella, measles, varicella-zoster, or diphtheria are at higher risk for schizophrenia [11,12]. Similarly, autism spectrum disorder (ASD) has been associated with perinatal rubella virus, cytomegalovirus, herpes simplex virus, varicella-zoster virus, enteroviruses and syphilis infection [reviewed in Ref. [13]]. There is increasing evidence for prenatal viral infection as the principal non-genetic cause of autism [14]. Finally, mood disorders have also been linked to perinatal infection [reviewed in Ref. [15]]. Animal models have emerged as critical tools for establishing the links between perinatal inflammation and psychiatric disorders and to elucidate underlying mechanisms.

2. Perinatal inflammation affects adult brain physiology and behavior

Two critical factors should be considered when developing animal models for the effects of perinatal inflammation on brain development: the nature of the inflammogen and the age of the animal. Researchers have used a variety of inflammatory stimuli, administered at different prenatal and postnatal ages, to test if perinatal infection in rodents affects adult behavior and brain function relevant to psychiatric disorders (Table 1).

2.1. Eliciting perinatal inflammation

Bacteria, viruses and parasites can trigger inflammatory responses in mammals, and the nature and extent of this response depends on the nature of the pathogen. Specific receptors recognize pathogen-associated molecular patterns that consist of molecular motifs that are conserved within a class of microbes. Consequently, the host's cellular and molecular responses are similar for any pathogen within each class. Therefore, some pathogen-free strategies are often used to model a bacterial or viral infection.

Bacterial infection is frequently modeled employing lipopolisaccharides (LPS). LPS is the main component of the outer membrane of Gram-negative bacteria, recognized by Toll-like receptors 4 (TLR4) present in microglia, monocytes, dendritic cells, macrophages and B lymphocytes. Similarly, viral infection is most commonly modeled using polyriboinosinic-polyribocytidilic acid (PolyI:C), a synthetic double-stranded RNA that binds to TLR3, also present in dendritic cells, macrophages and B lymphocytes. Upon binding these pathogen recognition receptors, both LPS and PolyI:C elicit cellular responses that result in the secretion of pro-inflammatory cytokines [68]. The use of these artificial inflammogens has the advantage of being independent of the pathogen, which allows for a tightly controlled dosage and control over exposure time. However, they have limited face validity as they produce effects that are distinct from human infections, which tend to trigger a longer lasting immune response involving different stages of cell activation, proliferation, and clearance.

Other models involve inflammogens such as turpentine, the product of distillated resin. Turpentine intramuscular injection is considered a model of clinical trauma. It generates a localized injury, followed by the activation and recruitment of peripheral immune cells to the site of injury and local release of cytokines, resulting in the delayed presence of cytokines in plasma and fever [69]. These models allow for the study of the effects of endogenous inflammatory effectors without the confounding effect of the inflammogen acting on the embryo and/or the fetal/pup brain.

Finally, some models directly administer pro-inflammatory cytokines or artificially express them at specific perinatal ages to elucidate their effects on brain development. Such strategies involve both peripheral injections (intravenous or intraperitoneal [27]), and injections in the brain (intracerebroventricular or in specific brain regions [54]). Moreover, the stimuli can be acute (protein injection [27]) or chronic (viral vectors expression [54] or transgenic animals [70]).

Some long-lasting effects of inflammation on behavior are independent of the nature of the inflammogen (Table 1). For example, eliciting an inflammatory response at GD15 results in reduced prepulse inhibition (PPI) in adult rats, regardless of the inflammogen used [LPS [43], PolyI:C [32–40], or turpentine [41,42]]. However, LPS and PolyI:C have different effects on the dam and on the postnatal development of the pups [71]. The common underlying mechanism that determines the effects of these various inflammogens on brain development and adult behavior remains unknown.

The differential effects of various inflammogens are more difficult to find in the literature, as disparity in behavioral effects usually leads investigators to study different features of behavior. For example, in mice administration of PolyI:C at GD9 results in reduced exploratory behavior and reduced PPI [19–23], while a LPS challenge at GD9 results in anxiety-related behaviors [55]. So, although reports suggest that different inflammatory stimuli at

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Table 1
Rodent models of psychiatric disease based on perinatal inflammation.

Psychiatric disorder modeled	Age	Inflammatory stimulus	Species	Behavioral effects	Physiological effects	References
Schizophrenia	GD1-21	LPS	Rat	↓PPI	↑DA in NAc ↑Glial activation	[16–18]
	GD9	PolyI:C	Mouse	↓PPI ↑Exploration	↓Reelin+ cells in Hip and PFC ↓DG neurogenesis ↑Sensitivity to DA-R agonists	[19–23]
	GD9.5	Human influenza virus	Mouse	↓PPI ↓Exploration ↓Sociability ↑Neophobia	↓Purkinje cell density ↑5-HT_{2A} in PFC ↓mGlu2 in PFC ↑Sensitivity to NMDA-R agonists	[24–26]
	GD9.5	PolyI:C	Mouse	↓PPI ↓Exploration ↓Sociability ↑Neophobia	↓Purkinje cell density	[24,25,27,28]
	GD9.5	IL-6	Mouse	↓PPI		[27]
	GD12-17	PolyI:C	Mouse	↓PPI	↑Sensitivity to DA-R agonists	[29]
	GD15	PolyI:C	Mouse	↓PPI ↑AS ↓Cognitive flexibility	↓DG neurogenesis	[30,31]
	GD15	PolyI:C	Rat	↓PPI ↓LI ↓Cognitive flexibility	↑Sensitivity to DA-R agonists ↓DG neurogenesis	[32–40]
	GD15	Turpentine	Rat	↓PPI	↑Sensitivity to DA-R agonists ↑DA in NAc	[41,42]
	GD15-16	LPS	Rat	↓PPI		[43]
	GD16	PolyI:C	Mouse	↓PPI		[44]
	GD17	PolyI:C	Mouse	↓Sociability ↑LI	↑Sensitivity to DA-R agonists	[45]
	GD17	PolyI:C	Rat	↓LI	↑Sensitivity to DA-R agonists	[34]
	GD18-19	LPS	Rat	↓PPI ↑AS	↑Sensitivity to DA-R agonists	[43,46]
Autism	GD9.5	LPS	Rat	↓Vocalizations ↓Sociability		[47,48]
	GD10.5, 12.5 and 14.5	PolyI:C	Mouse	↓Vocalizations ↓Sociability ↑Repetitive behaviors		[49]
	GD12.5	PolyI:C	Mouse	↓Vocalizations ↓Sociability ↑Repetitive behaviors		[50,51]
	GD15	LPS	Mouse	↓Vocalizations	↑Spine density in DG	[52]

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Table 1 (*Continued*)

Psychiatric disorder modeled	Age	Inflammatory stimulus	Species	Behavioral effects	Physiological effects	References
				↓Sociability ↑Repetitive behaviors		
	PD3	LPS	Rat	↓Vocalizations	↑Neurogenesis	[53]
	PD14-PD28	Hip TGF-β1 (adenoviral vector)	Mouse	↓Sociability ↑Repetitive behaviors	↓Reelin+ cells in DG of Hip	[54]
Anxiety	GD9	LPS	Mouse	↓Time open arms EPM ↓Time center OF ↓Lit zone L/D	↓5-HT and NA levels in Hip ↓Reelin+ cells in Hip =Neurogenesis	[55]
	GD10.5	LPS	Rat	↓Time open arms EPM ↓Time center OF	↓ DA in NAc ↓5-HT levels in Hip	[56]
	GD17	LPS	Mouse	↓Sociability ↓Time open arms EPM		[57]
	GD17	LPS	Mouse	↓Time open arms EPM ↓Lit zone L/D		[58]
	PD3 and 5	LPS	Mouse	↓Lit zone L/D ↓Time center OF		[59]
	PD3 and 5	LPS	Rat	↓Time open arms EPM ↓Sociability		[60,61]
	PD14	LPS	Rat	↑Neophobia		[62]
	PD14	PolyI:C	Rat	↓Time open field/defensive withdrawal		[63]
Depression	GD9	LPS	Mouse	↑Immobility TST ↑Immobility FST	↓5-HT and NA levels in Hip ↓Reelin+ cells in Hip =Neurogenesis	[55]
	GD10.5	LPS	Rat	↑Immobility FST	↓Neurogenesis ↓Spine number	[64]
	GD12.5	PolyI:C	Mouse	↑Immobility FST ↓Anhedonic behavior (sucrose preference)	↓LTP ↓Neurogenesis	[65]
	GD17	LPS	Mouse	↑Immobility TST ↑Immobility FST		[58,66]
	PD3 and 5	LPS	Mouse	↑Immobility TST ↑Immobility FST ↓Anhedonic behavior (sucrose preference)		[59]
	PD14	LPS	Mouse	↑Immobility FST		[67]
	PD14-PD28	Hip TGF-β1 (adenoviral vector)	Mouse	↑Immobility TST ↑Immobility FST	↓Reelin+ cells in DG of Hip	[54]

Abbreviations: AS, acoustic startle; D1, dopamine receptor type 1; DG, dentate gyrus; EPM, elevated plus maze; FST, forced swimming test; Hip, hippocampus; IL-6, interleukin 6; L/D, light/dark test; LI, latent inhibition; LPS, lipopolysaccharide; NAc, nucleus accumbens; NOR, novel object recognition; OF, open field test; PFC, prefrontal cortex; PolyI:C, polyriboinosinic-polyribocytidilic acid; PPI, pre-pulse inhibition; TST, tail suspension test.

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GD9 can have dissimilar effects on adult behavior in mice, specific studies testing this hypothesis should be designed and performed to support it. Such studies could shed light on some relevant clinical evidence, such as the higher risk for ASD in children born after maternal viral infection during the first trimester and maternal bacterial infection in the second trimester [72].

2.2. Developmental windows of susceptibility

At least two features could determine the windows of vulnerability to perinatal inflammation effects on development and long-term alterations in behavior and physiology. First, each stage of development is characterized by different populations of neurons proliferating, migrating, and differentiating. Second, both maternal and fetal/pup inflammatory responses change throughout pregnancy and postnatal life. In general, inflammatory responses earlier in pregnancy produce more marked effects in the offspring than later ones.

Brain development takes place both *in utero* and postnatally in rodents and humans, and different brain structures appear and mature at different ages [73]. So, each brain structure would have different periods of sensitivity to insult, and the behavioral effects of a perinatal stimulus could depend on the neuronal population affected at the time of inflammation. For example, PolyI:C injected at GD9 resulted in reduced spatial exploration, whereas the same stimulus administered at GD17 lead to perseverative behavior [19]. Moreover, PolyI:C at GD9 affects adult PPI, while no effects on PPI are observed when the inflammatory challenge is administered at GD17 [20]. Extended alterations in dopaminergic systems were observed in animals exposed to inflammation at GD9 [22], while those exposed at GD17 show more alterations in hippocampal neurons [20]. Structures like the cerebellum develop largely postnatally in the mouse [74], and accordingly, it is affected mainly by postnatal inflammatory agents [75]. Finally, the hippocampus continues to undergo neurogenesis, differentiation, and plasticity postnatally, extending throughout adulthood. Thus, postnatal inflammatory challenges mainly affect behaviors modulated by this structure [59,62,63,67], and intra-hippocampal inflammatory stimuli can have long-term effects even when administered late in the postnatal period [PD14-PD28; [54]].

The maternal, fetal and postnatal immune system responds differently to inflammatory stimuli. Hormonal changes during pregnancy modulate the maternal immune response, favoring anti-inflammatory molecules and reducing pro-inflammatory responses [76]. This effect is stronger later in pregnancy. For example, the maternal inflammatory response to locally administered turpentine is attenuated when injected at GD18, compared to GD15 [41] or to non-pregnant female rats [77]. These differences in maternal response could explain some of the disparities observed in offspring, as turpentine at GD15 affects adult PPI but turpentine at GD18 results in normal PPI [41]. The inflammatory response also changes throughout postnatal development. For example, the hypothalamus-pituitary-adrenal (HPA) axis goes through a period of hypo-response from PD1 to about PD12 [78], and this could have profound effects on the reaction of the organism to an inflammatory stimulus and its consequences.

Finally, recent evidence shows that microglia follow a specific pattern of perinatal development that can be shifted upon prenatal immune activation [79]. Consequently, perinatal inflammatory stimuli could have long-term effects on microglia function, which can in turn affect neuronal function and behavior.

2.3. Long-lasting effects on behavior

The various effects of perinatal inflammation on behavior are described in Table 1. Researchers base their claim of modeling a specific psychiatric disorder based on the domains of behavior affected. However, as some domains are affected in more than one human disorder, some authors claiming to model one disorder can be referred to model another. For example, repetitive behaviors are observed in ASD models [49,50,54], but these same models have been listed as Tourette's disorder models [80]. In Table 1 models are classified according to the claim made in the original paper.

2.3.1. Effects on schizophrenia-related behaviors

Perinatal inflammation can affect rodent behavioral tasks with translational relevance to domains affected in schizophrenia. This includes social withdrawal, cognitive impairment, and hyperactivity, each of which has been described in schizophrenia [81]. In prepulse inhibition of startle protocols (PPI), animals normally show a reduced response to a strong stimulus (auditory or tactile) when previously exposed to a weaker stimulus. Remarkably, reduction in the PPI is usually considered the main behavioral deficit of a rodent model of schizophrenia, as it models the preattentive information processing (i.e. before conscious attention) deficits observed in patients.

Reduced PPI has been observed in mice and rats prenatally exposed to inflammation, regardless of the inflammatory stimulus (LPS, PolyI:C, IL-6 or turpentine) or the prenatal age (from GD1 to GD19) (Table 1). Alterations in other behaviors are less robust as different studies show that exploration is increased after prenatal inflammation [19–23], but others show that exploration is decreased [24–28]. Latent inhibition (LI) refers to the ability to ignore irrelevant stimuli and focus on biologically important information. Schizophrenic patients show abnormalities in LI, and this has been modeled using classical conditioning protocols in rodents. Late prenatal inflammation (GD15 and GD17) results in altered LI, although the effects are different in mice and rats, being increased in the former [45] and decreased in the latter [32–40]. The physiological effect most frequently reported in prenatal inflammation models of schizophrenia is the increased sensitivity to DA receptors agonists, an effect that parallels the increased sensitivity of schizophrenic patients to psychotomimetic drugs [82].

2.3.2. Effects on autism-related behaviors

Rodent models of autism have been developed to manifest the core symptoms of ASD: inappropriate social interactions, deficits in communication, repetitive and stereotyped behaviors, and resistance to change. Therefore, the reduction in social interaction or social play, the decrease in amount and/or variety of vocalizations, the increased time spent in repetitive behaviors such as grooming or marble burying, and the resistance to change a learned task, are all considered autism-related behaviors [83].

Prenatal inflammatory challenges between GD9.5 and GD12.5 can affect all these domains [47–51]. In particular, the effects of maternal injection of PolyI:C at GD12.5 have been well characterized by different researchers, and this model shows a variety of biological alterations observed in individuals with autism [50,51,84]. In particular, animals prenatally exposed to PolyI:C show reduced sociability and more repetitive behaviors [50]. In addition, they show immune alterations that can be rescued by bone marrow transplantation [50]. Interestingly, grafted animals also undergo reversion of some behavioral deficits, showing that correcting immune function can have a positive effect on behavior. A role for gastrointestinal microbiota in the development of autism-related behavior has also been proven in animals exposed to PolyI:C at GD12.5 [51], and may be relevant to the chronic gastrointestinal inflammation observed in children with ASD [85].

Finally, the behavioral effects of cytokine transforming growth factor β1 (TGF-β1) overexpression in the brain depend on the brain structure affected and the animal's age at treatment [86]. In particular, adult TGF-β1 overexpression in the hippocam-

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pus results in decreased autism-related behaviors, whereas the opposite effect is observed when TGF-β1 overexpression occurs postnatally (between PD14 and PD28) [54]. Remarkably, early TGF-β1 overexpression results in reduced TGF-β1 expression in the adult hippocampus, suggesting that hippocampal levels of this cytokine can modulate sociability and repetitive behavior in adult animals.

2.3.3. Effects on anxiety-related behaviors

Various behavioral paradigms have been used to test anti-anxiety drugs in rodents [87]. Many of them exploit the innate tendency of rodents to explore a novel environment and the conflict elicited by a potential danger. Consequently, reduced time spent in the center of an open field (OF), in the open arms of an elevated plus maze (EPM) or in the lit zone of a light/dark box (L/D) are considered anxiety-related behaviors, and the administration of anxiolitic drugs reverts all these parameters. In addition, anxiolitic drugs increase sociability in rodents [87].

Perinatal exposure of mice or rats to LPS results in increased anxiety-related behavior, independently of the age of exposure [55–63]. This is remarkable, because it suggests that brain circuits regulating anxiety-related behaviors are susceptible to programming by inflammation throughout the entire perinatal period. When brain physiological markers were analyzed, changes in hippocampal serotonin (5-HT) levels and Reelin-positive cells were observed [55,56]. As granular cells in the dentate gyrus continue to proliferate, differentiate and remodel throughout life, changes in this neurogenic niche caused by perinatal inflammation could underlie the lasting effects observed on their function irrespective of the time of challenge [88].

2.3.4. Effects on depression-related behaviors

Antidepressant drugs diminish the immobile time that rodents show when exposed to inescapable adverse stimulus, such as water in the forced swimming test (FST) or hanging in the tail suspension test (TST) [89]. In addition, anhedonic responses to palatable sucrose solutions is also considered a depression-related behavior [90].

Similar to what is observed when anxiety-related behaviors are analyzed, perinatal inflammatory stimuli can increase depression-related behaviors in adulthood, irrespective of the time when inflammatory response was elicited [54,58,59,64–67]. Interestingly, some reports show increases in both anxiety- and depression-related behaviors after the same pro-inflammatory stimulus [55], suggesting a common biological pathway for these effects.

3. Other perinatal environmental factors can elicit an immune or inflammatory response

3.1. Stress

Not only immunological stress but also early exposure to psychological stress (e.g. maternal) can have long-term consequences on the development of the nervous system [6]. Most of our knowledge on this subject comes from animal studies, as moderate stress may not have clinical effects on the pregnant woman and/or the baby, and consequently they may not be recorded at the time of occurrence, precluding future correlational studies. However, some evidence suggests an increase of emotional disorders in subjects exposed to prenatal stress. For example, women exposed to a major earthquake are more prone to have children diagnosed with major depression later in life [91]. Similarly, children of mothers that experienced the ice storm of Quebec, Canada in 1998, showed reduced intellectual and language abilities [92]. Finally, stress at 21–34 weeks of gestation results in offspring having a higher incidence of autism [93], as did postnatal stressors during the first 6 months of life [94].

Animal models show that perinatal stress can affect neurodevelopment and adult behavior. Offspring of dams exposed to prenatal stress have increased anxiety- [95–99] and depression-related behaviors in adulthood [100–102], and they can show deficits in learning [103].

Psychological stress is transmitted from the brain to the body via two main pathways: glucocorticoid release from the HPA axis, and catecholamine release (noradrenaline/adrelanine) from the sympathetic nervous system. These stress hormones could directly affect brain development and function [104–106]. Glucocorticoids and catecholamine release initially cause an inflammatory response [107], but when the stressful stimulus persists continued exposure to glucocorticoids results in immunosuppression, which can in turn make the organism more prone to infection [108]. In addition, maternal corticotropin-releasing hormone (CRH) can cross the placenta, and the placenta itself can produce CRH in response to external or intrauterine stress [109]. CRH can then induce the expression of chemokines and cytokines in the myometrium [110]. So, prenatal stress can lead to the exposure of the fetus to inflammatory molecules, and the long-term effects on the nervous system could be due to this intra-uterine exposure to inflammation.

In addition, early life stress can affect microglia development, resulting in increased density, and altered morphology and expression profile [111]. Animal studies show that psychological stress can lead to an exacerbated inflammatory response in the brain after a subsequent immune challenge, and this increased inflammation is mediated by the priming of microglia [112]. Moreover, both psychological and inflammatory stressors can induce comparable neuroendocrine responses (activation of the HPA axis) and neurotransmitter alterations in the central nervous system (CNS), consequently sensitizing the brain to a second stressor (either psychological or immunological), thereby eliciting a state of increased stress vulnerability similar to what is observed in numerous psychiatric and neurodevelopmental disorders [113].

3.2. Maternal diet and obesity

According to the World Health Organization, overweight/obesity is among the main factors contributing to noncommunicable disease, including cardiovascular and respiratory diseases, and diabetes. In addition, under-nutrition and malnutrition are a common problem in developing countries and certain segments of society in developed countries, affecting a huge number of children born every year around the world. Emerging evidence is linking not only deficient diets but also highly caloric diets with mental health dysfunction [reviewed in [114]]. Indeed, both small and large for gestational age babies are at a higher risk of being diagnosed with psychiatric disorders later in life, including autism [10], depression and anxiety [115–118] [reviewed in [119]]. This overlap in the disorders suggests that common mechanisms could be acting when babies are exposed to restricted and excessive diets during gestation, affecting the normal development of their nervous systems.

Interestingly, obesity is considered a condition of systemic inflammation, with increased levels of circulating cytokines and chronically activated immune cells [120]. In turn, maternal malnutrition interferes with both the quality and quantity of immune factors transferred to the fetus during pregnancy and later to the breastfed neonate [121].

Research on animal models also shows a link between diet during pregnancy and lactation and changes in the offspring behavior and their inflammatory response. Maternal high fat

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diet results in increased anxiety- and depression-related behaviors, and decreased cognitive abilities in the offspring [122,123], along with hippocampal microglial activation, and increased pro-inflammatory cytokines expression in the hippocampus [124] or amygdala [125]. Moreover, animals perinatally exposed to high fat diet showed an exacerbated peripheral response to an inflammatory challenge and increased anxiety-related behavior [124,125].

Animal models of perinatal malnutrition show deficient working memory [126], increased anxiety- [119,127] and depression-related behavior [128,129], or hyperactivity [130]. Much like a perinatal high fat diet, a low protein diet can lead to altered brain expression of cytokines under normal conditions and after inflammatory and psychological stressors in the adult offspring [131], suggesting that inflammation could be underlying the neurodevelopmental effects of both deficient and excessive diets.

4. Mechanisms of inflammatory programming of adult behavior

The immune system allows mammals to fight foreign agents. Immune responses are elicited after a traumatic injury or pathogen invasion. First, pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides, peptidoglicans and nucleic acids, are recognized by Toll receptors (TLRs) present in the innate immune system cells, activating the expression of proinflammatory cytokines and chemokines. This generalized response is called inflammation, and it is mainly guided by macrophages, dendritic cells, and leukocites, which are concentrated in the infected tissue, creating an inflammatory focus. After the clearance of the pathogen and tissue repair, inflammatory responses usually deactivate. However, if the stimulus persists over time, or the response is deregulated, inflammation can turn chronic or lead to a harmful autoimmune disease. Another scenario in which inflammation can have detrimental effects is during development. Immune system responses can be essential for the fetus to survive if either the mother or the fetus is infected, but immune molecules can alter normal development with long-lasting effects on offspring.

To result in long-term consequences for adult behavior and neurophysiology, inflammatory responses must: 1) reach the brain and affect its development; 2) have effects that persist. Different mechanisms have been described to explain the lasting consequences of perinatal inflammation on adult brain function.

4.1. Peripheral and central inflammation can affect brain function and behavior

There are well-characterized pathways of communication between the peripheral immune system and the brain, including the autonomic nervous system, the HPA axis, and the direct effect of cytokines, chemokines and peripheral immune cells that enter the brain across the blood-brain barrier (BBB) [132]. Through these mechanisms it is well established that the immune system can impact behavior [133]. One well-characterized example is the effect of the inflammatory response in eliciting sickness behavior, an organized, adaptive response that involves various behaviors such as feeding, sociability, activity and sleep. It was long ago established that sickness behavior is the result of the action of one immune molecule (interleukin-1) in the brain [134]. Since then, it was demonstrated that sickness behavior is independent of the pathogen but results from the immune response, through the action of cytokines [135].

Beyond its traditional role in host defense, the immune system can communicate to the brain changes in different organs and elicit the signals necessary to change the metabolism and behavior, in order to regain homeostasis. Accordingly, sickness behavior is now regarded as an orchestrated response that promotes host survival produced by the concerted action of the brain and the immune system. The similarities between sickness behavior and some symptoms of psychiatric diseases such as depression, suggest that immune mechanisms acting on brain cells could be underlying these diseases.

Central inflammation modulates brain function. Both glia (the primary immunocompetent cells within the CNS) and peripheral immune cells communicate by releasing soluble molecules (cytokines and chemokines) and expressing their receptors. Microglia and astrocytes participate in many processes in the brain, including neuroinflammatory responses [136], neuronal activity and plasticity [137], development and integrity of the BBB [138], neuronal development [139], and adult neurogenesis [140]. During normal development, cytokines are expressed at very low levels in the CNS [141], but they can affect developing neurons and neuronal progenitors both of which express receptors for these immune molecules [142].

However, when glial cells are chronically activated they have the potential to persistently alter brain homeostasis and normal brain development, leading to disorders such as ASD or schizophrenia [143]. Accordingly, an imbalance favoring pro- over anti-inflammatory cytokines has been associated with altered brain development and higher risk of developmental disorders, such as schizophrenia [144], autism [145] and major depression [108]. Moreover, persistent microglia activation could directly affect brain function and behavior in adulthood, independently of the effects during development [146]. Finally, some early inflammatory stimuli may cause none or mild effects on brain function, but predispose the organism to a stronger response after a second hit later in life [147,148].

In summary, chronic peripheral and/or central inflammation can have profound effects on brain function and behavior. The perinatal inflammatory response, if sustained through life, could be the underlying factor affecting behaviors related to psychiatric disorders in both human patients and animal models.

4.2. Perinatal inflammation can affect brain development

Peripheral and central inflammation during the perinatal period can alter normal neuronal development [136,141], resulting in changes in neuronal function and/or brain connectivity. These changes are prime candidates as mediators of the behavioral alterations associated with perinatal inflammation. As can be observed in Table 1, different inflammatory stimuli can have diverse effects on neuronal protein expression, neurotransmitter synthesis, synaptic function, and even neuronal number. All these factors can affect neural circuits controlling specific behaviors.

In particular, schizophrenia models mainly show alterations in dopaminergic function [16–18,20,22,23,29,33–35,41–43,45,46] and reduced neurogenesis [19,25,30,31,37]. Rodent models of autism show increased spine density [52], increased neurogenesis [53] and reduced number of Reelin-positive cells [54] in the DG of the hippocampus. Finally, anxiety-related behaviors are mainly accompanied by a reduction in serotonin levels in the hippocampus [55,56], and depression-related behaviors by reduced neurogenesis [64,65]. Note that I have only included animal models of perinatal inflammation in which behavior was analyzed, but there exist many other reports that describe alterations in brain parameters that could also affect behavior.

4.3. Epigenetic mechanisms

Epigenesis plays a fundamental role in cell differentiation and is therefore a fundamental process during development. Epigenetic mechanisms that modulate gene expression include histone post-

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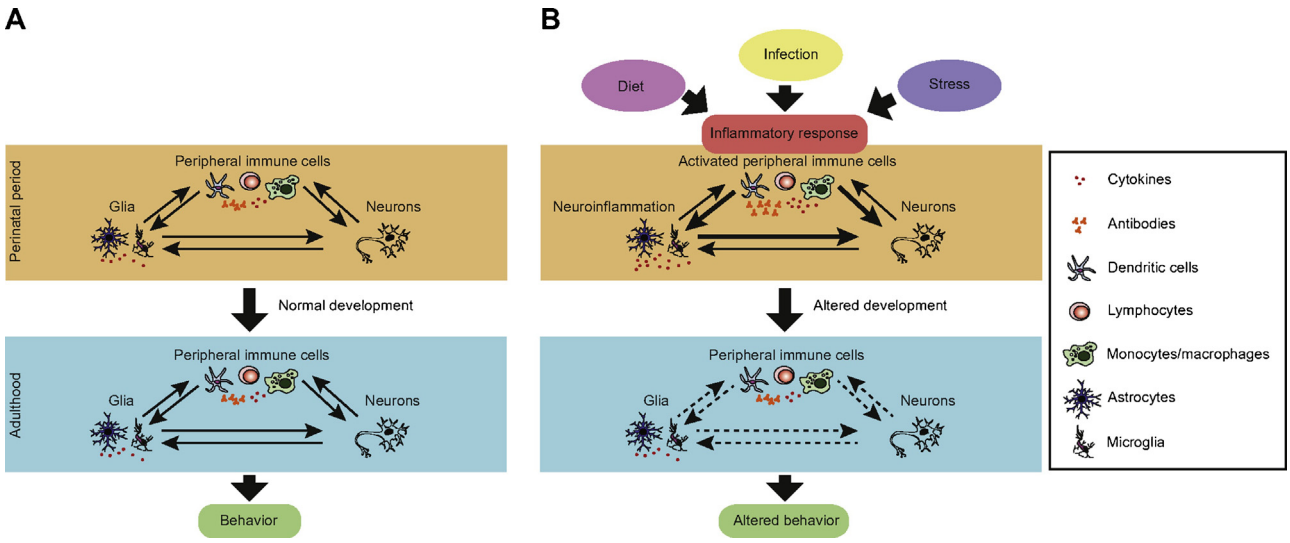

Fig. 1. Perinatal inflammation can affect adult behavior. (A) During the perinatal period, the interaction between peripheral immune cells, glia and neurons determine their development. In adulthood, behavior results from neuronal function and its regulation by immune and glial factors. (B) Infection, diet or stress can elicit an inflammatory response in the perinatal period, altering the normal path of development of peripheral immune cells, glia and neurons, along with their interplay. Then the function of these cells is permanently modified along with the interaction with the others, resulting in abnormal brain function and behavior.

translational modifications (including methylation, acetylation, phosphorilation, ubiquitination, and sumoylation), DNA methylation, noncoding long and short RNAs (including interference RNAs and microRNAs), among others. Some processes, such as X inactivation in females, occur in early stages of embryogenesis, but epigenetic modifications can happen through life. Epigenetic mechanisms generally result in the silencing or expression of genes, and therefore their occurrence during development can have significant impact on the individual.

Prenatal inflammation alters DNA methylation [149], histone methylation [150] and miRNA expression [151] in the brain. These epigenetic alterations can affect the expression of neuronal proteins, glucocorticoid receptors [152] and cytokines [153], and may therefore have long-term consequences on both brain and immune function. Moreover, the non-genetic transmission of behavioral traits is proposed to be mediated by epigenetic mechanisms and has been observed after different perinatal environmental stimuli. Interestingly, it was recently shown to occur also in a model of prenatal inflammation [PolyI:C at GD9; [154]], showing that the F2 reproduce some of the behavioral deficits observed in the F1 (reduced sociability and increased fear), do not present others (reduced PPI) and even show new behavioral alterations (increased depression-related behavior). Transgenerational transmission of behavioral deficits provides novel translational value to environmental models of psychiatric diseases, as they provide an opportunity to identify epigenetic mechanisms of increased risk for these diseases.

5. Conclusions

The evidence presented in this article is summarized in Fig. 1. In animal models, different perinatal stimuli can elicit an inflammatory response, which can affect the function and development not only of peripheral immune cells, but also glia and neurons. During development, peripheral immune cells (e.g. monocytes, dendritic cells and lymphocytes), glia, and neurons affect each other (Fig. 1A), and their interplay can be modulated by inflammation (Fig. 1B). In adulthood, such interactions determine the function of both the immune and the nervous system, and when either of these has been permanently affected, adult behavior is altered. Indeed, abundant evidence is accumulating regarding the effects of perinatal inflammation on behavioral domains relevant to different psychiatric disorders. This evidence supports clinical reports of increased susceptibility to these disorders in humans born after prenatal exposure to infection. Moreover, other risk factors such as malnutrition and stress are also linked to inflammation.

Nevertheless, the field lacks the systematic research necessary to disentangle the similarities and differences underlying the effects of various perinatal inflammatory stimuli. Although there have been attempts [155], a comprehensive assessment of the effects of different inflammogens at different ages and on different behaviors is lacking. Such an analysis could shed light on the pathways that produce lasting behavioral effects. Moreover, the evaluation of the maternal and fetal inflammatory response to various perinatal stimuli is also lacking, an understanding of which will be relevant to important questions regarding differences observed in human populations.

Finally, translation of the results from animal models to human health needs to take into account the differences in both immune and brain development between humans and rodents. As these processes do not always follow the same patterns in these species. Thus, translational value could be limited if differences are not accounted and measured [73].

Conflict of interest

The author declares no conflict of interest.

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References

[1] J. Hall, S. Trent, K.L. Thomas, M.C. O'Donovan, M.J. Owen, Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity, Biol. Psychiatry 77 (2015) 52–58.
[2] P. Lichtenstein, E. Carlstrom, M. Rastam, C. Gillberg, H. Anckarsater, The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood, Am. J. Psychiatry 167 (2010) 1357–1363.

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[3] J. Hallmayer, S. Cleveland, A. Torres, J. Phillips, B. Cohen, T. Torigoe, et al., Genetic heritability and shared environmental factors among twin pairs with autism, Arch. Genet. Psychiatry 68 (2011).
[4] L. Bennet, A.J. Gunn, The fetal origins of adult mental illness, in: E.M. Wintour, J.A. Owens (Eds.), Early Life Origins of Health and Disease, Springer, New York, 2006, pp. 204–218.
[5] P. Grandjean, P.J. Landrigan, Developmental neurotoxicity of industrial chemicals, Lancet 368 (2006) 2167–2178.
[6] S.J. Lupien, B.S. McEwen, M.R. Gunnar, C. Heim, Effects of stress throughout the lifespan on the brain, behaviour and cognition, Nat. Rev. Neurosci. 10 (2009) 434–445.
[7] A.S. Brown, Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism, Dev. Neurobiol. 72 (2012) 1272–1276.
[8] E.J. Ross, D.L. Graham, K.M. Money, G.D. Stanwood, Developmental consequences of fetal exposure to drugs: what we know and what we still must learn, Neuropsychopharmacology 40 (2015) 61–87.
[9] E.P. Riley, C.L. McGee, Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior, Exp. Biol. Med. (Maywood) 230 (2005) 357–365.
[10] P. Krakowiak, C.K. Walker, A.A. Bremer, A.S. Baker, S. Ozonoff, R.L. Hansen, et al., Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders, Pediatrics 129 (2012) e1121–1128.
[11] S.A. Mednick, R.A. Machon, M.O. Huttunen, D. Bonett, Adult schizophrenia following prenatal exposure to an influenza epidemic, Arch. Gen. Psychiatry 45 (1988) 189–192.
[12] A.S. Brown, C.A. Schaefer, R.J. Wyatt, R. Goetz, M.D. Begg, J.M. Gorman, et al., Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study, Schizophr. Bull. 26 (2000) 287–295.
[13] M. Hornig, W.I. Lipkin, Infectious and immune factors in the pathogenesis of neurodevelopmental disorders: epidemiology, hypotheses, and animal models, Ment. Retard. Dev. Disabil Res. Rev. 7 (2001) 200–210.
[14] A.L. Ciaranello, R.D. Ciaranello, The neurobiology of infantile autism, Annu. Rev. Neurosci. 18 (1995) 101–128.
[15] A.M. Simanek, H.C. Meier, Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature, Curr. Probl. Pediatr. Adolesc. Health Care 45 (2015) 325–364.
[16] E. Romero, C. Ali, E. Molina-Holgado, B. Castellano, C. Guaza, J. Borrell, Neurobehavioral and immunological consequences of prenatal immune activation in rats. Influence of antipsychotics, Neuropsychopharmacology 32 (2007) 1791–1804.
[17] J. Borrell, J.M. Vela, A. Arevalo-Martin, E. Molina-Holgado, C. Guaza, Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia, Neuropsychopharmacology 26 (2002) 204–215.
[18] E. Romero, C. Guaza, B. Castellano, J. Borrell, Ontogeny of sensorimotor gating and immune impairment induced by prenatal immune challenge in rats: implications for the etiopathology of schizophrenia, Mol. Psychiatry 15 (2010) 372–383.
[19] U. Meyer, M. Nyffeler, A. Engler, A. Urwyler, M. Schedlowski, I. Knuesel, et al., The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology, J. Neurosci. 26 (2006) 4752–4762.
[20] U. Meyer, M. Nyffeler, B.K. Yee, I. Knuesel, J. Feldon, Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice, Brain Behav. Immun. 22 (2008) 469–486.
[21] Q. Li, C. Cheung, R. Wei, E.S. Hui, J. Feldon, U. Meyer, et al., Prenatal immune challenge is an environmental risk factor for brain and behavior change relevant to schizophrenia: evidence from MRI in a mouse model, PLoS One 4 (2009) e6354.
[22] S. Vuillermot, L. Weber, J. Feldon, U. Meyer, A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia, J. Neurosci. 30 (2010) 1270–1287.
[23] S. Vuillermot, E. Joodmardi, T. Perlmann, S.O. Ogren, J. Feldon, U. Meyer, Prenatal immune activation interacts with genetic Nurr1 deficiency in the development of attentional impairments, J. Neurosci. 32 (2012) 436–451.
[24] L. Shi, S.H. Fatemi, R.W. Sidwell, P.H. Patterson, Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring, J. Neurosci. 23 (2003) 297–302.
[25] L. Shi, S.E. Smith, N. Malkova, D. Tse, Y. Su, P.H. Patterson, Activation of the maternal immune system alters cerebellar development in the offspring, Brain Behav. Immun. 23 (2009) 116–123.
[26] J.L. Moreno, M. Kurita, T. Holloway, J. Lopez, R. Cadagan, L. Martinez-Sobrido, et al., Maternal influenza viral infection causes schizophrenia-like alterations of 5-HTA and mGlu receptors in the adult offspring, J. Neurosci. 31 (2011) 1863–1872.
[27] S.E. Smith, J. Li, K. Garbett, K. Mirnics, P.H. Patterson, Maternal immune activation alters fetal brain development through interleukin-6, J. Neurosci. 27 (2007) 10695–10702.
[28] M. Makinodan, K. Tatsumi, T. Manabe, T. Yamauchi, E. Makinodan, H. Matsuyoshi, et al., Maternal immune activation in mice delays myelination and axonal development in the hippocampus of the offspring, J. Neurosci. Res. 86 (2008) 2190–2200.
[29] K. Ozawa, K. Hashimoto, T. Kishimoto, E. Shimizu, H. Ishikura, M. Iyo, Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia, Biol. Psychiatry 59 (2006) 546–554.
[30] S.A. Wolf, A. Melnik, G. Kempermann, Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia, Brain Behav. Immun. 25 (2011) 971–980.
[31] Z. Zhang, H. van Praag, Maternal immune activation differentially impacts mature and adult-born hippocampal neurons in male mice, Brain Behav. Immun. 45 (2015) 60–70.
[32] A.R. Wolff, D.K. Bilkey, Immune activation during mid-gestation disrupts sensorimotor gating in rat offspring, Behav. Brain Res. 190 (2008) 156–159.
[33] L. Zuckerman, M. Rehavi, R. Nachman, I. Weiner, Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia, Neuropsychopharmacology 28 (2003) 1778–1789.
[34] L. Zuckerman, I. Weiner, Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring, J. Psychiatr. Res. 39 (2005) 311–323.
[35] Y. Piontkewitz, M. Arad, I. Weiner, Risperidone administered during asymptomatic period of adolescence prevents the emergence of brain structural pathology and behavioral abnormalities in an animal model of schizophrenia, Schizophr. Bull. 37 (2011) 1257–1269.
[36] Y. Piontkewitz, M. Arad, I. Weiner, Abnormal trajectories of neurodevelopment and behavior following in utero insult in the rat, Biol. Psychiatry 70 (2011) 842–851.
[37] Y. Piontkewitz, H.G. Bernstein, H. Dobrowolny, B. Bogerts, I. Weiner, G. Keilhoff, Effects of risperidone treatment in adolescence on hippocampal neurogenesis, parvalbumin expression, and vascularization following prenatal immune activation in rats, Brain Behav. Immun. 26 (2012) 353–363.
[38] D.D. Dickerson, A.R. Wolff, D.K. Bilkey, Abnormal long-range neural synchrony in a maternal immune activation animal model of schizophrenia, J. Neurosci. 30 (2010) 12424–12431.
[39] A.R. Wolff, K.R. Cheyne, D.K. Bilkey, Behavioural deficits associated with maternal immune activation in the rat model of schizophrenia, Behav. Brain Res. 225 (2011) 382–387.
[40] Y. Zhang, B.N. Cazakoff, C.A. Thai, J.G. Howland, Prenatal exposure to a viral mimetic alters behavioural flexibility in male, but not female, rats, Neuropharmacology 62 (2012) 1299–1307.
[41] A. Aguilar-Valles, G.N. Luheshi, Alterations in cognitive function and behavioral response to amphetamine induced by prenatal inflammation are dependent on the stage of pregnancy, Psychoneuroendocrinology 36 (2011) 634–648.
[42] A. Aguilar-Valles, C. Flores, G.N. Luheshi, Prenatal inflammation-induced hypoferremia alters dopamine function in the adult offspring in rat: relevance for schizophrenia, PLoS One 5 (2010) e10967.
[43] M.E. Fortier, G.N. Luheshi, P. Boksa, Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy, Behav. Brain Res. 181 (2007) 270–277.
[44] J. De Miranda, K. Yaddanapudi, M. Hornig, G. Villar, R. Serge, W.I. Lipkin, Induction of Toll-like receptor 3-mediated immunity during gestation inhibits cortical neurogenesis and causes behavioral disturbances, mBio 1 (2010).
[45] B.K. Bitanihirwe, D. Peleg-Raibstein, F. Mouttet, J. Feldon, U. Meyer, Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia, Neuropsychopharmacology 35 (2010) 2462–2478.
[46] M.E. Fortier, R. Joober, G.N. Luheshi, P. Boksa, Maternal exposure to bacterial endotoxin during pregnancy enhances amphetamine-induced locomotion and startle responses in adult rat offspring, J. Psychiatr. Res. 38 (2004) 335–345.
[47] T.B. Kirsten, G.P. Chaves-Kirsten, L.M. Chaible, A.C. Silva, D.O. Martins, L.R. Britto, et al., Hypoactivity of the central dopaminergic system and autistic-like behavior induced by a single early prenatal exposure to lipopolysaccharide, J. Neurosci. Res. 90 (2012) 1903–1912.
[48] T.B. Kirsten, M. Taricano, P.C. Maiorka, J. Palermo-Neto, M.M. Bernardi, Prenatal lipopolysaccharide reduces social behavior in male offspring, Neuroimmunomodulation 17 (2010) 240–251.
[49] N.V. Malkova, C.Z. Yu, E.Y. Hsiao, M.J. Moore, P.H. Patterson, Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism, Brain Behav. Immun. 26 (2012) 607–616.
[50] E.Y. Hsiao, S.W. McBride, J. Chow, S.K. Mazmanian, P.H. Patterson, Modeling an autism risk factor in mice leads to permanent immune dysregulation, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 12776–12781.
[51] E.Y. Hsiao, S.W. McBride, S. Hsien, G. Sharon, E.R. Hyde, T. McCue, et al., Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders, Cell 155 (2013) 1451–1463.
[52] L. Fernandez de Cossio, A. Guzman, S. van der Veldt, G.N. Luheshi, Prenatal infection leads to ASD-like behavior and altered synaptic pruning in the mouse offspring, Brain Behav. Immun. 63 (2017) 88–98.
[53] Y. Pang, X. Dai, A. Roller, K. Carter, I. Paul, A.J. Bhatt, et al., Early postnatal lipopolysaccharide exposure leads to enhanced neurogenesis and impaired communicative functions in rats, PLoS One 11 (2016) e0164403.

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[54] A.M. Depino, L. Lucchina, F. Pitossi, Early and adult hippocampal TGF-beta1 overexpression have opposite effects on behavior, Brain Behav. Immun. 25 (2011) 1582–1591.
[55] A.M. Depino, Early prenatal exposure to LPS results in anxiety- and depression-related behaviors in adulthood, Neuroscience 299 (2015) 56–65.
[56] Y.L. Lin, S.Y. Lin, S. Wang, Prenatal lipopolysaccharide exposure increases anxiety-like behaviors and enhances stress-induced corticosterone responses in adult rats, Brain Behav. Immun. 26 (2012) 459–468.
[57] G. Hava, L. Vered, M. Yael, H. Mordechai, H. Mahoud, Alterations in behavior in adult offspring mice following maternal inflammation during pregnancy, Dev. Psychobiol. 48 (2006) 162–168.
[58] S. Babri, M.H. Doosti, A.A. Salari, Strain-dependent effects of prenatal maternal immune activation on anxiety- and depression-like behaviors in offspring, Brain Behav. Immun. 37 (2014) 164–176.
[59] J. Majidi, M. Kosari-Nasab, A.A. Salari, Developmental minocycline treatment reverses the effects of neonatal immune activation on anxiety- and depression-like behaviors, hippocampal inflammation, and HPA axis activity in adult mice, Brain Res. Bull. 120 (2016) 1–13.
[60] F.R. Walker, J. March, D.M. Hodgson, Endotoxin exposure in early life alters the development of anxiety-like behaviour in the Fischer 344 rat, Behav. Brain Res. 154 (2004) 63–69.
[61] T. Breivik, M. Stephan, G.E. Brabant, R.H. Straub, R. Pabst, S. von Horsten, Postnatal lipopolysaccharide-induced illness predisposes to periodontal disease in adulthood, Brain Behav. Immun. 16 (2002) 421–438.
[62] S.J. Spencer, J.G. Heida, Q.J. Pittman, Early life immune challenge–effects on behavioural indices of adult rat fear and anxiety, Behav. Brain Res. 164 (2005) 231–238.
[63] G.W. Konat, B.E. Lally, A.A. Toth, A.K. Salm, Peripheral immune challenge with viral mimic during early postnatal period robustly enhances anxiety-like behavior in young adult rats, Metab. Brain Dis. 26 (2011) 237–240.
[64] Y.L. Lin, S. Wang, Prenatal lipopolysaccharide exposure increases depression-like behaviors and reduces hippocampal neurogenesis in adult rats, Behav. Brain Res. 259 (2014) 24–34.
[65] D. Khan, P. Fernando, A. Cicvaric, A. Berger, A. Pollak, F.J. Monje, et al., Long-term effects of maternal immune activation on depression-like behavior in the mouse, Transl Psychiatry 4 (2014) e363.
[66] M. Enayati, J. Solati, M.H. Hosseini, H.R. Shahi, G. Saki, A.A. Salari, Maternal infection during late pregnancy increases anxiety- and depression-like behaviors with increasing age in male offspring, Brain Res. Bull. 87 (2012) 295–302.
[67] A.L. Dinel, C. Joffre, P. Trifilieff, A. Aubert, A. Foury, P. Le Ruyet, et al., Inflammation early in life is a vulnerability factor for emotional behavior at adolescence and for lipopolysaccharide-induced spatial memory and neurogenesis alteration at adulthood, J. Neuroinflamm. 11 (2014) 155.
[68] J. Maelfait, E. Vercammen, S. Janssens, P. Schotte, M. Haegman, S. Magez, et al., Stimulation of Toll-like receptor 3 and 4 induces interleukin-1beta maturation by caspase-8, J. Exp. Med. 205 (2008) 1967–1973.
[69] G.N. Luheshi, A. Stefferl, A.V. Turnbull, M.J. Dascombe, S. Brouwer, S.J. Hopkins, et al., Febrile response to tissue inflammation involves both peripheral and brain IL-1 and TNF-alpha in the rat, Am. J. Physiol. 272 (1997) R862–868.
[70] U. Meyer, P.J. Murray, A. Urwyler, B.K. Yee, M. Schedlowski, J. Feldon, Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling, Mol. Psychiatry 13 (2008) 208–221.
[71] D. Arsenault, I. St-Amour, G. Cisbani, L.S. Rousseau, F. Cicchetti, The different effects of LPS and poly I:C prenatal immune challenges on the behavior, development and inflammatory responses in pregnant mice and their offspring, Brain Behav. Immun. 38 (2014) 77–90.
[72] H.O. Atladottir, P. Thorsen, L. Ostergaard, D.E. Schendel, S. Lemcke, M. Abdallah, et al., Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders, J. Autism Dev. Disord. 40 (2010) 1423–1430.
[73] B.D. Semple, K. Blomgren, K. Gimlin, D.M. Ferriero, L.J. Noble-Haeusslein, Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species, Prog. Neurobiol. 106 (107) (2013) 1–16.
[74] B. Carletti, F. Rossi, Neurogenesis in the cerebellum, Neuroscientist 14 (2008) 91–100.
[75] J.F. Hoffman, C.L. Wright, M.M. McCarthy, A critical period in purkinje cell development is mediated by local estradiol synthesis, disrupted by inflammation, and has enduring consequences only for males, J. Neurosci. 36 (2016) 10039–10049.
[76] D.P. Robinson, S.L. Klein, Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis, Horm. Behav. 62 (2012) 263–271.
[77] A. Aguilar-Valles, S. Poole, Y. Mistry, S. Williams, G.N. Luheshi, Attenuated fever in rats during late pregnancy is linked to suppressed interleukin-6 production after localized inflammation with turpentine, J. Physiol. 583 (2007) 391–403.
[78] M.V. Schmidt, L. Enthoven, M. van der Mark, S. Levine, E.R. de Kloet, M.S. Oitzl, The postnatal development of the hypothalamic-pituitary-adrenal axis in the mouse, Int. J. Dev. Neurosci. 21 (2003) 125–132.
[79] O. Matcovitch-Natan, D.R. Winter, A. Giladi, S. Vargas Aguilar, S. Spinrad, S. Sarrazin, et al., Microglia development follows a stepwise program to regulate brain homeostasis, Science 353 (2016) (aad8670).
[80] M. Hornig, W.I. Lipkin, Immune-mediated animal models of Tourette syndrome, Neurosci. Biobehav. Rev. 37 (2013) 1120–1138.
[81] C.M. Powell, T. Miyakawa, Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? Biol. Psychiatry 59 (2006) 1198–1207.
[82] M. Wang, L. Pei, P.J. Fletcher, S. Kapur, P. Seeman, F. Liu, Schizophrenia, amphetamine-induced sensitized state and acute amphetamine exposure all show a common alteration: increased dopamine D2 receptor dimerization, Mol. Brain 3 (2010) 25.
[83] J.N. Crawley, Designing mouse behavioral tasks relevant to autistic-like behaviors, Ment. Retard. Dev. Disabil Res. Rev. 10 (2004) 248–258.
[84] E.Y. Hsiao, P.H. Patterson, Activation of the maternal immune system induces endocrine changes in the placenta via IL-6, Brain Behav. Immun. 25 (2011) 604–615.
[85] J.B. Adams, L.J. Johansen, L.D. Powell, D. Quig, R.A. Rubin, Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity, BMC Gastroenterol. 11 (2011) 22.
[86] A.M. Depino, Role of TGF-beta1 in the behavior disorders, Adv. Neuroimmune Biol. 6 (2015) 19–23.
[87] J.N. Crawley, Exploratory behavior models of anxiety in mice, Neurosci. Biobehav. Rev. 9 (1985) 37–44.
[88] M. Graciarena, A.M. Depino, F.J. Pitossi, Prenatal inflammation impairs adult neurogenesis and memory related behavior through persistent hippocampal TGFbeta(1) downregulation, Brain Behav. Immun. 24 (2010) 1301–1309.
[89] J.N. Crawley, Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests, Brain Res. 835 (1999) 18–26.
[90] J.F. Cryan, C. Mombereau, In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice, Mol. Psychiatry 9 (2004) 326–357.
[91] B.R. Van den Bergh, B. Van Calster, T. Smits, S. Van Huffel, L. Lagae, Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood, Neuropsychopharmacology 33 (2008) 536–545.
[92] D.P. Laplante, R.G. Barr, A. Brunet, G. Galbaud du Fort, M.L. Meaney, J.F. Saucier, et al., Stress during pregnancy affects general intellectual and language functioning in human toddlers, Pediatr. Res. 56 (2004) 400–410.
[93] D.Q. Beversdorf, S.E. Manning, A. Hillier, S.L. Anderson, R.E. Nordgren, S.E. Walters, et al., Timing of prenatal stressors and autism, J. Autism Dev. Disord. 35 (2005) 471–478.
[94] D.K. Kinney, K.M. Munir, D.J. Crowley, A.M. Miller, Prenatal stress and risk for autism, Neurosci. Biobehav. Rev. 32 (2008) 1519–1532.
[95] M. Vallee, W. Mayo, F. Dellu, M. Le Moal, H. Simon, S. Maccari, Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion, J. Neurosci. 17 (1997) 2626–2636.
[96] T. Poltyrev, E. Gorodetsky, C. Bejar, D. Schorer-Apelbaum, M. Weinstock, Effect of chronic treatment with ladostigil (TV-3326) on anxiogenic and depressive-like behaviour and on activity of the hypothalamic-pituitary-adrenal axis in male and female prenatally stressed rats, Psychopharmacology (Berl) 181 (2005) 118–125.
[97] M.E. Pallares, P.A. Scacchi Bernasconi, C. Feleder, R.A. Cutrera, Effects of prenatal stress on motor performance and anxiety behavior in Swiss mice, Physiol. Behav. 92 (2007) 951–956.
[98] H.N. Richardson, E.P. Zorrilla, C.D. Mandyam, C.L. Rivier, Exposure to repetitive versus varied stress during prenatal development generates two distinct anxiogenic and neuroendocrine profiles in adulthood, Endocrinology 147 (2006) 2506–2517.
[99] R. Rimondini, G. Agren, S. Borjesson, W. Sommer, M. Heilig, Persistent behavioral and autonomic supersensitivity to stress following prenatal stress exposure in rats, Behav. Brain Res. 140 (2003) 75–80.
[100] S.J. Alonso, C. Damas, E. Navarro, Behavioral despair in mice after prenatal stress, J. Physiol. Biochem. 56 (2000) 77–82.
[101] C.A. Frye, J. Wawrzycki, Effect of prenatal stress and gonadal hormone condition on depressive behaviors of female and male rats, Horm. Behav. 44 (2003) 319–326.
[102] S. Morley-Fletcher, M. Darnaudery, M. Koehl, P. Casolini, O. Van Reeth, Prenatal stress in rats predicts immobility behavior in the forced swim test. Effects of a chronic treatment with tianeptine, Brain Res. 989 (2003) 246–251.
[103] V. Lemaire, M. Koehl, M. Le Moal, D.N. Abrous, Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 11032–11037.
[104] J.S. Meyer, Early adrenalectomy stimulates subsequent growth and development of the rat brain, Exp. Neurol. 82 (1983) 432–446.
[105] S. Morley-Fletcher, M. Darnaudery, E. Mocaer, N. Froger, L. Lanfumey, G. Laviola, et al., Chronic treatment with imipramine reverses immobility behaviour, hippocampal corticosteroid receptors and cortical 5-HT(1A) receptor mRNA in prenatally stressed rats, Neuropharmacology 47 (2004) 841–847.

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[106] H.E. Ward, E.A. Johnson, A.K. Salm, D.L. Birkle, Effects of prenatal stress on defensive withdrawal behavior and corticotropin releasing factor systems in rat brain, Physiol. Behav. 70 (2000) 359–366.
[107] B.S. McEwen, Protective and damaging effects of stress mediators: central role of the brain, Dialogues Clin. Neurosci. 8 (2006) 367–381.
[108] F.S. Dhabhar, Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology, Neuroimmunomodulation 16 (2009) 300–317.
[109] M. Torricelli, R. Novembri, E. Bloise, M. De Bonis, J.R. Challis, F. Petraglia, Changes in placental CRH, urocortins, and CRH-receptor mRNA expression associated with preterm delivery and chorioamnionitis, J. Clin. Endocrinol. Metab. 96 (2011) 534–540.
[110] X. You, J. Liu, C. Xu, W. Liu, X. Zhu, Y. Li, et al., Corticotropin-releasing hormone (CRH) promotes inflammation in human pregnant myometrium: the evidence of CRH initiating parturition? J. Clin. Endocrinol. Metab. 99 (2014) E199–208.
[111] J.C. Delpech, L. Wei, J. Hao, X. Yu, C. Madore, O. Butovsky, et al., Early life stress perturbs the maturation of microglia in the developing hippocampus, Brain Behav. Immun. 57 (2016) 79–93.
[112] M.G. Frank, M.V. Baratta, D.B. Sprunger, L.R. Watkins, S.F. Maier, Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses, Brain Behav. Immun. 21 (2007) 47–59.
[113] S. Hayley, Z. Merali, H. Anisman, Stress and cytokine-elicited neuroendocrine and neurotransmitter sensitization: implications for depressive illness, Stress 6 (2003) 19–32.
[114] J.L. Bolton, S.D. Bilbo, Developmental programming of brain and behavior by perinatal diet: focus on inflammatory mechanisms, Dialogues Clin. Neurosci. 16 (2014) 307–320.
[115] I. Colman, A. Ataullahjan, K. Naicker, R.J. Van Lieshout, Birth weight, stress, and symptoms of depression in adolescence: evidence of fetal programming in a national Canadian cohort, Can. J. Psychiatry 57 (2012) 422–428.
[116] G.S. Moore, A.W. Kneitel, C.K. Walker, W.M. Gilbert, G. Xing, Autism risk in small- and large-for-gestational-age infants, Am. J. Obstet. Gynecol. 206 (314) (2012) e311–e319.
[117] D.L. Rofey, R.P. Kolko, A.M. Iosif, J.S. Silk, J.E. Bost, W. Feng, et al., A longitudinal study of childhood depression and anxiety in relation to weight gain, Child Psychiatry Hum. Dev. 40 (2009) 517–526.
[118] L.B. Dahl, P.I. Kaaresen, J. Tunby, B.H. Handegard, S. Kvernmo, J.A. Ronning, Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight, Pediatrics 118 (2006) e449–459.
[119] N.M. Grissom, T.M. Reyes, Gestational overgrowth and undergrowth affect neurodevelopment: similarities and differences from behavior to epigenetics, Int. J. Dev. Neurosci. 31 (2013) 406–414.
[120] T.D. Kanneganti, V.D. Dixit, Immunological complications of obesity, Nat. Immunol. 13 (2012) 707–712.
[121] A.C. Palmer, Nutritionally mediated programming of the developing immune system, Adv. Nutr. 2 (2011) 377–395.
[122] H. Yu, Y. Bi, W. Ma, L. He, L. Yuan, J. Feng, et al., Long-term effects of high lipid and high energy diet on serum lipid, brain fatty acid composition, and memory and learning ability in mice, Int. J. Dev. Neurosci. 28 (2010) 271–276.
[123] D. Peleg-Raibstein, E. Luca, C. Wolfrum, Maternal high-fat diet in mice programs emotional behavior in adulthood, Behav. Brain Res. 233 (2012) 398–404.
[124] S.D. Bilbo, V. Tsang, Enduring consequences of maternal obesity for brain inflammation and behavior of offspring, FASEB J. 24 (2010) 2104–2115.
[125] A. Sasaki, W.C. de Vega, S. St-Cyr, P. Pan, P.o. McGowan, Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood, Neuroscience 240 (2013) 1–12.
[126] S.C. Ranade, A. Rose, M. Rao, J. Gallego, P. Gressens, S. Mani, Different types of nutritional deficiencies affect different domains of spatial memory function checked in a radial arm maze, Neuroscience 152 (2008) 859–866.
[127] L.A. Reyes-Castro, J.S. Rodriguez, R. Charco, C.J. Bautista, F. Larrea, P.W. Nathanielsz, et al., Maternal protein restriction in the rat during pregnancy and/or lactation alters cognitive and anxiety behaviors of female offspring, Int. J. Dev. Neurosci. 30 (2012) 39–45.
[128] Z. Vucetic, K. Totoki, H. Schoch, K.W. Whitaker, T. Hill-Smith, I. Lucki, et al., Early life protein restriction alters dopamine circuitry, Neuroscience 168 (2010) 359–370.
[129] L.M. Belluscio, C.D. Alberca, N. Pregi, E.T. Canepa, Altered gene expression in hippocampus and depressive-like behavior in young adult female mice by early protein malnutrition, Genes Brain Behav. 15 (2016) 741–749.
[130] A.A. Naik, I.K. Patro, N. Patro, Slow physical growth, delayed reflex ontogeny, and permanent behavioral as well as cognitive impairments in rats following intra-generational protein malnutrition, Front. Neurosci. 9 (2015) 446.
[131] N.M. Grissom, R. George, T.M. Reyes, Suboptimal nutrition in early life affects the inflammatory gene expression profile and behavioral responses to stressors, Brain Behav. Immun. 63 (2017) 115–126.
[132] K.J. Tracey, Reflex control of immunity, Nat. Rev. Immunol. 9 (2009) 418–428.
[133] R. Dantzer, J.C. O'Connor, G.G. Freund, R.W. Johnson, K.W. Kelley, From inflammation to sickness and depression: when the immune system subjugates the brain, Nat. Rev. Neurosci. 9 (2008) 46–56.
[134] S. Kent, R.M. Bluthe, R. Dantzer, A.J. Hardwick, K.W. Kelley, N.J. Rothwell, et al., Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 9117–9120.
[135] R. Dantzer, K.W. Kelley, Twenty years of research on cytokine-induced sickness behavior, Brain Behav. Immun. 21 (2007) 153–160.
[136] H.F. Green, Y.M. Nolan, Inflammation and the developing brain: consequences for hippocampal neurogenesis and behavior, Neurosci. Biobehav. Rev. 40 (2014) 20–34.
[137] V. Parpura, M.T. Heneka, V. Montana, S.H. Oliet, A. Schousboe, P.G. Haydon, et al., Glial cells in (patho)physiology, J. Neurochem. 121 (2012) 4–27.
[138] W.A. Banks, The blood-brain barrier: connecting the gut and the brain, Regul. Pept. 149 (2008) 11–14.
[139] R.C. Paolicelli, G. Bolasco, F. Pagani, L. Maggi, M. Scianni, P. Panzanelli, et al., Synaptic pruning by microglia is necessary for normal brain development, Science 333 (2011) 1456–1458.
[140] S. Das, A. Basu, Inflammation: a new candidate in modulating adult neurogenesis, J. Neurosci. Res. 86 (2008) 1199–1208.
[141] B.E. Deverman, P.H. Patterson, Cytokines and CNS development, Neuron 64 (2009) 61–78.
[142] R. Yirmiya, I. Goshen, Immune modulation of learning, memory, neural plasticity and neurogenesis, Brain Behav. Immun. 25 (2011) 181–213.
[143] S.D. Bilbo, J.M. Schwarz, Early-life programming of later-life brain and behavior: a critical role for the immune system, Front. Behav. Neurosci. 3 (14) (2009).
[144] U. Meyer, J. Feldon, Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia, Psychopharmacology (Berl) 206 (2009) 587–602.
[145] A.M. Depino, Peripheral and central inflammation in autism spectrum disorders, Mol. Cell. Neurosci. 53 (2013) 69–76.
[146] L. Lucchina, A.M. Depino, Altered peripheral and central inflammatory responses in a mouse model of autism, Autism Res. 7 (2014) 273–289.
[147] S. Giovanoli, H. Engler, A. Engler, J. Richetto, J. Feldon, M.A. Riva, et al., Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia, Transl. Psychiatry 6 (2016) e772.
[148] S. Giovanoli, H. Engler, A. Engler, J. Richetto, M. Voget, R. Willi, et al., Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice, Science 339 (2013) 1095–1099.
[149] P. Basil, Q. Li, E.L. Dempster, J. Mill, P.C. Sham, C.C. Wong, et al., Prenatal maternal immune activation causes epigenetic differences in adolescent mouse brain, Transl. Psychiatry 4 (2014) e434.
[150] C.M. Connor, A. Dincer, J. Straubhaar, J.R. Galler, I.B. Houston, S. Akbarian, Maternal immune activation alters behavior in adult offspring, with subtle changes in the cortical transcriptome and epigenome, Schizophr. Res. 140 (2012) 175–184.
[151] S.L. Hollins, K. Zavitsanou, F.R. Walker, M.J. Cairns, Alteration of imprinted Dlk1-Dio3 miRNA cluster expression in the entorhinal cortex induced by maternal immune activation and adolescent cannabinoid exposure, Transl. Psychiatry 4 (2014) e452.
[152] I.C. Weaver, J. Diorio, J.R. Seckl, M. Szyf, M.J. Meaney, Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites, Ann. N. Y. Acad. Sci. 1024 (2004) 182–212.
[153] S.L. Kigar, L. Chang, A.P. Auger, Gadd45b is an epigenetic regulator of juvenile social behavior and alters local pro-inflammatory cytokine production in the rodent amygdala, Brain Behav. Immun. 46 (2015) 60–69.
[154] U. Weber-Stadlbauer, J. Richetto, M.A. Labouesse, J. Bohacek, I.M. Mansuy, U. Meyer, Transgenerational transmission and modification of pathological traits induced by prenatal immune activation, Mol. Psychiatry 22 (2017) 102–112.
[155] U. Meyer, J. Feldon, M. Schedlowski, B.K. Yee, Immunological stress at the maternal-foetal interface: a link between neurodevelopment and adult psychopathology, Brain Behav. Immun. 20 (2006) 378–388.

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