Titolo rivista/libro: Nature reviews. Neurology Online

Titolo articolo/sezione: Maternal immune activation and neuroinflammation in human neurodevelopmental disorders

Autore/i: Velda X. Han, Shrujna Patel, Hannah F. Jones & Russell C. Dale

ISSN: 1759-4766

DOI: 10.1038/s41582-021-00530-8

Anno: 2021

Volume: 17

Fascicolo: 564

Editore:

Pag. iniziale: 579

Pag. finale:

Maternal immune activation and neuroinflammation in human neurodevelopmental disorders

Velda X. Han[1,2], *Shrujna Patel*[1,3], *Hannah F. Jones*[1,4] *and Russell C. Dale*[1,3,5]✉

Abstract | Maternal health during pregnancy plays a major role in shaping health and disease risks in the offspring. The maternal immune activation hypothesis proposes that inflammatory perturbations in utero can affect fetal neurodevelopment, and evidence from human epidemiological studies supports an association between maternal inflammation during pregnancy and offspring neurodevelopmental disorders (NDDs). Diverse maternal inflammatory factors, including obesity, asthma, autoimmune disease, infection and psychosocial stress, are associated with an increased risk of NDDs in the offspring. In addition to inflammation, epigenetic factors are increasingly recognized to operate at the gene–environment interface during NDD pathogenesis. For example, integrated brain transcriptome and epigenetic analyses of individuals with NDDs demonstrate convergent dysregulated immune pathways. In this Review, we focus on the emerging human evidence for an association between maternal immune activation and childhood NDDs, including autism spectrum disorder, attention-deficit/hyperactivity disorder and Tourette syndrome. We refer to established pathophysiological concepts in animal models, including immune signalling across the placenta, epigenetic 'priming' of offspring microglia and postnatal immune–brain crosstalk. The increasing incidence of NDDs has created an urgent need to mitigate the risk and severity of these conditions through both preventive strategies in pregnancy and novel postnatal therapies targeting disease mechanisms.

Neurodevelopmental disorders (NDDs) with onset in early childhood, including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and Tourette syndrome (TS), are increasing in prevalence and should be considered a health priority[1]. The estimated prevalence of ASD in the USA was 1 in 10,000 in the 1970s, 1 in 150 in 2000 and 1 in 54 in 2016 (REF.[2]), and NDDs combined currently affect 1 in 6 children in the US population[1]. NDDs are more commonly diagnosed in males than in females and often coexist with overlapping symptoms, including repetitive patterns of behaviour and deficits in social cognition, sensorimotor control and executive function[3]. ASD has been described as the human disorder with the highest economic impact on society, yet aetiology-specific treatments are lacking[4].

The genetic contribution to NDD risk has been demonstrated in twin, familial and genome-wide association studies[5]. However, the genomic risk of NDDs is mostly attributed to vulnerability alleles with low penetrance, and highly penetrant monogenic aetiologies account for a small minority of cases[5]. Evidence is accumulating of shared genetic aetiologies in NDDs, with factors such as gene–environment interactions and the sex of the offspring influencing the phenotypic expression of disease[6,7]. The increasing prevalence of NDDs probably reflects changing diagnostic practices and alterations in environmental influences rather than an increase in de novo DNA variants[1]. Over the past century, the prevalence of infectious diseases, such as tuberculosis, has decreased, whereas the prevalence of inflammatory disorders, such as autoimmune disease, asthma and allergies, has increased[8]. The same period has seen rapid urbanization and alterations in diet, along with increasing obesity[9]. As we discuss in this Review, maternal exposure to these factors could be linked to an increased risk of NDDs in the offspring.

The role of inflammation and epigenetic factors at the gene–environment interface during NDD pathogenesis is increasingly recognized[10–13]. Environmental factors, including diet, exercise, sleep, socioeconomic status, stress, exposure to pollutants and the gut microbiome, collectively termed the exposome, have been proposed to alter the transcription of susceptibility genes and to modulate the expression of NDDs[14–17]. When individuals

✉*e-mail: russell.dale@sydney.edu.au*

https://doi.org/10.1038/s41582-021-00530-8

Key points

- Human studies are uncovering a role for maternal immune activation (MIA) in the pathogenesis of common neurodevelopmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder and Tourette syndrome, in the offspring.
- Prenatal, in utero and postnatal embedding of environmental factors in the epigenetic architecture of both the brain and the peripheral immune system can modulate individual susceptibility to neurodevelopmental disorders.
- The effects of MIA, mediated by acute and chronic inflammation in pregnancy, are transduced to the fetus through inflammatory cell signalling pathways and epigenetic mechanisms.
- Pathogen-associated molecular patterns, damage-associated molecular patterns and Toll-like receptors represent a convergent cellular pathway between heterogeneous environmental factors and innate immune activation.
- In conjunction with individual genetic risk, sex-related factors and second 'immune' hits during life, MIA-induced aberrant immune programming results in a loss of immune homeostasis, which is associated with behavioural abnormalities in animal models.

are faced with environmental threats, the activation of an inflammatory response provides protection from pathogens and promotes tissue recovery to maintain cellular homeostasis[18]. However, excessive or dysregulated inflammation can cause pathological imprinting of the immune system, resulting in susceptibility to chronic diseases[19]. Inflammation plays a prominent role in signalling at the cellular–environmental interface and the resulting cellular responses are regulated through finely tuned epigenetic mechanisms[20] (BOX 1). Environmental factors throughout life can cause specific, long-lasting 'biological embedding' of external exposures into the epigenetic architecture of the individual[21,22].

During pregnancy, environmental insults experienced by the mother are hypothesized to programme the immune and developmental epigenetic code of the offspring, thereby influencing vulnerability to NDDs later in life[23,24] (FIG. 1). The maternal immune activation (MIA) hypothesis proposes that exposure to a dysregulated maternal immune milieu in utero affects fetal neurodevelopment[25,26]. The gestation period is a time of particular vulnerability as key brain processes and networks are rapidly established in the developing fetus[25] (FIG. 1). 'Critical periods' of neurodevelopment are directed by the genetic code and shaped through interactions with the development of the immune system, gut microbiome, stress axis and sexual characteristics in the fetus[27,28] (FIG. 1). Perturbations to the developing brain during these critical periods can interfere with the typical developmental trajectory, resulting in enduring effects on the individual[28].

Author addresses

[1]Kids Neuroscience Centre, The Children's Hospital at Westmead, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia.
[2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore.
[3]The Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia.
[4]Department of Neuroservices, Starship Children's Hospital, Auckland, New Zealand.
[5]The Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia.

Several previous reviews have provided in-depth discussions of MIA in animal models[29–33]; however, a complementary review on the emerging human data has been lacking until now. In this Review, we focus on evidence that maternal inflammation in pregnancy has a deleterious effect on fetal neurodevelopment in humans. In animal models, the transfer of maternal inflammation to the offspring during pregnancy can be readily observed through the examination of maternal blood, placenta and offspring brain. However, access to such tissues is more limited in humans and the evidence has been acquired through multiple methodologies, including epidemiological studies. Therefore, although we focus on emerging human evidence of MIA as a risk factor for NDDs, we also refer to immune and epigenetic mechanisms that have been demonstrated in animal models. Finally, we discuss potential therapeutic opportunities to target abnormal immune or epigenetic processes.

Epidemiological evidence of MIA in humans

Clinical observations of elevated rates of ASD and schizophrenia in the offspring of pregnancies that coincided with seasonal outbreaks and epidemics of rubella, influenza, measles, mumps and polio highlighted a possible link between gestational infections and neurodevelopmental outcomes[34]. Subsequently, a wide range of maternal infections, including viral, bacterial and protozoan infections, were found to increase the risk of neurological and neuropsychiatric disorders in the offspring[34]. Although some agents, such as TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex) and Zika virus, can directly infect the fetus through vertical transmission, other non-transmissible maternal infections occurring during pregnancy have been shown to increase the risk of NDDs in the offspring. A meta-analysis of 15 studies found that common maternal bacterial infections during pregnancy, including genitourinary and skin infections, increased the odds of offspring ASD by 13%[35]. Maternal genitourinary infections increased the odds of offspring ADHD by 26–33% and mothers with viral respiratory infections during pregnancy had a threefold increased risk of having a child with ADHD[36–38]. The association between heterogeneous prenatal infections and a spectrum of NDDs suggested common immune mechanistic pathways.

Beyond infections, evidence is increasing that diverse chronic inflammatory conditions during pregnancy are notable risk factors for offspring NDDs[39,40] (FIG. 2). Acute infections can provoke high-grade acute inflammatory responses, and other environmental, psychosocial and biological factors might prevent the resolution of acute inflammation and promote a state of low-grade sterile systemic chronic inflammation[41]. Maternal autoimmune disease during pregnancy is an independent risk factor for ASD, ADHD and TS[42–45], and maternal asthma was associated with offspring ASD and ADHD in several population-based studies[46–49]. Maternal obesity has a dose-dependent relationship with offspring ASD and ADHD[50,51]. In addition, mothers with low socioeconomic status are twice as likely to have a child with ADHD or TS than are mothers with middle or high

Box 1 | **Overview of epigenetics**

Epigenetics is defined as "the study of changes in gene function that are heritable and do not entail a change in DNA sequence"[20]. Epigenetic modifications comprise chemical or physical changes to chromatin — a DNA–protein complex in which DNA is wrapped around histone proteins to form nucleosomes, which are further compressed into chromosomes.

The four main epigenetic modifying factors are DNA methylation, histone modifications, chromatin modelling and microRNA. DNA methylation involves the covalent transfer of a methyl group to the cytosine ring of DNA by DNA methyltransferases. DNA methylation in promoter regions known as CpG sites represses gene transcription, whereas DNA methylation in the gene body promotes transcription[58]. Histone modifications on specific residues control the relaxation or tightening of the chromatin structure, thereby regulating DNA accessibility to transcription factors[20]. Many different types of histone modification have been observed but histone acetylation and methylation are the most studied[20]. Histone acetylation results in increased gene transcription, whereas histone deacetylation is associated with transcriptional inhibition[20]. Histone methylation increases or represses gene transcription depending on the specific amino acids in the histone that are methylated and the degree of methylation[20]. MicroRNAs, which are short non-coding nucleic acids, bind to mRNA and regulate gene expression by blocking translation or inducing degradation of the target mRNA[58]. These epigenetic factors are further divided into writers, readers and erasers depending on the specific chemical modification that they catalyse as well as on their roles in interpreting the modifications[20].

Epigenetic mechanisms play crucial roles in normal brain development and are highly sensitive to environmental factors such as inflammatory responses[124]. Dynamic changes to the epigenetic pattern in response to environmental stimuli during development calibrate and refine cell differentiation, maturation and homeostasis[124].

socioeconomic status[52,53]. Other heterogeneous maternal inflammatory states, including gestational diabetes, pre-eclampsia, depression and exposure to smoking or other air pollutants, are also associated with an increased risk of offspring NDDs[40].

The timing of maternal exposure influences the development of offspring NDDs. For example, maternal asthma in the first and second trimesters was found to be associated with childhood ASD[54], whereas maternal bacterial infections and negative life events in the third trimester increased the odds of ASD and ADHD in the offspring[35,55].

Overall, data linkage studies provide convincing evidence that individual and cumulative maternal pro-inflammatory states confer risk of a range of offspring NDDs[40,56] (FIG. 2). However, each pro-inflammatory state could have numerous mechanisms of action. Autoimmune disease and asthma are clearly immunological, whereas obesity and stress, although pro-inflammatory, might also affect neurodevelopment through metabolic stress, oxidative stress and neuroendocrine mechanisms.

Maternal inflammatory response during pregnancy

Evidence from MIA animal models. Studies in animal models have established that the maternal immune response is sufficient to cause NDDs independently of the inciting pathogen or risk factor[25] (FIG. 1). In early rodent models of maternal influenza infection during pregnancy, the offspring showed aberrant brain morphology mediated by altered gene regulation as well as behavioural and cognitive deficits consistent with ASD[57]. These findings prompted the use of immunostimulants, including viral mimic polyinosinic:polycytidylic acid (poly(I:C)) and bacterial mimic lipopolysaccharide (LPS), to study the effects of maternal and fetal cytokine immune responses on offspring brain development[31,58]. These MIA animal models showed changes in offspring brain and immune function in association with behavioural problems consistent with NDDs[31,58]. Subsequently, other immunostimulants, including cytokines, and maternal exposure to non-infectious environmental factors, such as a high-fat diet, stress, pollution and asthma, were found to produce similar histological, transcriptional and behavioural manifestations in the offspring brain to those seen in classic poly(I:C) and LPS MIA models[59–61]. These preclinical findings were consistent with human epidemiological data.

Experiments in multi-exposure animal models revealed that a combination of environmental factors could have synergistic or multiplicative effects on offspring neurobehavioural outcomes[60,62]. The initial studies indicated that earlier MIA, more intense immunogenic stimuli and elevated maternal immune responses resulted in worse offspring neurobehavioural outcomes[63,64]. Subsequent studies demonstrated that offspring displayed different — but not necessarily more severe — behavioural outcomes depending on the timing, intensity and specificity of the immune insult as well as on the degree of maternal immune response[65,66].

Inflammatory factors converge on common immune pathways. Animal studies have established that Toll-like receptors (TLRs), triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), are a potential convergent molecular pathway linking heterogeneous maternal inflammatory factors and immune-mediated disruption of offspring brain development (FIG. 3). PAMPs and DAMPs, which are the first signals induced by exogenous and endogenous threats, respectively, are detected by TLRs, which activate the innate immune system to produce pro-inflammatory cytokines[67] (FIG. 3). TLRs are pattern recognition receptors expressed on peripheral immune cells and CNS cells, including microglia and neurons[68]. Classic animal models of MIA use the PAMPs poly(I:C) and LPS, which stimulate TLR3 and TLR4, respectively, to trigger a maternal inflammatory response[31]. DAMPs, such as self RNA, self DNA, high mobility group protein B1 (HMGB1) and heat shock proteins (HSPs), are normal cell constituents that are released from endogenous damaged cells[67,68]. Diverse factors from the exposome as well as disease states, including obesity, pre-eclampsia, depression and asthma, result in an increased cellular release of DAMPs[69–71].

In humans, chronic inflammatory conditions, such as diabetes, pre-eclampsia and depression, lead to elevation of HMGB1 levels, which stimulates TLR4 (REFS[69,70,72]). In autoimmune diseases, such as psoriasis and systemic lupus erythematosus (SLE), inappropriate accumulation of self RNA and self DNA causes activation of intracellular TLRs[73].

The available evidence indicates that a range of environmental factors and disease states that can complicate pregnancy converge on TLR pathways, with potential downstream effects on adaptive immunity in the maternal blood, placenta and fetal brain. Evidence of TLR

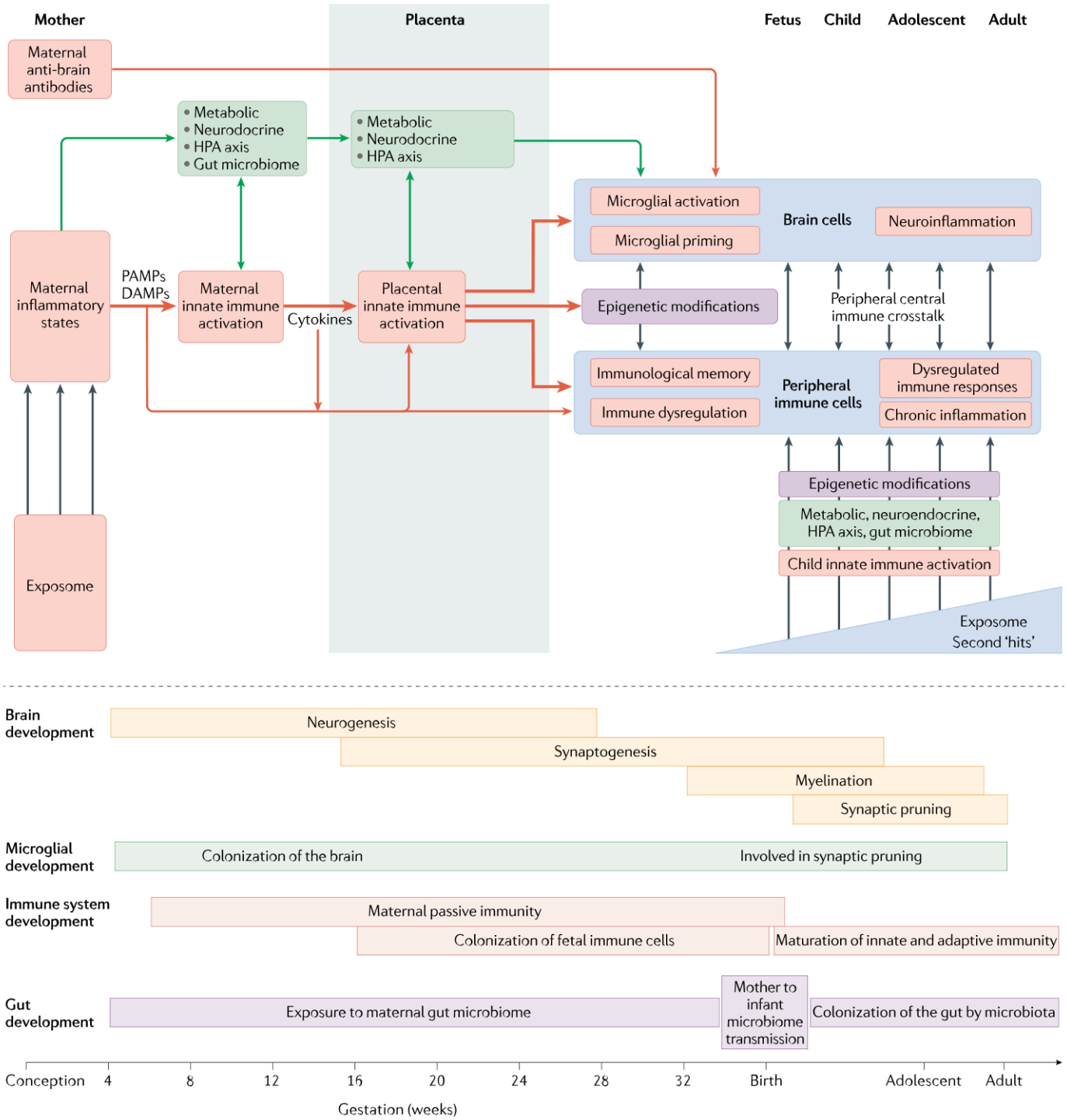

Fig. 1 | **Maternal immune activation and offspring development.** Evidence from human and animal studies indicates that maternal immune activation programmes the fetal brain and immune system through inflammatory and epigenetic mechanisms during key periods of CNS, microglial and immune system development, and colonization of gut microbiota. Heterogeneous infectious and non-infectious maternal inflammatory factors induce the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which activate Toll-like receptors on maternal peripheral innate immune cells and placental cells, leading to cytokine production[67,68,70]. Across the placenta, passive transport and active placental production of immune mediators occur and interact with transplacental metabolic, neuroendocrine and stress (hypothalamic–pituitary–adrenal (HPA)) signalling pathways[101]. The effects of maternal inflammation are proposed to induce long-lasting epigenetic memory on fetal microglia and immune cells during critical developmental periods[25,115]. The lower part of the figure shows the timings of key developmental processes in the offspring brain, immune system and gut microbiome. Postnatally, dynamic peripheral–central immune crosstalk occurs, involving peripheral inflammatory signals triggered by environmental immune-modifying factors and brain immune cells[166]. Interactions among offspring aberrant immune programming, genetic risk, sex and second immune 'hits' in life result in a state of chronic inflammation in both the brain and periphery, which manifest as lifelong neurobehavioural abnormalities[25,26,178]. Adapted from REF.[178], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

activation during human pregnancy is emerging but is still limited. In pregnant women with diabetes mellitus or SLE, elevations in TLR4 expression, phosphorylation of proteins downstream of TLR4 and cytokine levels in peripheral mononuclear cells have been observed[74,75]. Human umbilical vein endothelial cells isolated from infants born to mothers with inactive SLE showed a pro-inflammatory profile, including elevated HSP and TLR9 levels[76].

Transduction of MIA to the offspring

Role of cytokines and other immune molecules. Immune mechanisms that are proposed to transmit the effects of MIA to the developing fetus include dysregulated maternal innate, adaptive and complement pathways, and maternal autoantibodies[26]. In animal models, cytokines have been shown to play crucial roles in mediating the effects of MIA on the developing fetus[77,78]. The mother produces pro-inflammatory cytokines ('sensors') in response to environmental insults, with accompanying increases in pro-inflammatory cytokines in the placenta, amniotic fluid and fetal brain ('transducers'), resulting in altered fetal behavioural outcomes ('effectors')[77,79] (FIG. 1). Animal studies have delineated key roles for IL-6, IL-17, tumour necrosis factor (TNF) and IL-1β in mediating the effects of MIA to the fetus[18,77,78,80]. Cytokines expressed in the fetal brain play multiple roles in immunity and are important for normal brain development[63]. MIA disrupts the precise balance between pro-inflammatory and anti-inflammatory cytokines in the fetal brain, with long-lasting effects on neurodevelopmental processes[63] (FIG. 1). Cytokines are expressed in synapses in conjunction with complement, chemokines and major histocompatibility complex proteins[81]. Changes in cytokine expression can disrupt synaptic function, thereby perturbing the refinement of neural connectivity[25].

Risk factor	Author (year)	Developmental disorder	Effect estimate (95% CI)
Autoimmune disease	Chen et al. (2016)[44]	ASD	OR 1.34 (1.23–1.46)
	Nielsen et al. (2021)[43]	ADHD	OR 1.20 (1.04–1.38)
	Dalsgaard et al. (2015)[42]	TS	IRR 1.22 (1.01–1.48)
	Mataix-Cols et al. (2018)[45]	TS	OR 1.40 (1.30–1.51)
Asthma	Gong et al. (2019)[46]	ASD	OR 1.43 (1.38–1.49)
	Hisle-Gorman et al. (2018)[47]	ASD	OR 1.49 (1.29–1.74)
	Liu et al. (2019)[48]	ADHD	OR 1.41 (1.36–1.46)
	Instanes et al. (2017)[49]	ADHD	OR 1.50 (1.50–1.60)
Obesity	Lei et al. (2019)[208]	ASD	OR 1.41 (1.19–1.67)
	Jenabi et al. (2019)[209]	ADHD	OR 1.42 (1.23–1.61)
Low SES	He et al. (2018)[210]	ASD	Low:high tertile 2.27 (1.39–3.70)
	Durkin et al. (2010)[211]	ASD	Low:medium PR 0.70 (0.64–0.76)
	Russell et al. (2016)[52]	ADHD	OR 2.21 (1.33–3.66)
	Miller et al. (2014)[53]	TS	OR 2.78 (1.42–5.43)

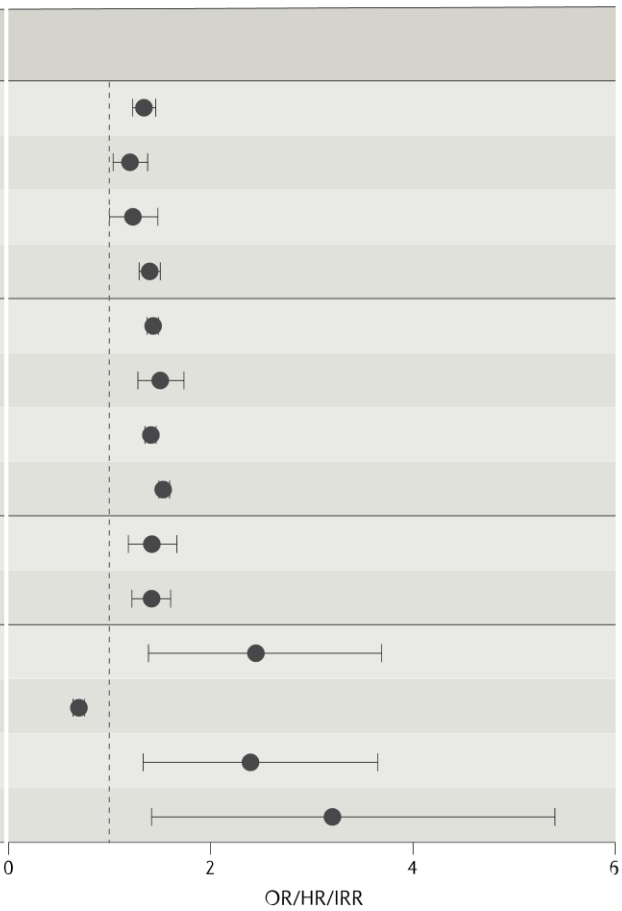

Fig. 2 | **Maternal chronic inflammation and offspring neurodevelopmental disorders.** Forest plot of selected human data linkage studies demonstrating that maternal immune activation secondary to acute and chronic inflammation in pregnancy is associated with neurodevelopmental disorders (NDDs) in the offspring. The plot shows the associations of non-infectious maternal inflammatory risk factors, including autoimmune disease, asthma, obesity and low socioeconomic status (SES), with offspring autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and Tourette syndrome (TS). On the basis of a previously published search strategy and forest plots[40], four maternal risk factors were selected as prototypical immunological and pro-inflammatory factors to illustrate associations with offspring NDDs. The largest meta-analysis with the most participants, along with several population-based studies, were chosen as representative studies and included in the forest plot. Most of the studies showed a positive association between maternal inflammatory risk factors and NDDs in children, although conflicting results were obtained for the link between low SES and ASD[42–49,52,53,208–211]. Differences in ASD case ascertainment in studies, owing to differences in health-care access in various countries, were thought to explain these divergent results. CI, confidence interval; HR, hazard ratio; IRR, incidence risk ratio; OR, odds ratio; PR, prevalence ratio. Adapted from REF.[40], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

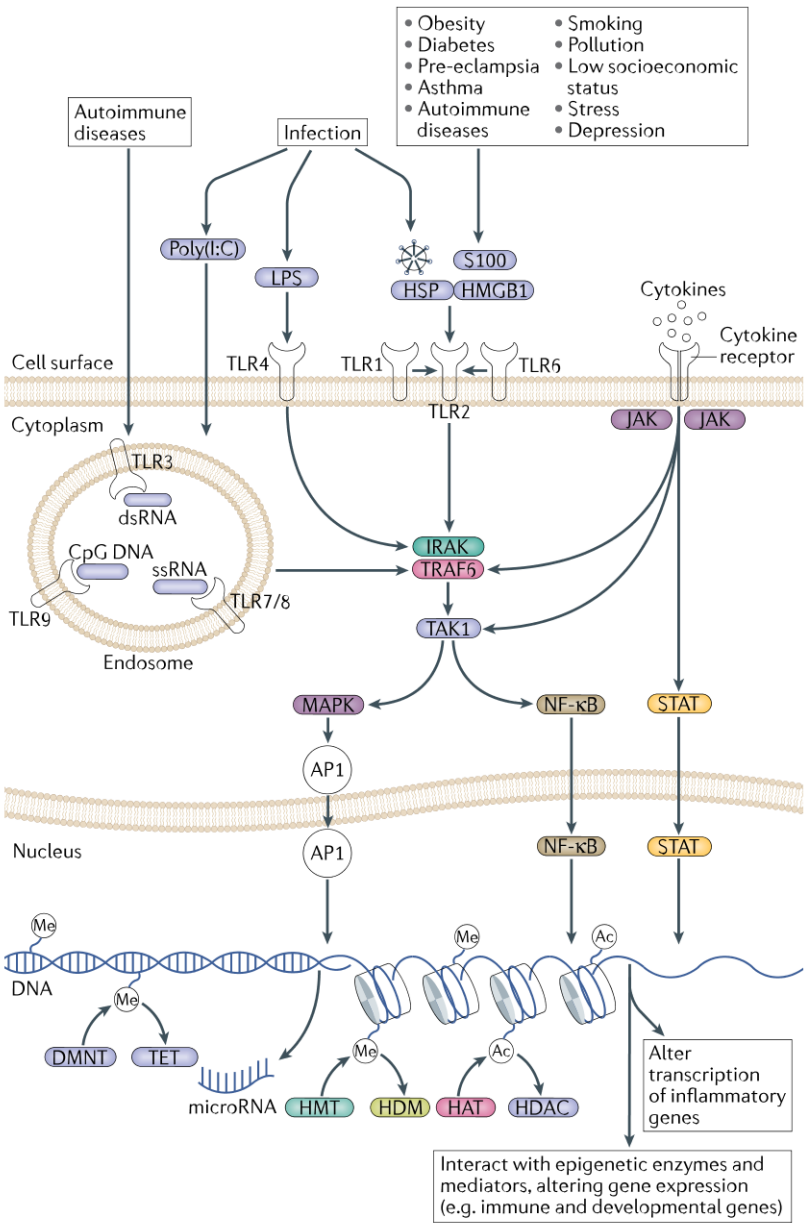

Fig. 3 | **Cell signalling pathways linking diverse environmental factors to inflammation and epigenetic programming of DNA.** Inflammation is increasingly recognized at the gene–environment interface[41]. Microbial pathogens release pathogen-associated molecular patterns[41,58]. Heterogeneous environmental factors and disease states implicated in chronic inflammation, including obesity, diabetes, pre-eclampsia, asthma, autoimmune disease, smoking, pollution, low socioeconomic status, stress and depression, stimulate the release of damage-associated molecular patterns[41,58]. Pathogen-associated molecular patterns and damage-associated molecular patterns trigger cell-surface and intracellular Toll-like receptors (TLRs) to activate an inflammatory cascade involving phosphorylated adaptor proteins such as NF-κB, MAPK and activator protein (AP1)[58]. Translocation of NF-κB and AP1 to the nucleus activates the transcription of genes encoding pro-inflammatory cytokines and other immune mediators[58]. The activation of cytokine receptors through the JAK–STAT pathway by cytokines also contributes to NF-κB signalling. NF-κB and JAK–STAT signalling upregulates and interacts with epigenetic enzymes and transcription factors to induce epigenetic modifications[134]. Epigenetic modifying factors include DNA methylation, histone modifications, chromatin modelling and microRNA. DNA methylation activity is catalysed by DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) proteins. Histone acetylation is regulated by histone acetyltransferase (HAT) and histone deacetylase (HDAC), and histone methylation is controlled by histone methyltransferase (HMT) and histone demethylase (HDM)[20]. Environmental and biological factors drive epigenetic alterations, which modify the cellular expression of immune as well as developmental genes[134]. Ac, acetylation; dsRNA, double-stranded RNA; HMGB1, high mobility group protein B1; HSP, heat shock protein; LPS, lipopolysaccharide; Me, methylation; poly(I:C), polyinosinic:polycytidylic acid; ssRNA, single-stranded RNA.

Consistent with the preclinical findings, human cohort studies have demonstrated that alterations in the levels of inflammatory biomarkers such as cytokines, chemokines and C-reactive protein (CRP) in maternal or offspring tissue are associated with offspring ASD and ADHD[79,82–92] (TABLE 1). IL-6 stimulates *CRP* gene expression, which is a well-established non-specific marker of inflammation. Socioeconomic adversity is associated with reduced maternal serum IL-8 levels in the second and third trimesters and, in turn, with altered child neurodevelopment, including deficits in self-regulation[93,94]. Further studies showed a link between increased maternal serum IL-6 levels during pregnancy and offspring neuroanatomical changes, including alterations in amygdala and brain connectivity, which are commonly seen in children with NDDs[79,95].

The general trends indicate an association between biomarkers of maternal inflammation and offspring NDD. However, the findings are not consistent or comparable across studies, partly owing to methodological differences (TABLE 1). In some instances, conflicting associations were found. For example, an increased incidence of ASD diagnosis was associated with elevated neonatal IL-4 levels in one study[89] but with reduced levels in another[91]. Pooled analyses of multicentre studies with similar methodologies are needed to verify these associations. Postnatal evidence of elevated cytokine expression in the CNS has also been found in individuals with NDDs[96]. Specific cytokines, including IL-6, TNF and IFNγ, are frequently upregulated in the brain and cerebrospinal fluid of individuals with ASD[96].

Transplacental transfer of maternal pathogenic antibodies targeting fetal brain antigens, known as anti-brain antibodies, might explain the effects of MIA in a subset of offspring with NDDs[97,98] (FIG. 1). Maternal IgG begins to cross the placenta during the second trimester of pregnancy and can penetrate the fetal brain parenchyma owing to the immaturity of the fetal blood–brain barrier[97]. Up to 10% of mothers of children with ASD harbour anti-brain antibodies, compared with 2.6% of mothers of typically developing children[99]. Specific antibodies identified in the mothers of children with ASD include contactin-associated protein-like 2 (CASPR2)

Table 1 | **Inflammatory mediators and neurodevelopmental outcomes in humans**

Reference	Study design	Sample size	Timing	Cytokines measured	Outcome measures	Results
Maternal in utero blood cytokine and CRP levels and ASD in offspring						
Goines et al. (2011)[82]	Population-based case–control	84 M_{ASD}, 49 M_{DD} and 159 controls	Mid-gestation	Eotaxin, GM-CSF, IFNγ, IL-10, IL-12, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, CXCL10, CCL3, CCL4, RANTES and TNF	ASD or developmental delay diagnosis via DSM-IV criteria	Increased maternal IL-4, IL-5 and IFNγ levels associated with 50% increased risk of ASD, with or without ID, in offspring
Jones et al. (2017)[83]	Population-based nested case–control	415 M_{ASD} (184 M_{ASD+ID} and 201 $M_{ASD-noID}$), 188 M_{DD} and 428 controls	Mid-gestation	GM-CSF, IFNγ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-17, CXCL10, CCL2, CCL3, CCL4, TNF, eotaxin, sIL-2Rα and IL-1RA	ASD or developmental delay diagnosis via DSM-IV criteria	Increased maternal GM-CSF, IFNγ, IL-1α and IL-6 levels associated with ASD+ID in offspring; reduced maternal IL-1β and CCL2 levels associated with ASD-noID in offspring
Nadeem et al. (2020)[205]	Meta-analysis of three population-based nested case–control studies	Total participants: 5,258	First and second trimesters, before 18 weeks' gestation or 15–19 weeks' gestation	CRP	ASD diagnosis via ICD-10 criteria, DSM-IV criteria or SRS and PDP scale at 6 years of age	M_{ASD} have an adjusted odds ratio of 1.02 (95% CI 0.948–1.103) of having an elevated CRP level during pregnancy compared with controls
Maternal in utero blood cytokine and CRP levels and ADHD in offspring						
Graham et al. (2018)[79]	Prospective	86 pregnant women	Early, mid and late pregnancy	IL-6	Neonatal structural and functional brain MRI, impulse control task at 2 years of age	Increased maternal IL-6 levels associated with lower impulse control in offspring at 24 months of age, attributed to enlarged right amygdala in newborn
Gustafsson et al. (2020)[84]	Prospective	62 pregnant women	Third trimester	IL-6, TNF and CCL2	Various assessments between 48 and 72 months of age: K-SADS-EC, SDQ, ADHD-RS and SWAN	Increased levels of maternal IL-6, TNF and CCL2 in combination associated with ADHD in offspring at 4–6 years of age
Thürmann et al. (2019)[85]	Prospective	293 pregnant women	Third trimester	IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, CCL2, TNF and IFNγ	SDQ at 8 years of age	Increased maternal IL-13 levels associated with offspring hyperactive–inattentive behaviour at 8 years of age
Chudal et al. (2020)[207]	Population-based case–control	1,079 M_{ADHD} and 1,079 controls	First and second trimesters	CRP	ADHD diagnosis via ICD-10 criteria	No association between CRP levels in early pregnancy and ADHD in offspring
Amniotic fluid cytokine and chemokine levels and ASD in offspring						
Abdallah et al. (2012)[87]	Population-based case–control	414 M_{ASD} and 820 controls	Amniotic fluid	CCL2, CCL3 and RANTES	ASD diagnosis via ICD-8 and ICD-10	Increased amniotic fluid CCL2 levels associated with ASD in offspring
Abdallah et al. (2013)[86]	Population-based case–control	331 M_{ASD} and 698 controls	Amniotic fluid	IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, TNF, TNFβ, TREM1, sIL-6Rα and GM-CSF	ASD diagnosis via ICD-8 and ICD-10	Increased amniotic fluid IL-4, IL-10, TNF and TNFβ levels associated with ASD in offspring
Neonatal blood cytokine and chemokine levels and ASD in offspring						
Krakowiak et al. (2017)[89]	Population-based case–control	214 ASD, 27 DD and 62 controls	Neonatal blood spot	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IFNγ, TNF, IL-8, CCL2, CCL3, CCL4, eotaxin, CXCL10 and RANTES	ASD diagnosis via ADI-R, ADOS and DSM-5 at 2–5 years of age	Increased neonatal IL-1β and IL-4 levels associated with ASD
Abdallah et al. (2012)[91]	Population-based case–control	359 ASD and 741 controls	Neonatal dried blood sample	IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, TNF, TNFβ, TREM1, sIL-6Rα and GM-CSF	ASD diagnosis via ICD-8 and ICD-10	Reduced neonatal IFNγ, IL-4 and IL-10 levels associated with ASD

Table 1 (cont.) | **Inflammatory mediators and neurodevelopmental outcomes in humans**

Reference	Study design	Sample size	Timing	Cytokines measured	Outcome measures	Results
Neonatal blood cytokine and chemokine levels and ASD in offspring (cont.)						
Heuer et al. (2019)[92]	Population-based case–control	370 ASD, 140 DD and 378 controls	Neonatal dried blood sample	IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, TNF, IL-12p70, MIF, CX3CL1, CXCL1, CXCL2, CXCL3 CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CCL12, CXCL13, CXCL16, CCL1, CCL2, CCL7, CCL8, CCL11, CCL13, CCL15, CCL17, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27 and GM-CSF	ASD diagnosis via DSM-IV criteria	Increased neonatal IL-6 and IL-8 levels associated with ASD
Zerbo et al. (2014)[90]	Population based case–control	84 ASD, 49 DD and 159 controls	Neonatal dried blood sample	IFNγ, IL-2, IL-4, IL-5, IL-6, IL-1β, IL-8, IL-10, IL-12p40, TNF, GM-CSF, CXCL10, CCL2, CCL3, CCL4, RANTES and eotaxin	ASD diagnosis via DSM-IV criteria	Increased CCL2 and reduced RANTES levels in neonates later diagnosed with ASD
Abdallah et al. (2013)[88]	Population based case–control	359 ASD and 741 controls	Neonatal dried blood sample	CCL2, CCL3 and RANTES	ASD diagnosis via ICD-8 and ICD-10	No difference in chemokine levels between ASD and controls

Studies that examined developmental outcomes, such as memory, executive function and cognition, are not included. ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, ADHD Rating Scale; ADI-R, Autism Diagnostic Interview — Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; CRP, C-reactive protein; DD, developmental delay; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Statistical Classification of Diseases and Related Health Problems; ID, intellectual disability; K-SADS-EC, Kiddie Schedule for Affective Disorders and Schizophrenia for Early Childhood; M_{ADHD}, mothers of children with ADHD; M_{ASD}, mothers of children with ASD; M_{ASD+ID}, mothers of children with ASD and ID; $M_{ASD\text{-}noID}$, mothers of children with ASD but not ID; M_{DD}, mothers of children with DD; PDP, pervasive developmental problems; SDQ, Strengths and Difficulties Questionnaire; SRS, Social Responsiveness Scale; SWAN, Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour Scale; TNF, tumour necrosis factor.

and *N*-methyl-D-aspartate receptor (NMDAR) antibodies and thyroid autoantibodies[100]. Behavioural changes were elicited when NMDAR and CASPR2 antibodies derived from mothers of children with ASD were transferred to murine models, supporting a putative pathogenic role for these antibodies[97,98].

The role of the placenta in MIA. The placenta plays a pivotal role in maintaining immune homeostasis across the maternal–fetal interface. However, the active placental inflammatory response to maternal environmental factors is proposed to contribute to offspring developmental abnormalities[101] (FIG. 2). Studies in animal models have demonstrated that maternal inflammation is transduced to the fetus via direct and indirect mechanisms at the placenta, involving immune, metabolic and endocrine factors, stress (leading to hypothalamic–pituitary–adrenal (HPA) axis activation) and reactive oxygen species[101,102] (FIG. 1). Immune signals can be transmitted through passive transfer of maternal cytokines to the fetal brain or through placental inflammatory responses, which trigger endogenous fetal cytokine production[101–103]. Maternal stress and obesity stimulate maternal and placental cytokine production and also increase glucocorticoid levels, alter nutrient availability and disrupt leptin and insulin signalling[101,103]. In addition, an MIA-induced placental inflammatory response can cause placental insufficiency and result in fetal hypoxaemia[104].

In humans, pro-inflammatory maternal factors, including maternal obesity, depression, socioeconomic adversity and smoking, induce placental inflammatory histological changes and pro-inflammatory cytokine production[105–107]. Obese mothers showed a 3–9-fold increase in *TLR4* mRNA expression in placental immune and non-immune cells, correlating with placental IL-6 expression[108,109]. In a prospective study of 2,926 pregnant women, maternal anxiety was associated with elevated placental *CRP* mRNA expression and parental reports of hyperactivity symptoms in male offspring[110]. The direct impact of placental inflammation on offspring neurodevelopmental outcomes is difficult to isolate and measure in humans because it is likely to be multifactorial, including the consequences of prematurity and low birthweight as well as the involvement of placental ischaemia, vascular dysfunction and oxidative stress[111].

Effects of MIA on the offspring

Behaviour, brain function and immune system. The behavioural phenotypes of the offspring in MIA animal models can resemble the core features of ASD and, to a lesser extent, ADHD and TS, including memory and other cognitive impairments, anxiety, depression-like behaviour, sensorimotor deficits, social deficits and repetitive behaviour[29,58]. Animal models show that MIA affects offspring brain structure, neuronal morphology and function, and synaptic and neuronal connectivity and causes dysregulation of neurotransmitter systems[25,112]. Immune changes in the offspring include long-lasting alterations in the activation states and cytokine expression of central and peripheral immune cells[58,113] (FIG. 1).

Microglia are the resident immune cells of the brain and are emerging as key players in MIA as they are a primary source of cytokine and immune molecules in the brain[114]. Microglia participate in complex brain

developmental processes both prenatally and postnatally, including neurogenesis, synaptic pruning and organization of functional neural circuits[114,115]. Together with various immune proteins, microglia are involved in engulfing excess synaptic structures — also known as synaptic pruning — to develop functionally mature synapses and sculpt neuronal circuits[116,117]. In animal studies, MIA has been shown to disrupt microglial development and impair the microglia-dependent phagocytic actions involved in synaptic pruning[118,119]. Despite methodological differences and inconsistences of findings, animal studies have generally indicated a link between maternal inflammation and increased microglial density and/or activation in the offspring brain[29]. An activated microglial cell adopts a pro-inflammatory state with increased cytokine production in response to cell injury and death in its vicinity (FIG. 1).

Evidence is emerging for the presence of microglial activation in humans with NDDs. In PET studies using radiotracers that bind to activated microglia, such as translocator protein (TSPO), adults with ASD and children with ADHD or TS showed excessive region-specific microglial activation compared with controls[120,121]. However, the single finding of altered TSPO binding or expression in patients should be interpreted with caution as TSPO binding can be affected by other pathophysiological processes and is not specific to microglial activation[122].

Although microglia have been the main focus of MIA studies, other cells, particularly astrocytes, are increasingly recognized to play immunological roles[123]. In addition, maternal inflammation and epigenetic modifications induced by environmental factors and disease states are likely to affect not only microglia but also other glial cells and neurons.

Epigenetics in the immune system and brain. Preliminary evidence from animal studies indicates that MIA exposure can induce long-lasting DNA methylation alterations, histone modifications and changes in microRNA expression in the offspring brain[124–128] (BOX 1; FIG. 1). Methylation and histone modifications detected in the cortex of offspring born to MIA-challenged pregnant mice correlated with alterations in the expression of genes involved in neuronal development, synaptic transmission and immune signalling[24,128]. MIA disrupts the epigenetic regulation of microglia in the offspring[129]. In addition, MIA causes methylation changes in genomic regions that encode proteins involved in epigenetic modulation (methyl CpG binding protein 2 (MECP2)) or in neurotransmitter signalling (including GABAergic and dopaminergic pathways)[125,126,130].

In animal models, epigenetic mechanisms have been proposed to mediate differences in behavioural manifestations in offspring exposed to time-specific immune insults[24]. In addition, longitudinal studies in animal models of MIA have demonstrated dynamic variations in DNA methylation and histone patterning in the offspring brain across the lifespan[24,128]. These findings indicate that MIA continues to have effects on the offspring's epigenetic code postnatally by interfering with the epigenetic machinery[24]. Other factors, including a maternal high-fat diet and gestational diabetes, also affect epigenetic programming of brain and peripheral immunity in the offspring, leading to a series of metabolic and immunogenic changes that can affect brain function[61,131]. Animal models have also demonstrated transgenerational effects of prenatal environmental adversities, with second-generation and third-generation offspring exhibiting epigenetic alterations in the brain in association with behavioural abnormalities[23,130,132,133].

Emerging preclinical research is exploring the link between inflammation and epigenetic alterations. Cytokines can activate epigenetic enzymes or recruit chromatin regulators to the DNA[124] (FIG. 3). For example, IL-6 can activate DNA methyltransferase 1 and IL-17A inhibits histone deacetylase activity[124]. In addition, the stimulation of cellular stress through innate immune pathways can induce the expression of epigenetic mediators, such as the histone demethylase Jumonji domain-containing protein D3, resulting in altered immune and neurodevelopmental gene expression[134]. Maternal inflammation during pregnancy can also alter the epigenetic code of the offspring via other modifiers such as oxidative stress, availability of maternal folic acid (a major dietary source of methyl groups) and short-chain fatty acids induced by changes in the offspring's gut microbiome[135–137].

In humans, maternal factors that have been implicated in MIA, including anxiety, depression and exposure to smoking, are associated with epigenetic modifications in the placenta, offspring umbilical cord blood, peripheral blood and buccal cells[14,138]. However, only a handful of studies have attempted to link specific maternal gestational risk factors with epigenetic changes across the maternal–fetal interface and to correlate these changes with subsequent offspring neurodevelopmental deficits[14,138]. The studies to date have mainly adopted a targeted approach to examine genes that are involved in the HPA axis or directly influence brain function (for example, neurotransmitters or neurotrophins)[138]. Mothers with prenatal depression, anxiety or socioeconomic adversity were found to have placental DNA methylation changes in *NR3C1* (encoding glucocorticoid receptor) and *HSD11B2* (encoding 11β-hydroxysteroid dehydrogenase type 2), which were predictive of poor neurodevelopmental outcomes in the offspring[16,17]. Increased methylation of *HSD11B2* results in transcriptional silencing of the gene, causing decreased placental cortisol inactivation and allowing increased cortical exposure in the developing fetus, which is detrimental to brain development[138]. Maternal prenatal anxiety and depression also showed associations with umbilical cord blood methylation changes in *NR3C1* and *SLC6A* (the serotonin transporter gene) as well as buccal DNA methylation changes in *BDNF*, the gene encoding brain-derived neurotrophic factor[139–141].

Human studies also showed that maternal inflammatory risk factors, including obesity, gestational diabetes, depression and asthma, were associated with umbilical cord blood epigenetic changes in immune pathways in addition to metabolic and oxidative stress pathways[142–145]. Intriguingly, long-lasting epigenetic

changes in immune pathways, resulting in altered gene expression and increased cytokine responses, were identified in adolescents born to mothers exposed to natural disasters during pregnancy[22]. However, these studies did not specifically examine the long-term neurodevelopmental outcomes in the children.

Other studies have attempted to elucidate whether epigenetic modifications in umbilical cord blood samples are predictive of poor neurodevelopmental outcomes in the offspring. Epigenetic methylation changes in the *HES1* gene, which encodes a transcription factor involved in neuronal differentiation, in umbilical cord blood samples were found to be associated with cognitive and behavioural outcomes later in childhood[146].

Collectively, these studies suggest that prenatal exposure to inflammatory factors is associated with an altered epigenetic signature in the offspring, which is long-lasting and has the potential to cause both immune and neurobehavioural deficits during childhood. However, proving that a specific prenatal environmental exposure in the mother causes an epigenetically mediated neurodevelopmental disorder in the offspring is extremely challenging in humans. To address this issue, prospective longitudinal studies, including exploration of the link between the maternal exposome and immune mediator expression as well as sequential epigenetic evaluation of tissues across the mother–fetus interface, will be required. However, the ability to perform such studies is substantially limited by the challenge of sampling various tissues and the requirement for long-term follow-up. In addition, the origins of epigenetic changes in older children — for example, paternal, maternal, pregnancy-related or postnatal factors secondary to ongoing environmental exposures — are difficult to determine (FIG. 1).

Evidence of neuroinflammation in people with NDDs. The most robust evidence of a role for inflammation and epigenetics in NDDs has come from human brain epigenetic studies integrated with transcriptomics. Over the past decade, post mortem brain studies in individuals with NDDs who died from other causes have revealed region-specific microglial activation and neuroinflammation, with associated epigenetic changes[10,147–149]. In individuals with ASD or TS, brain transcriptome analysis showed upregulation of genes involved in microglia-related and astrocyte-related inflammation[10,11]. In terms of brain epigenetic changes, individuals with ASD and neurotypical controls showed differences in DNA methylation and histone acetylation involving immune-related, synaptic and neuronal genes[13,150,151]. Integrated omics analysis of brain tissue from people with ASD brain uncovered dysregulated histone acetylation associated with downregulation of neuronal gene expression and hypomethylation associated with upregulation of glial–immune genes[12]. The upregulation of immune-related genes was suggested to be secondary to environmental factors or compensatory in nature[11].

As the brain analyses were performed in adults with NDDs, it was not possible to determine whether the inflammation was primary and causal or secondary and reactive. Despite clear evidence of neuroinflammation in humans with NDDs, no studies have yet demonstrated a direct link between MIA and neuroinflammation in newborn infants. Given the invasive nature of neonatal brain biopsies needed to prove this association, surrogate cerebrospinal fluid or PET biomarkers will be needed to provide the necessary evidence.

Factors promoting risk and resilience to MIA

Maternal factors. Owing to the poor reproducibility and heterogeneity of phenotypic outcomes in offspring, researchers are turning their attention to elucidating the factors that promote neurodevelopmental resilience and susceptibility to MIA[66,152]. Even in animal MIA models with the same genetic background and controlled environmental factors, subgroups of offspring displayed disparate brain network, transcriptional, behavioural and immunological profiles[152]. In animals, the response to immune challenge in the pregnant mother is influenced by maternal age and social isolation and confers susceptibility to MIA-induced molecular and behavioural abnormalities in the offspring[65,66]. Other susceptibility factors to MIA in animals include maternal hypoferraemia and anaemia as well as maternal gut microbiome alterations that can induce intestinal T helper 17 cells to produce IL-17A[80,153]. On exposure to a high-fat diet, the maternal gut microbiome produces pro-inflammatory bacterial metabolites that can activate maternal innate immune cells[80]. Alterations in the maternal microbiome during pregnancy owing to infection, antibiotic use, altered diet and/or stress, influence neurogenesis and modulate the gut microbiome and peripheral immune system in the offspring[80,154–156]. Changes in the offspring gut microbiota can result in the increased production of short-chain fatty acids, which modulates the microbiota–gut–brain axis through neural, hormonal and epigenetic pathways[157].

Factors that promote resilience to MIA in animal models include high maternal iron, zinc, vitamin D, omega-3 fatty acid and choline levels[153,158]. In animal studies, the inflammatory and anti-inflammatory effects of maternal diet and macronutrient and micronutrient intake have substantial effects on maternal inflammatory status, with consequences for offspring brain development[159].

Postnatal factors. In most human pregnancies, the offspring tend to be resilient to the effects of maternal infection during pregnancy. There is increasing evidence that complex gene–exposome interactions before and after birth are involved in the modulation of NDD expression[66,153]. Studies in animal models indicate that MIA can act as a disease primer and the offspring's genetic make-up, sex and environmental exposures after birth can act as second and third hits, thereby altering the manifestation of NDDs[160–164] (FIG. 1). A single severe immune insult during a critically sensitive developmental period might cause severe neurological impairment in the offspring. However, a less potent immune stimulus may only cause 'sub-threshold MIA' and prime the immune memory of microglia and peripheral immune cells to a maladaptive state, resulting in dysregulated

inflammatory responses to subsequent immune hits[113,162,165] (BOX 2).

In animal studies, postnatal immunogenic 'second-hit' events, such as infection and stress, communicate with brain immune cells via central–peripheral immune crosstalk and trigger microglia to adopt an activated state with heightened pro-inflammatory responses[161,164,166,167] (BOX 3). Over time, chronic immune activation promotes chronic inflammation in the brain, leading to behavioural deficits. Hypothetically, these postnatal environmental factors also have the potential to disrupt the individual's epigenetic signature, thereby increasing vulnerability to NDDs[168]. Examples in humans include the biological imprinting of childhood trauma and adversity onto the individual's epigenetic landscape, which accentuates vulnerability to mental health, immune and metabolic disorders later in life[169]. Similar epigenetic mechanisms might be operating in the context of other postnatal 'second-hit' events.

The current literature exploring two-hit models in humans is limited. MIA is challenging to ascertain in humans owing to substantial heterogeneity in environmental exposures and a lack of large-scale longitudinal studies. However, psychosocial stress and infections are commonly observed to be associated with the onset or exacerbation of neurobehavioural symptoms in children with NDDs[56]. These findings might reflect a second-hit phenomenon or postnatal susceptibility to neurodevelopmental problems related to early-life exposure to inflammation. In children with TS, psychosocial stress increases the severity of tics and obsessive–compulsive and depressive symptoms, and additive interactions between psychosocial stress and group A streptococcal (GAS) infections predict future tic severity[170]. Children who required hospitalization for infection or were exposed to antibiotics in early childhood had an increased risk of ADHD[171,172]. Further population studies showed that diverse infections, including GAS infection, non-streptococcal throat infection and enterovirus infection, were associated with an increased risk of tic disorder[171,173,174]. Compared with controls, patients with TS showed elevated GAS and *Chlamydia trachomatis* antibody responses, suggesting a role for dysregulated immune–inflammatory responses towards common pathogens in tic disorders[175,176]. However, whether these infections are specific activators of the immune system or reflect more global immune dysregulation is unknown.

Other evidence for peripheral immune dysregulation in children with NDDs includes altered cytokine expression, immunoglobulin levels and immune cell composition as well as abnormal innate or adaptive cell responses to stimuli[81,177,178]. Furthermore, observational studies show a high prevalence of gut inflammation, atopic diseases and autoimmunity in children with NDDs[179–181]. Thus, there is strong evidence for chronic immune dysregulation in the peripheral blood and brains of individuals with NDDs. The biological effects of postnatal second hits on offspring NDDs in relation to MIA and the critical periods of susceptibility to these hits require further investigation.

Sex differences in response to MIA. NDDs are two to four times more frequently diagnosed in males than in females; however, the reasons are unclear[182]. The male predominance does not seem to be directly attributable to genetic factors, as sex-skewed expression of neurodevelopmental risk genes has not been found[183]. Some studies argue that current gender-biased standardized instruments in humans result in underdiagnosis in females[184]. In addition, males with ASD tend to display more externalizing behaviour (for example, repetitive and restricted behaviour), whereas females are more likely to present with more internalizing behaviour (for example, emotional symptoms), which might affect the diagnostic approach[185].

Another hypothesis is that males have inherent vulnerabilities to genetic mutations and/or environmental insults[186]. Animal studies have demonstrated differential sex-specific vulnerability to a range of different antenatal inflammatory insults[186]. Sex differences in placental responses to MIA, in fetal brain structure and function, and in the characteristics of immune cells might account for these differences[187,188]. Findings in animals that the innate immune system is involved in directing brain masculinization led to the hypothesis that the male brain has a more inflammatory environment than the female brain during development, resulting in male vulnerability to MIA[186].

Research in humans has suggested that the brains of people with ASD show sexual dimorphism of neuron–glial interactions[189]. Transcriptomic analysis of post-mortem brain samples revealed that genes naturally expressed at higher levels in healthy males than in healthy females overlapped with genes that were upregulated in brain samples from individuals with ASD[189]. A substantial proportion of the upregulated genes encoded astrocytic or microglial markers[189]. Longitudinal brain transcriptome analyses will be required to establish whether sexually dimorphic pathways in microglia underlie differential vulnerabilities to MIA and the development of NDDs.

Box 2 | **Microglial development and programming**

Microglia are permanent resident macrophages of the brain that originate from the yolk sac during a remarkably restricted embryonic period and are only occasionally replaced from the peripheral haemopoietic cell pool during the life of the individual[114,115]. The longevity of microglia is attributable to their extremely slow turnover (with a median annual rate of renewal of 28%)[212]. Human microglia have a median lifespan of 4.2 years, with some living and remaining functionally active for up to 20 years[212]. Early-life in utero immune perturbations influence microglial function in a region-specific and sex-specific manner, depending on the timing, dose, type of stimulus and individual genetic make-up[25,58,115].

The long-lived nature of microglia might explain how early-life aberrant programming of the microglia, also known as microglial priming, can have long-term adverse effects on brain development as observed in animal studies[114,115,212]. After the initial exposure to an inflammatory stimulus, specific histone marks deposited at genomic regions related to inflammatory pathways maintain microglial priming and long-lasting memory[213]. On subsequent immune challenge, prompt transcriptional changes occur, resulting in abnormal activation of inflammatory pathways in the microglia and leading to loss of immune homeostasis[213]. Thus, early-life immune challenges are hypothesized to leave specific long-lasting epigenetic marks on the offspring brain, which drive microglial plasticity through immune training and memory[115]. This process leads to maladaptive activated or primed microglial states with increased reactivity towards stressors in the future[25,115].

Box 3 | **Central–peripheral immune crosstalk**

Bidirectional communication between peripheral immune cells and the CNS is essential for brain homeostasis in development and disease. Findings from animal models indicate that immune–brain interactions occur via several pathways. When the CNS is threatened by pathogens and other danger signals, peripheral macrophages and microglia are alerted and initiate an immune response, recruiting both central and peripheral immune cells. Danger signals can communicate directly with microglia via circumventricular organs, which are devoid of a blood–brain barrier (BBB)[166,167]. However, other components of the peripheral immune system, including lymphocytes, cytokines and chemokines, can enter the CNS through the BBB and other entry points under highly specific conditions. Furthermore, microglia can impair BBB function, allowing more direct infiltration of peripheral activated immune cells[214]. Peripheral pro-inflammatory cytokine signals can also be relayed to the brain via the afferent vagal nerve, which triggers innate brain cells to produce endogenous cytokines[167]. In addition, peripheral monocytes can be trafficked into the brain via a rolling action along brain endothelial cells, even in the presence of an intact BBB[166]. Through these interactions, the microglia undergo changes in pathways associated with inflammation, phagocytosis and oxidative stress, leading to an activated, pro-inflammatory state[215]. Importantly, the pathways and mechanisms described above have not yet been demonstrated in humans.

Future perspectives

Implications for clinical assessment. Although the capacity for sophisticated omics analysis across different tissues and disorders has increased exponentially in recent years, the bedside clinical assessment of children with NDDs has not yet evolved to include detailed maternal environmental exposures during pregnancy. Questions regarding the family history of neurodevelopmental and neuropsychiatric disorders are commonly asked to determine 'genetic' risk. However, comprehensive assessment of individual or cumulative maternal environmental factors that might contribute to inflammation in pregnancy, including diet, sleep, exercise, exposure to pollution and smoking, and other immunological conditions such as infection, autoimmune disease and atopies, is also essential to uncover the synergistic or additive effects of MIA in humans. In addition, assessment of the child's postnatal exposome, including stress (for example, bereavement or trauma) as well as immunological factors (for example, infections or stressors) and comorbidities, should be evaluated, along with a history of recurrent infections, autoimmunity and the gut microbiome. Large birth cohort studies, such as Growing Up in Singapore Towards healthy Outcomes (GUSTO) and the Western Australian Pregnancy Cohort (Raine) study, have incorporated comprehensive environmental histories and omics analyses and could serve as valuable sources to influence clinical practice[190,191].

Future research priorities. One of the main limitations of research into NDDs in humans is the inability to examine brain samples and, therefore, the focus has been on peripheral blood. A large body of evidence has been obtained for peripheral immune dysregulation in patients with NDDs[81,177,178]. However, immune and epigenetic changes detected peripherally do not necessarily reflect changes in the brain[148]. A transcriptomic meta-analysis of 11 different tissues from patients with ASD showed that genes related to inflammation and immunity were upregulated in the brain but downregulated in the blood[148]. This finding raised the question of whether suppression of the immune transcriptome — that is, immune deficiency — in the blood is the primary problem or whether it represents a compensatory response to brain inflammation[148]. In addition, conflicting data have been obtained on innate immune responses in cohorts of individuals with NDDs. For example, TLR stimulation responses on monocytes were elevated in children with ASD or obsessive–compulsive disorder but suppressed in adults with TS[177,192,193].

The use of systems biology involving omics technology and human neural progenitor cell models, such as organoids, is expected to revolutionize our ability to dissect mechanistic pathways in the brain and blood[194]. In addition, the use of drug and biomarker discovery approaches, such as brain transcriptomic reactome pathway-driven drug discovery and drug repurposing resources, has the potential to expedite the development of precision medicine to target neuroinflammation in NDDs[195].

Potential treatments. On the basis of our current knowledge of maternal–offspring neuroimmune dysfunction from MIA, animal studies have focused on therapeutic agents that target key immune, epigenetic or gut–brain pathways. Animal models have been used to test dietary interventions, including oral probiotics, vitamin D, zinc and omega-3 polyunsaturated fatty acid supplementation, which have shown some success in reducing the maternal inflammatory response and improving offspring behaviour[196]. The nanoparticle-assisted delivery of dietary supplements to increase the bioavailability of nutrients is a promising approach to modulate neuroinflammatory pathways[197,198].

In terms of postnatal interventions into immune and epigenetic pathways, animal models have demonstrated benefits from polyunsaturated fatty acid supplementation, manipulation of the gut microbiome, antipurinergic therapy, antipsychotic drugs and minocycline — an antibiotic that inhibits microglial activation[199–201]. In humans, postnatal immunomodulatory interventions that have been trialled in NDDs, including antibiotics (macrolides and cephalosporin), intravenous immunoglobulin, minocycline and faecal microbiota transplantation, have yielded mixed results[196,202,203]. To date, most drugs that have been used to treat NDDs in humans have focused on neurons but microglia and the gut microbiome are potential future therapeutic targets. The institution of preventive strategies at the population level to optimize maternal and child health, especially in at-risk pregnancies, will be an increasing priority. Non-pharmacological interventions, such as environmental enrichment for mothers or offspring exposed to MIA, has been shown to protect the offspring from behavioural dysfunction in animal models and should be considered in humans[204,205].

Conclusions

Many questions remain unanswered regarding the role of MIA in the pathogenesis of offspring NDDs in humans. Despite the challenges of obtaining direct evidence for this association in humans, multiple experimental approaches are providing converging evidence to support the MIA hypothesis. Collectively, the human

studies affirm the findings from animal models, which indicate vital roles for maternal immune-related exposures in fetal brain and immune programming, with long-lasting effects on offspring neurodevelopment. As NDDs are associated with an increasing global health burden, the identification of critical windows of opportunity to intervene in molecular pathways disrupted by MIA could lead to the development of preventive and mechanism-based therapies for at-risk pregnancies and individuals.

Published online 2 August 2021

1. Zablotsky, B. et al. Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. *Pediatrics* **144**, e20190811 (2019).
2. Maenner, M. J. et al. Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2016. *MMWR Surveill. Summ.* **69**, 1–12 (2020).
3. Kern, J. K. et al. Shared brain connectivity issues, symptoms, and comorbidities in autism spectrum disorder, attention deficit/hyperactivity disorder, and Tourette syndrome. *Brain Connect.* **5**, 321–335 (2015).
4. Iemmi, V., Knapp, M. & Ragan, I. The autism dividend: reaping the rewards of better investment. (National Autistic Taskforce, 2017).
5. Smoller, J. W. et al. Psychiatric genetics and the structure of psychopathology. *Mol. Psychiatry* **24**, 409–420 (2019).
6. Anttila, V. et al. Analysis of shared heritability in common disorders of the brain. *Science* **360**, eaap8757 (2018).
7. Hallmayer, J. et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch. Gen. Psychiatry* **68**, 1095–1102 (2011).
8. Bach, J.-F. The effect of infections on susceptibility to autoimmune and allergic diseases. *N. Engl. J. Med.* **347**, 911–920 (2002).
9. Poston, L. et al. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol.* **4**, 1025–1036 (2016).
10. Lennington, J. B. et al. Transcriptome analysis of the human striatum in Tourette syndrome. *Biol. Psychiatry* **79**, 372–382 (2016).
11. Voineagu, I. et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* **474**, 380–384 (2011).
12. Ramaswami, G. et al. Integrative genomics identifies a convergent molecular subtype that links epigenomic with transcriptomic differences in autism. *Nat. Commun.* **11**, 4873 (2020).
13. Nardone, S. et al. DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways. *Transl. Psychiatry* **4**, e433 (2014).
14. Banik, A. et al. Maternal factors that induce epigenetic changes contribute to neurological disorders in offspring. *Genes* **8**, 150 (2017).
15. Renz, H. et al. An exposome perspective: early-life events and immune development in a changing world. *J. Allergy Clin. Immunol.* **140**, 24–40 (2017).
16. Conradt, E., Lester, B. M., Appleton, A. A., Armstrong, D. A. & Marsit, C. J. The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics* **8**, 1321–1329 (2013).
17. Appleton, A. A. et al. Patterning in placental 11-B hydroxysteroid dehydrogenase methylation according to prenatal socioeconomic adversity. *PLoS ONE* **8**, e74691 (2013).
18. Bennett, J. M., Reeves, G., Billman, G. E. & Sturmberg, J. P. Inflammation — nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases. *Front. Med.* **5**, 316 (2018).
19. Straub, R. H. & Schradin, C. Chronic inflammatory systemic diseases: an evolutionary trade-off between acutely beneficial but chronically harmful programs. *Evol. Med. Public. Health* **2016**, 37–51 (2016).
20. Dupont, C., Armant, D. R. & Brenner, C. A. Epigenetics: definition, mechanisms and clinical perspective. *Semin. Reprod. Med.* **27**, 351–357 (2009).
21. Aristizabal, M. J. et al. Biological embedding of experience: a primer on epigenetics. *Proc. Natl Acad. Sci. USA* **117**, 23261–23269 (2020).
22. Cao-Lei, L. et al. DNA methylation mediates the effect of exposure to prenatal maternal stress on cytokine production in children at age 13½ years: Project Ice Storm. *Clin. Epigenet.* **8**, 54 (2016).
23. Weber-Stadlbauer, U. Epigenetic and transgenerational mechanisms in infection-mediated neurodevelopmental disorders. *Transl. Psychiatry* **7**, e1113 (2017).
24. Richetto, J. et al. Genome-wide DNA methylation changes in a mouse model of infection-mediated neurodevelopmental disorders. *Biol. Psychiatry* **81**, 265–276 (2017).
25. Estes, M. L. & McAllister, A. K. Maternal immune activation: implications for neuropsychiatric disorders. *Science* **353**, 772–777 (2016).
26. Knuesel, I. et al. Maternal immune activation and abnormal brain development across CNS disorders. *Nat. Rev. Neurol.* **10**, 643–660 (2014).
27. Pronovost, G. N. & Hsiao, E. Y. Perinatal Interactions between the microbiome, immunity, and neurodevelopment. *Immunity* **50**, 18–36 (2019).
28. VanRyzin, J. W., Pickett, L. A. & McCarthy, M. M. Microglia: driving critical periods and sexual differentiation of the brain. *Dev. Neurobiol.* **78**, 580–592 (2018).
29. Gumusoglu, S. B. & Stevens, H. E. Maternal inflammation and neurodevelopmental programming: a review of preclinical outcomes and implications for translational psychiatry. *Biol. Psychiatry* **85**, 107–121 (2019).
30. Careaga, M., Murai, T. & Bauman, M. D. Maternal immune activation and autism spectrum disorder: from rodents to nonhuman and human primates. *Biol. Psychiatry* **81**, 391–401 (2017).
31. Meyer, U. Prenatal poly(I:C) exposure and other developmental immune activation models in rodent systems. *Biol. Psychiatry* **75**, 307–315 (2014).
32. Solek, C. M., Farooqi, N., Verly, M., Lim, T. K. & Ruthazer, E. S. Maternal immune activation in neurodevelopmental disorders. *Dev. Dyn.* **247**, 588–619 (2018).
33. Brown, A. S. & Meyer, U. Maternal immune activation and neuropsychiatric illness: a translational research perspective. *Am. J. Psychiatry* **175**, 1073–1083 (2018).
34. Minakova, E. & Warner, B. B. Maternal immune activation, central nervous system development and behavioral phenotypes. *Birth Defects Res.* **110**, 1539–1550 (2018).
35. Jiang, H. Y. et al. Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. *Brain Behav. Immun.* **58**, 165–172 (2016).
36. Mann, J. R. & McDermott, S. Are maternal genitourinary infection and pre-eclampsia associated with ADHD in school-aged children? *J. Atten. Disord.* **15**, 667–673 (2011).
37. Silva, D., Colvin, L., Hagemann, E. & Bower, C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics* **133**, e14–e22 (2014).
38. Pineda, D. A. et al. Environmental influences that affect attention deficit/hyperactivity disorder: study of a genetic isolate. *Eur. Child. Adolesc. Psychiatry* **16**, 337–346 (2007).
39. Kim, J. Y. et al. Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. *Lancet Psychiatry* **6**, 590–600 (2019).
40. Han, V. X. et al. Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. *Transl. Psychiatry* **11**, 71 (2021).
41. Furman, D. et al. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* **25**, 1822–1832 (2019).
42. Dalsgaard, S., Waltoft, B. L., Leckman, J. F. & Mortensen, P. B. Maternal history of autoimmune disease and later development of Tourette syndrome in offspring. *J. Am. Acad. Child. Adolesc. Psychiatry* **54**, 495–501.e1 (2015).
43. Nielsen, T. C. et al. Association of maternal autoimmune disease with attention-deficit/hyperactivity disorder in children. *JAMA Pediatr.* **175**, e205487 (2021).
44. Chen, S. W. et al. Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis. *Behav. Brain Res.* **296**, 61–69 (2016).
45. Mataix-Cols, D. et al. A total-population multigenerational family clustering study of autoimmune diseases in obsessive–compulsive disorder and Tourette's/chronic tic disorders. *Mol. Psychiatry* **23**, 1652–1658 (2018).
46. Gong, T. et al. Parental asthma and risk of autism spectrum disorder in offspring: a population and family-based case-control study. *Clin. Exp. Allergy* **49**, 883–891 (2019).
47. Hisle-Gorman, E. et al. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. *Pediatr. Res.* **84**, 190–198 (2018).
48. Liu, X. et al. Parental asthma occurrence, exacerbations and risk of attention-deficit/hyperactivity disorder. *Brain Behav. Immun.* **82**, 302–308 (2019).
49. Instanes, J. T. et al. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. *Biol. Psychiatry* **81**, 452–459 (2017).
50. Wang, Y., Tang, S., Xu, S., Weng, S. & Liu, Z. Maternal body mass index and risk of autism spectrum disorders in offspring: a meta-analysis. *Sci. Rep.* **6**, 34248 (2016).
51. Li, L. et al. Maternal pre-pregnancy overweight/obesity and the risk of attention-deficit/hyperactivity disorder in offspring: a systematic review, meta-analysis and quasi-experimental family-based study. *Int. J. Epidemiol.* **49**, 857–875 (2020).
52. Russell, A. E., Ford, T., Williams, R. & Russell, G. The association between socioeconomic disadvantage and attention deficit/hyperactivity disorder (ADHD): a systematic review. *Child. Psychiatry Hum. Dev.* **47**, 440–458 (2016).
53. Miller, L. L., Scharf, J. M., Mathews, C. A. & Ben-Shlomo, Y. Tourette syndrome and chronic tic disorder are associated with lower socio-economic status: findings from the Avon Longitudinal Study of Parents and Children cohort. *Dev. Med. Child. Neurol.* **56**, 157–163 (2014).
54. Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R. & Van de Water, J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch. Pediatr. Adolesc. Med.* **159**, 151–157 (2005).
55. Manzari, N., Matvienko-Sikar, K., Baldoni, F., O'Keeffe, G. W. & Khashan, A. S. Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. *Soc. Psychiatry Psychiatr. Epidemiol.* **54**, 1299–1309 (2019).
56. Jones, H. F. et al. Maternal autoimmunity and inflammation are associated with childhood tics and obsessive–compulsive disorder: transcriptomic data show common enriched innate immune pathways. *Brain Behav. Immun.* **94**, 308–317 (2021).
57. Fatemi, S. H., Pearce, D. A., Brooks, A. I. & Sidwell, R. W. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. *Synapse* **57**, 91–99 (2005).
58. Bergdolt, L. & Dunaevsky, A. Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. *Prog. Neurobiol.* **175**, 1–19 (2019).
59. Church, J. S., Tamayo, J. M., Ashwood, P. & Schwartzer, J. J. Repeated allergic asthma in early versus late pregnancy differentially impacts offspring brain and behavior development. *Brain Behav. Immun.* **93**, 66–79 (2020).
60. Bilbo, S. D., Block, C. L., Bolton, J. L., Hanamsagar, R. & Tran, P. K. Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp. Neurol.* **299**, 241–251 (2018).
61. Maldonado-Ruiz, R., Garza-Ocañas, L. & Camacho, A. Inflammatory domains modulate autism spectrum

disorder susceptibility during maternal nutritional programming. *Neurochem. Int.* **126**, 109–117 (2019).
62. Money, K. M. et al. Gestational diabetes exacerbates maternal immune activation effects in the developing brain. *Mol. Psychiatry* **23**, 1920–1928 (2018).
63. Meyer, U., Feldon, J. & Yee, B. K. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr. Bull.* **35**, 959–972 (2009).
64. Meyer, U., Yee, B. K. & Feldon, J. The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? *Neuroscientist* **13**, 241–256 (2007).
65. Bronson, S. L., Ahlbrand, R., Horn, P. S., Kern, J. R. & Richtand, N. M. Individual differences in maternal response to immune challenge predict offspring behavior: contribution of environmental factors. *Behav. Brain Res.* **220**, 55–64 (2011).
66. Estes, M. L. et al. Baseline immunoreactivity before pregnancy and poly(I:C) dose combine to dictate susceptibility and resilience of offspring to maternal immune activation. *Brain Behav. Immun.* **88**, 619–630 (2020).
67. Tang, D., Kang, R., Coyne, C. B., Zeh, H. J. & Lotze, M. T. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. *Immunol. Rev.* **249**, 158–175 (2012).
68. Akira, S. & Takeda, K. Toll-like receptor signalling. *Nat. Rev. Immunol.* **4**, 499–511 (2004).
69. Liu, J., Buisman-Pijlman, F. & Hutchinson, M. R. Toll-like receptor 4: innate immune regulator of neuroimmune and neuroendocrine interactions in stress and major depressive disorder. *Front. Neurosci.* **8**, 309 (2014).
70. Afkham, A. et al. Toll-like receptors signaling network in pre-eclampsia: an updated review. *J. Cell. Physiol.* **234**, 2229–2240 (2019).
71. Di Candia, L. et al. HMGB1 is upregulated in the airways in asthma and potentiates airway smooth muscle contraction via TLR4. *J. Allergy Clin. Immunol.* **140**, 584–587.e8 (2017).
72. Dasu, M. R., Devaraj, S., Park, S. & Jialal, I. Increased toll-like receptor (TLR) activation and TLR ligands in recently diagnosed type 2 diabetic subjects. *Diabetes Care* **33**, 861–868 (2010).
73. Farrugia, M. & Baron, B. The role of Toll-like receptors in autoimmune diseases through failure of the self-recognition mechanism. *Int. J. Inflamm.* **2017**, 8391230 (2017).
74. Qu, X., Yu, X., Liu, J., Wang, J. & Liu, J. Pro-inflammatory cytokines are elevated in pregnant women with systemic lupus erythematosus in association with the activation of TLR4. *Clin. Lab.* **62**, 535–544 (2016).
75. Kuzmicki, M. et al. The expression of genes involved in NF-κB activation in peripheral blood mononuclear cells of patients with gestational diabetes. *Eur. J. Endocrinol.* **168**, 419–427 (2013).
76. Rodriguez, E. et al. The altered expression of inflammation-related molecules and secretion of IL-6 and IL-8 by HUVEC from newborns with maternal inactive systemic lupus erythematosus is modified by estrogens. *Lupus* **17**, 1086–1095 (2008).
77. Smith, S. E., Li, J., Garbett, K., Mirnics, K. & Patterson, P. H. Maternal immune activation alters fetal brain development through interleukin-6. *J. Neurosci.* **27**, 10695–10702 (2007).
78. Choi, G. B. et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science* **351**, 933–939 (2016).
79. Graham, A. M. et al. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. *Biol. Psychiatry* **83**, 109–119 (2018).
80. Kim, S. et al. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. *Nature* **549**, 528–532 (2017).
81. Estes, M. L. & McAllister, A. K. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. *Nat. Rev. Neurosci.* **16**, 469–486 (2015).
82. Goines, P. E. et al. Increased midgestational IFN-γ, IL-4 and IL-5 in women bearing a child with autism: a case–control study. *Mol. Autism* **2**, 13 (2011).
83. Jones, K. L. et al. Autism with intellectual disability is associated with increased levels of maternal cytokines and chemokines during gestation. *Mol. Psychiatry* **22**, 273–279 (2017).
84. Gustafsson, H. C. et al. Evaluation of maternal inflammation as a marker of future offspring ADHD symptoms: a prospective investigation. *Brain Behav. Immun.* **89**, 350–356 (2020).
85. Thürmann, L. et al. Elevated gestational IL-13 during fetal development is associated with hyperactivity and inattention in eight-year-old children. *Front. Immunol.* **10**, 1658 (2019).
86. Abdallah, M. W. et al. Amniotic fluid inflammatory cytokines: potential markers of immunologic dysfunction in autism spectrum disorders. *World J. Biol. Psychiatry* **14**, 528–538 (2013).
87. Abdallah, M. W. et al. Amniotic fluid chemokines and autism spectrum disorders: an exploratory study utilizing a Danish Historic Birth Cohort. *Brain Behav. Immun.* **26**, 170–176 (2012).
88. Abdallah, M. W. et al. Neonatal chemokine levels and risk of autism spectrum disorders: findings from a Danish historic birth cohort follow-up study. *Cytokine* **61**, 370–376 (2013).
89. Krakowiak, P. et al. Neonatal cytokine profiles associated with autism spectrum disorder. *Biol. Psychiatry* **81**, 442–451 (2017).
90. Zerbo, O. et al. Neonatal cytokines and chemokines and risk of autism spectrum disorder: the Early Markers for Autism (EMA) study: a case–control study. *J. Neuroinflammation* **11**, 113 (2014).
91. Abdallah, M. W. et al. Neonatal levels of cytokines and risk of autism spectrum disorders: an exploratory register-based historic birth cohort study utilizing the Danish Newborn Screening Biobank. *J. Neuroimmunol.* **252**, 75–82 (2012).
92. Heuer, L. S. et al. An exploratory examination of neonatal cytokines and chemokines as predictors of autism risk: the Early Markers for Autism study. *Biol. Psychiatry* **86**, 255–264 (2019).
93. Yu, J. et al. Maternal Immune activity during pregnancy and socioeconomic disparities in children's self-regulation. *Brain Behav. Immun.* **90**, 346–352 (2020).
94. Gilman, S. E. et al. Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. *Proc. Natl Acad. Sci. USA* **114**, 6728–6733 (2017).
95. Rudolph, M. D. et al. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. *Nat. Neurosci.* **21**, 765–772 (2018).
96. Xu, N., Li, X. & Zhong, Y. Inflammatory cytokines: potential biomarkers of immunologic dysfunction in autism spectrum disorders. *Mediators Inflamm.* **2015**, 531518 (2015).
97. Bagnall-Moreau, C. et al. In utero exposure to endogenous maternal polyclonal anti-Caspr2 antibody leads to behavioral abnormalities resembling autism spectrum disorder in male mice. *Sci. Rep.* **10**, 14446 (2020).
98. Pröbstel, A. K. & Zamvil, S. S. Do maternal anti-N-methyl-D-aspartate receptor antibodies promote development of neuropsychiatric disease in children? *Ann. Neurol.* **86**, 653–655 (2019).
99. Brimberg, L., Sadiq, A., Gregersen, P. K. & Diamond, B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Mol. Psychiatry* **18**, 1171–1177 (2013).
100. Brown, A. S. et al. Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **57**, 86–92 (2015).
101. Howerton, C. L. & Bale, T. L. Prenatal programing: at the intersection of maternal stress and immune activation. *Horm. Behav.* **62**, 237–242 (2012).
102. Hsiao, E. Y. & Patterson, P. H. Activation of the maternal immune system induces endocrine changes in the placenta via IL-6. *Brain Behav. Immun.* **25**, 604–615 (2011).
103. Hsiao, E. Y. & Patterson, P. H. Placental regulation of maternal–fetal interactions and brain development. *Dev. Neurobiol.* **72**, 1317–1326 (2012).
104. Carpentier, P. A., Dingman, A. L. & Palmer, T. D. Placental TNF-α signaling in illness-induced complications of pregnancy. *Am. J. Pathol.* **178**, 2802–2810 (2011).
105. Keenan-Devlin, L. S. et al. Maternal income during pregnancy is associated with chronic placental inflammation at birth. *Am. J. Perinatol.* **34**, 1003–1010 (2017).
106. de Melo, J. O. et al. Inhalation of fine particulate matter during pregnancy increased IL-4 cytokine levels in the fetal portion of the placenta. *Toxicol. Lett.* **232**, 475–480 (2015).
107. Altmäe, S. et al. Maternal pre-pregnancy obesity is associated with altered placental transcriptome. *PLoS ONE* **12**, e0169223 (2017).
108. Koga, K. & Mor, G. Expression and function of toll-like receptors at the maternal-fetal interface. *Reprod. Sci.* **15**, 231–242 (2008).
109. Yang, X. et al. Causal relationship between obesity-related traits and TLR4-driven responses at the maternal–fetal interface. *Diabetologia* **59**, 2459–2466 (2016).
110. Shao, S. et al. Prenatal pregnancy-related anxiety predicts boys' ADHD symptoms via placental C-reactive protein. *Psychoneuroendocrinology* **120**, 104797 (2020).
111. Gumusoglu, S. B., Chilukuri, A. S. S., Santillan, D. A., Santillan, M. K. & Stevens, H. E. Neurodevelopmental outcomes of prenatal preeclampsia exposure. *Trends Neurosci.* **43**, 253–268 (2020).
112. Cieślik, M. et al. Maternal immune activation induces neuroinflammation and cortical synaptic deficits in the adolescent rat offspring. *Int. J. Mol. Sci.* **21**, 4097 (2020).
113. Bordeleau, M. et al. Microglial and peripheral immune priming is partially sexually dimorphic in adolescent mouse offspring exposed to maternal high-fat diet. *J. Neuroinflammation* **17**, 264 (2020).
114. Bilbo, S. & Stevens, B. Microglia: the brain's first responders. *Cerebrum* **2017**, cer-14-17 (2017).
115. Cheray, M. & Joseph, B. Epigenetics control microglia plasticity. *Front. Cell. Neurosci.* **12**, 243 (2018).
116. Neniskyte, U. & Gross, C. T. Errant gardeners: glial-cell-dependent synaptic pruning and neurodevelopmental disorders. *Nat. Rev. Neurosci.* **18**, 658–670 (2017).
117. Schafer, D. P. et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* **74**, 691–705 (2012).
118. Mattei, D. et al. Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. *Transl. Psychiatry* **7**, e1120 (2017).
119. Matcovitch-Natan, O. et al. Microglia development follows a stepwise program to regulate brain homeostasis. *Science* **353**, aad8670 (2016).
120. Kumar, A., Williams, M. T. & Chugani, H. T. Evaluation of basal ganglia and thalamic inflammation in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and Tourette syndrome: a positron emission tomographic (PET) study using 11C-[R]-PK11195. *J. Child. Neurol.* **30**, 749–756 (2015).
121. Suzuki, K. et al. Microglial activation in young adults with autism spectrum disorder. *JAMA Psychiatry* **70**, 49–58 (2013).
122. Notter, T., Coughlin, J. M., Sawa, A. & Meyer, U. Reconceptualization of translocator protein as a biomarker of neuroinflammation in psychiatry. *Mol. Psychiatry* **23**, 36–47 (2018).
123. de Souza, D. F. et al. Changes in astroglial markers in a maternal immune activation model of schizophrenia in Wistar rats are dependent on sex. *Front. Cell. Neurosci.* **9**, 489 (2015).
124. Nardone, S. & Elliott, E. The interaction between the immune system and epigenetics in the etiology of autism spectrum disorders. *Front. Neurosci.* **10**, 329 (2016).
125. Basil, P. et al. Prenatal maternal immune activation causes epigenetic differences in adolescent mouse brain. *Transl. Psychiatry* **4**, e434 (2014).
126. Labouesse, M. A., Dong, E., Grayson, D. R., Guidotti, A. & Meyer, U. Maternal immune activation induces GAD1 and GAD2 promoter remodeling in the offspring prefrontal cortex. *Epigenetics* **10**, 1143–1155 (2015).
127. Connor, C. M. et al. Maternal immune activation alters behavior in adult offspring, with subtle changes in the cortical transcriptome and epigenome. *Schizophr. Res.* **140**, 175–184 (2012).
128. Tang, B., Jia, H., Kast, R. J. & Thomas, E. A. Epigenetic changes at gene promoters in response to immune activation in utero. *Brain Behav. Immun.* **30**, 168–175 (2013).
129. Vogel Ciernia, A., Careaga, M., LaSalle, J. M. & Ashwood, P. Microglia from offspring of dams with allergic asthma exhibit epigenomic alterations in genes dysregulated in autism. *Glia* **66**, 505–521 (2018).
130. Weber-Stadlbauer, U., Richetto, J., Zwamborn, R. A. J., Slieker, R. C. & Meyer, U. Transgenerational modification of dopaminergic dysfunctions induced by maternal immune activation. *Neuropsychopharmacology* **46**, 404–412 (2021).
131. Sureshchandra, S. et al. Maternal pregravid obesity remodels the DNA methylation landscape of cord blood monocytes disrupting their inflammatory program. *J. Immunol.* **199**, 2729–2744 (2017).
132. Ronovsky, M. et al. Maternal immune activation transgenerationally modulates maternal care and offspring depression-like behavior. *Brain Behav. Immun.* **63**, 127–136 (2017).

133. Weber-Stadlbauer, U. et al. Transgenerational transmission and modification of pathological traits induced by prenatal immune activation. *Mol. Psychiatry* **22**, 102–112 (2017).
134. Zhang, X., Liu, L., Yuan, X., Wei, Y. & Wei, X. JMJD3 in the regulation of human diseases. *Protein Cell* **10**, 864–882 (2019).
135. Hsiao, E. Y. et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* **155**, 1451–1463 (2013).
136. Joubert, B. R. et al. Maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. *Nat. Commun.* **7**, 10577 (2016).
137. Chen, Z. et al. Epigenetic down-regulation of Sirt 1 via DNA methylation and oxidative stress signaling contributes to the gestational diabetes mellitus-induced fetal programming of heart ischemia-sensitive phenotype in late life. *Int. J. Biol. Sci.* **15**, 1240–1251 (2019).
138. Hodyl, N. A., Roberts, C. T. & Bianco-Miotto, T. Cord blood DNA methylation biomarkers for predicting neurodevelopmental outcomes. *Genes* **7**, 117 (2016).
139. Devlin, A. M., Brain, U., Austin, J. & Oberlander, T. F. Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. *PLoS ONE* **5**, e12201 (2010).
140. Mansell, T. et al. Maternal mental well-being during pregnancy and glucocorticoid receptor gene promoter methylation in the neonate. *Dev. Psychopathol.* **28**, 1421–1430 (2016).
141. Braithwaite, E. C., Kundakovic, M., Ramchandani, P. G., Murphy, S. E. & Champagne, F. A. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. *Epigenetics* **10**, 408–417 (2015).
142. Wu, S. et al. Prenatal stress, methylation in inflammation-related genes, and adiposity measures in early childhood: the Programming Research in Obesity, Growth Environment and Social Stress Cohort Study. *Psychosom. Med.* **80**, 34–41 (2018).
143. Ruchat, S. M. et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. *Epigenetics* **8**, 935–943 (2013).
144. Gunawardhana, L. P. et al. Differential DNA methylation profiles of infants exposed to maternal asthma during pregnancy. *Pediatr. Pulmonol.* **49**, 852–862 (2014).
145. Nemoda, Z. et al. Maternal depression is associated with DNA methylation changes in cord blood T lymphocytes and adult hippocampi. *Transl. Psychiatry* **5**, e545 (2015).
146. Lillycrop, K. A. et al. Association between perinatal methylation of the neuronal differentiation regulator HES1 and later childhood neurocognitive function and behaviour. *Int. J. Epidemiol.* **44**, 1263–1276 (2015).
147. Morgan, J. T. et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol. Psychiatry* **68**, 368–376 (2010).
148. He, Y., Zhou, Y., Ma, W. & Wang, J. An integrated transcriptomic analysis of autism spectrum disorder. *Sci. Rep.* **9**, 11818 (2019).
149. Morgan, J. T. et al. Abnormal microglial–neuronal spatial organization in the dorsolateral prefrontal cortex in autism. *Brain Res.* **1456**, 72–81 (2012).
150. Wong, C. C. Y. et al. Genome-wide DNA methylation profiling identifies convergent molecular signatures associated with idiopathic and syndromic autism in post-mortem human brain tissue. *Hum. Mol. Genet.* **28**, 2201–2211 (2019).
151. Sun, W. et al. Histone acetylome-wide association study of autism spectrum disorder. *Cell* **167**, 1385–1397.e11 (2016).
152. Mueller, F. S. et al. Behavioral, neuroanatomical, and molecular correlates of resilience and susceptibility to maternal immune activation. *Mol. Psychiatry* **26**, 396–410 (2021).
153. Meyer, U. Neurodevelopmental resilience and susceptibility to maternal immune activation. *Trends Neurosci.* **42**, 793–806 (2019).
154. Vuong, H. E. et al. The maternal microbiome modulates fetal neurodevelopment in mice. *Nature* **586**, 281–286 (2020).
155. Buffington, S. A. et al. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* **165**, 1762–1775 (2016).
156. Jašarević, E. et al. The maternal vaginal microbiome partially mediates the effects of prenatal stress on offspring gut and hypothalamus. *Nat. Neurosci.* **21**, 1061–1071 (2018).
157. Rogers, G. B. et al. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol. Psychiatry* **21**, 738–748 (2016).
158. Madore, C. et al. Essential omega-3 fatty acids tune microglial phagocytosis of synaptic elements in the mouse developing brain. *Nat. Commun.* **11**, 6133 (2020).
159. Bordeleau, M., Fernández de Cossío, L., Chakravarty, M. M. & Tremblay, M. From maternal diet to neurodevelopmental disorders: a story of neuroinflammation. *Front. Cell. Neurosci.* **14**, 612705 (2020).
160. Schaafsma, S. M. et al. Sex-specific gene–environment interactions underlying ASD-like behaviors. *Proc. Natl Acad. Sci. USA* **114**, 1383–1388 (2017).
161. Giovanoli, S. et al. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. *Science* **339**, 1095–1099 (2013).
162. Perry, V. H. & Holmes, C. Microglial priming in neurodegenerative disease. *Nat. Rev. Neurol.* **10**, 217–224 (2014).
163. Carlezon, W. A. et al. Maternal and early postnatal immune activation produce sex-specific effects on autism-like behaviors and neuroimmune function in mice. *Sci. Rep.* **9**, 16928 (2019).
164. Hollins, S. L., Zavitsanou, K., Walker, F. R. & Cairns, M. J. Alteration of transcriptional networks in the entorhinal cortex after maternal immune activation and adolescent cannabinoid exposure. *Brain Behav. Immun.* **56**, 187–196 (2016).
165. Shimizu, Y. et al. Exposure to maternal immune activation causes congenital unfolded protein response defects and increases the susceptibility to postnatal inflammatory stimulation in offspring. *J. Inflamm. Res.* **14**, 355–365 (2021).
166. Wohleb, E. S. & Delpech, J. C. Dynamic cross-talk between microglia and peripheral monocytes underlies stress-induced neuroinflammation and behavioral consequences. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **79**, 40–48 (2017).
167. Dantzer, R. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiol. Rev.* **98**, 477–504 (2018).
168. Morandini, A. C., Santos, C. F. & Yilmaz, Ö. Role of epigenetics in modulation of immune response at the junction of host–pathogen interaction and danger molecule signaling. *Pathog. Dis.* **74**, ftw082 (2016).
169. Nöthling, J., Malan-Müller, S., Abrahams, N., Hemmings, S. M. J. & Seedat, S. Epigenetic alterations associated with childhood trauma and adult mental health outcomes: a systematic review. *World J. Biol. Psychiatry* **21**, 493–512 (2020).
170. Lin, H. et al. Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. *Biol. Psychiatry* **67**, 684–691 (2010).
171. Köhler-Forsberg, O. et al. A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry* **76**, 271–279 (2019).
172. Lavebratt, C. et al. Early exposure to antibiotic drugs and risk for psychiatric disorders: a population-based study. *Transl. Psychiatry* **9**, 317 (2019).
173. Orlovska, S. et al. Association of streptococcal throat infection with mental disorders: testing key aspects of the PANDAS hypothesis in a nationwide study. *JAMA Psychiatry* **74**, 740–746 (2017).
174. Tsai, C. S. et al. Association of tic disorders and enterovirus infection: a nationwide population-based study. *Medicine* **95**, e3347 (2016).
175. Krause, D. et al. Association between intracellular infectious agents and Tourette's syndrome. *Eur. Arch. Psychiatry Clin. Neurosci.* **260**, 359–363 (2010).
176. Müller, N. et al. Increased titers of antibodies against streptococcal M12 and M19 proteins in patients with Tourette's syndrome. *Psychiatry Res.* **101**, 187–193 (2001).
177. Enstrom, A. M., Onore, C. E., Van de Water, J. A. & Ashwood, P. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. *Brain Behav. Immun.* **24**, 64–71 (2010).
178. Martino, D., Johnson, I. & Leckman, J. F. What does immunology have to do with normal brain development and the pathophysiology underlying Tourette syndrome and related neuropsychiatric disorders? *Front. Neurol.* **11**, 567407 (2020).
179. Ashwood, P., Anthony, A., Torrente, F. & Wakefield, A. J. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. *J. Clin. Immunol.* **24**, 664–673 (2004).
180. Chua, R. X. Y. et al. Understanding the link between allergy and neurodevelopmental disorders: a current review of factors and mechanisms. *Front. Neurol.* **11**, 603571 (2020).
181. Leffa, D. T., Torres, I. L. S. & Rohde, L. A. A review on the role of inflammation in attention-deficit/hyperactivity disorder. *Neuroimmunomodulation* **25**, 328–333 (2018).
182. May, T., Adesina, I., McGillivray, J. & Rinehart, N. J. Sex differences in neurodevelopmental disorders. *Curr. Opin. Neurol.* **32**, 622–626 (2019).
183. Loomes, R., Hull, L. & Mandy, W. P. L. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *J. Am. Acad. Child. Adolesc. Psychiatry* **56**, 466–474 (2017).
184. Goldman, S. Opinion: sex, gender and the diagnosis of autism — a biosocial view of the male preponderance. *Res. Autism Spectr. Disord.* **7**, 675–679 (2013).
185. Duvekot, J. et al. Factors influencing the probability of a diagnosis of autism spectrum disorder in girls versus boys. *Autism* **21**, 646–658 (2017).
186. McCarthy, M. M. & Wright, C. L. Convergence of sex differences and the neuroimmune system in autism spectrum disorder. *Biol. Psychiatry* **81**, 402–410 (2017).
187. Braun, A. E. et al. "Females are not just 'protected' males": sex-specific vulnerabilities in placenta and brain after prenatal immune disruption. *eNeuro* https://doi.org/10.1523/ENEURO.0358-19.2019 (2019).
188. Frost, E. L., Lammert, C. R., Johanson, D. M., Zunder, E. R. & Lukens, J. R. Sex bias in maternal immune activation-induced neurodevelopmental disease begins at the maternal–fetal interface. *J. Immunol.* **204** (Suppl. 1), 79.13 (2020).
189. Werling, D. M., Parikshak, N. N. & Geschwind, D. H. Gene expression in human brain implicates sexually dimorphic pathways in autism spectrum disorders. *Nat. Commun.* **7**, 10717 (2016).
190. Straker, L. et al. Cohort profile: the Western Australian Pregnancy Cohort (Raine) study-generation 2. *Int. J. Epidemiol.* **46**, 1384–1385j (2017).
191. Soh, S. E. et al. Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. *Int. J. Epidemiol.* **43**, 1401–1409 (2014).
192. Weidinger, E. et al. Impaired activation of the innate immune response to bacterial challenge in Tourette syndrome. *World J. Biol. Psychiatry* **15**, 453–458 (2014).
193. Rodríguez, N. et al. Inflammatory dysregulation of monocytes in pediatric patients with obsessive–compulsive disorder. *J. Neuroinflammation* **14**, 261 (2017).
194. Chan, W. K., Griffiths, R., Price, D. J. & Mason, J. O. Cerebral organoids as tools to identify the developmental roots of autism. *Mol. Autism* **11**, 58 (2020).
195. Corsello, S. M. et al. The Drug Repurposing Hub: a next-generation drug library and information resource. *Nat. Med.* **23**, 405–408 (2017).
196. Bauman, M. D. & Van de Water, J. Translational opportunities in the prenatal immune environment: promises and limitations of the maternal immune activation model. *Neurobiol. Dis.* **141**, 104864 (2020).
197. Kim, M. J., Rehman, S. U., Amin, F. U. & Kim, M. O. Enhanced neuroprotection of anthocyanin-loaded PEG-gold nanoparticles against Aβ(1-42)-induced neuroinflammation and neurodegeneration via the NF-(K)B /JNK/GSK3β signaling pathway. *Nanomedicine* **13**, 2533–2544 (2017).
198. Ali, T., Kim, M. J., Rehman, S. U., Ahmad, A. & Kim, M. O. Anthocyanin-loaded PEG-gold nanoparticles enhanced the neuroprotection of anthocyanins in an Aβ(1-42) mouse model of Alzheimer's disease. *Mol. Neurobiol.* **54**, 6490–6506 (2017).
199. Saunders, J. M. et al. Gut microbiota manipulation during the prepubertal period shapes behavioral abnormalities in a mouse neurodevelopmental disorder model. *Sci. Rep.* **10**, 4697 (2020).
200. Zhu, F., Zheng, Y., Liu, Y., Zhang, X. & Zhao, J. Minocycline alleviates behavioral deficits and inhibits microglial activation in the offspring of pregnant mice after administration of polyriboinosinic-polyribocytidilic acid. *Psychiatry Res.* **219**, 680–686 (2014).

201. Basta-Kaim, A. et al. Maternal immune activation leads to age-related behavioral and immunological changes in male rat offspring — the effect of antipsychotic drugs. *Pharmacol. Rep.* **64**, 1400–1410 (2012).
202. Pardo, C. A. et al. A pilot open-label trial of minocycline in patients with autism and regressive features. *J. Neurodev. Disord.* **5**, 9 (2013).
203. Vendrik, K. E. W. et al. Fecal microbiota transplantation in neurological disorders. *Front. Cell. Infect. Microbiol.* **10**, 98 (2020).
204. Kentner, A. C., Khoury, A., Lima Queiroz, E. & MacRae, M. Environmental enrichment rescues the effects of early life inflammation on markers of synaptic transmission and plasticity. *Brain Behav. Immun.* **57**, 151–160 (2016).
205. Zhao, X. et al. Therapeutic efficacy of environmental enrichment on behavioral, endocrine, and synaptic alterations in an animal model of maternal immune activation. *Brain Behav. Immun. Health* **3**, 100043 (2020).
206. Nadeem, R., Hussain, T. & Sajid, H. C reactive protein elevation among children or among mothers' of children with autism during pregnancy, a review and meta-analysis. *BMC Psychiatry* **20**, 251 (2020).
207. Chudal, R. et al. Maternal serum C-reactive protein (CRP) and offspring attention deficit hyperactivity disorder (ADHD). *Eur. Child. Adolesc. Psychiatry* **29**, 239–247 (2020).
208. Lei, X. Y., Li, Y. J., Ou, J. J. & Li, Y. M. Association between parental body mass index and autism spectrum disorder: a systematic review and meta-analysis. *Eur. Child. Adolesc. Psychiatry* **28**, 933–947 (2019).
209. Jenabi, E., Bashirian, S., Khazaei, S. & Basiri, Z. The maternal prepregnancy body mass index and the risk of attention deficit hyperactivity disorder among children and adolescents: a systematic review and meta-analysis. *Korean J. Pediatr.* **62**, 374–379 (2019).
210. He, P. et al. Socioeconomic status and childhood autism: a population-based study in China. *Psychiatry Res.* **259**, 27–31 (2018).
211. Durkin, M. S. et al. Socioeconomic inequality in the prevalence of autism spectrum disorder: Evidence from a U.S. cross-sectional study. *PLoS ONE* **5**, e11551 (2010).
212. Rēu, P. et al. The lifespan and turnover of microglia in the human brain. *Cell Rep.* **20**, 779–784 (2017).
213. Rodriguez, R. M., Suarez-Alvarez, B. & Lopez-Larrea, C. Therapeutic epigenetic reprogramming of trained immunity in myeloid cells. *Trends Immunol.* **40**, 66–80 (2019).
214. Haruwaka, K. et al. Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. *Nat. Commun.* **10**, 5816 (2019).
215. Lehmann, M. L. et al. Decoding microglia responses to psychosocial stress reveals blood–brain barrier breakdown that may drive stress susceptibility. *Sci. Rep.* **8**, 11240 (2018).

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Neurology thanks U. Meyer, A. Sanders, who co-reviewed with M. Kimmel, and K. Gildawie, who co-reviewed with H. Brenhouse, for their contribution to the peer review of this work.

Review criteria
We conducted a literature search using the PubMed/Medline and EMBASE electronic databases to locate relevant articles and abstracts published between January 1997 and December 2020, using a comprehensive list of search terms related to maternal inflammation during pregnancy, epigenetics and child development, in particular neurodevelopmental disorders (namely, autism spectrum disorder, attention-deficit/hyperactivity disorder and Tourette syndrome), in both human and animal model studies. Search terms used for maternal state included "mother", "pregnancy", "maternal", "prenatal" and "perinatal". Search terms used for maternal inflammation included "maternal immune activation", "maternal inflammation", "gestational diabetes mellitus", "preeclampsia", "pollution", "mood disorder", "trauma and stressor related disorders", "socioeconomic factor", "autoimmune disease", "asthma", "infection", "cytokines", "immune molecules", "C reactive protein" and "antibodies". Search terms used for epigenetics included "epigenetics", "methylation", "histone" and "miRNA". Search terms used for child development included "neurodevelopment", "brain development", "autism spectrum disorder", "attention deficit hyperactivity disorder", "tics" and "Tourette syndrome". The combination of search terms for maternal inflammation or epigenetics and maternal state and child development was employed, using the 'explode' function for MESH/Emtree terms and including terms as keywords. Duplicates and irrelevant studies were removed and full-text articles were assessed. Further individual studies were handpicked from review articles.