Review

Biological Psychiatry:
Celebrating
50 Years

Maternal Inflammation and Neurodevelopmental Programming: A Review of Preclinical Outcomes and Implications for Translational Psychiatry

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ABSTRACT
Early disruptions to neurodevelopment are highly relevant to understanding both psychiatric risk and underlying pathophysiology that can be targeted by new treatments. Much convergent evidence from the human literature associates inflammation during pregnancy with later neuropsychiatric disorders in offspring. Preclinical models of prenatal inflammation have been developed to examine the causal maternal physiological and offspring neural mechanisms underlying these findings. Here we review the strengths and limitations of preclinical models used for these purposes and describe selected studies that have shown maternal immune impacts on the brain and behavior of offspring. Maternal immune activation in mice, rats, nonhuman primates, and other mammalian model species have demonstrated convergent outcomes across methodologies. These outcomes include shifts and/or disruptions in the normal developmental trajectory of molecular and cellular processes in the offspring brain. Prenatal developmental origins are critical to a mechanistic understanding of maternal immune activation–induced alterations to microglia and immune molecules, brain growth and development, synaptic morphology and physiology, and anxiety- and depression-like, sensorimotor, and social behaviors. These phenotypes are relevant to brain functioning across domains and to anxiety and mood disorders, schizophrenia, and autism spectrum disorder, in which they have been identified. By turning a neurodevelopmental lens on this body of work, we emphasize the importance of acute changes to the prenatal offspring brain in fostering a better understanding of potential mechanisms for intervention. Collectively, overlapping results across maternal immune activation studies also highlight the need to examine preclinical offspring neurodevelopment alterations in terms of a multifactorial immune milieu, or immunome, to determine potential mechanisms of psychiatric risk.

Keywords: Animal model, Behavioral neuroscience, Maternal immune activation, Molecular and cellular psychiatry, Neurodevelopment, Prenatal inflammation

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Cross-pollination between research on maternal inflammation during pregnancy and prenatal neurodevelopment has yielded a strong and growing field of investigation. In part, this field uses preclinical animal models to uncover mechanistic links between immune perturbation during gestation and offspring neurobiological and behavioral outcomes of relevance to mental health. Mammalian animal models have been essential to uncovering molecular and cellular processes involved in maternal inflammation's effects on the brain of offspring (1). In this review, we first examine some strengths and limitations of model systems in understanding these interactions. We then explore how maternal inflammatory changes elicit postnatal neurobiological and behavioral outcomes in nonhuman offspring via impacts on neurodevelopmental processes.

Brain development does not occur in isolation but interacts with pregnancy immunology and physiology, complicating the understanding of psychiatric risk and disease etiologies. Maternal immune perturbations alter fetal developmental trajectories, prenatally programming changes to the offspring brain that may present immediately and/or later in development. We discuss throughout this review phenomena of prenatal programming, which we define as enduring or later-in-life alterations of the offspring brain structure and function owing to conditions during gestation. This definition has been employed to link perturbations during early life to long-term disease—for example, classic studies linked prenatal and childhood health and socioeconomic status to heart and respiratory disease in adulthood (2–4). We discuss exemplar studies of preclinical prenatal programming after maternal immune disruption by brain and behavior outcome. We first review common maternal immune activation (MIA) models and neurodevelopmental mechanisms (Figure 1) that interact in programming before turning to mechanisms in the postnatal brain that most proximally underlie behavioral changes (Figure 2).

TRANSLATIONAL ISSUES

Preclinical studies are of greatest translational value when they focus on clinically relevant, conserved mechanisms and behaviors (5). The most common animal models used in biological psychiatry are mice and rats, which adequately capture many features of human prenatal forebrain development (e.g., neurulation, neural differentiation, proliferation, and migration) despite proceeding along different time scales (Figure 1). MIA in rodents can indirectly influence postnatal developmental processes through impacts initiated early. Direct effects of MIA on synaptogenesis and myelination, which occur postnatally in rodents but begin prenatally in humans, are better studied in mammals with similarly protracted intrauterine periods, including nonhuman primates, guinea pigs, and pigs (6–10).

Furthermore, despite some conserved pregnancy-specific immune mechanisms (11), mice are generally more resilient to inflammatory challenge than are humans. Given this, the use of multiple MIA methods and models may be beneficial (12,13). Differences also exist between rodents and humans in placental morphology (14), development, hormone production (15), and immunoregulatory protein expression (16). While not a focus here, the placenta is highly immunologically specialized and acts as both a conduit for and regulator of immune factor traffic at the maternal-fetal interface, playing a significant role in prenatal immune-neurodevelopmental interactions (17).

Despite some limited alignment of rodent models to human pregnancy and immune physiology, we contend, as others have (18), that these models provide a useful way to study conserved MIA physiology and offspring neurobiological outcomes and mechanisms, especially at the molecular level. These mechanistic studies may ultimately lead to clinically viable molecular interventions.

MODELING MATERNAL INFLAMMATION

Commonly used methods of MIA include maternal administration of polyinosinic:polycytidylic acid (PolyI:C) or lipopolysaccharide (LPS), which mimic viral or bacterial insult, respectively. Both stimulate the production of many endogenous proinflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha, which, along with other factors, recruit, activate, and stimulate the production of immune cells (19,20).

PolyI:C is a potent, well-validated, and well-characterized viral-mimetic activator of mammalian innate immunity that targets multiple intra- and extracellular signaling pathways (21). Its high face validity as an MIA model stems from its similarity to maternal exposures associated with human offspring psychopathology (i.e., influenza) and to offspring behavioral phenotypes that overlap with functional domains of psychiatric problems (e.g., prepulse inhibition deficits [PPI]) (22). Predictive validity of PolyI:C arises from efficacy of pharmacotherapy in reversing PolyI:C-caused offspring phenotypes—for example, antipsychotic medication rescues latent inhibition (LI) deficits in rats (23). Despite these advantages, PolyI:C is short acting (1.5–2 hours) relative to ecological pathogens and does not recruit immune system factors as efficiently as true viruses, such as influenza (22,24). Similar to PolyI:C, MIA via LPS, a gram-negative bacterial cell wall component (25,26), has high face validity (e.g., association with offspring anxiety-like phenotypes) and predictive validity (e.g., LPS-induced anxiety-like behaviors in offspring are corrected by fluoxetine) (27).

While both LPS and PolyI:C offer significant benefits of laboratory safety and experimental control, neither fully recapitulates complex human MIA with live agents (e.g., influenza) (18), nor do they result in identical maternal or offspring effects. In a direct comparison, mouse dams exhibited poorer appetitive behavior after LPS but more anxiety-like behavior after PolyI:C, while offspring exhibited reduced glial and neuronal protein expression after LPS but more disrupted growth and motor development after PolyI:C (28). Further inconsistencies can arise from variability in dosing, animal strain, source, microbiome, and outcome measurement across studies (29).

More discrete preclinical maternal manipulations include exposure to or blockade of individual cytokines. Specific cytokines play pro- and anti-inflammatory roles via autocrine, paracrine, and endocrine signaling and activation of intracellular nuclear factor kappa-light-chain-enhancer of activated B cells and Janus kinase/signal transducers and activators of transcription pathways, which are central to neural proliferation, differentiation, and migration (30). Elevations in proinflammatory

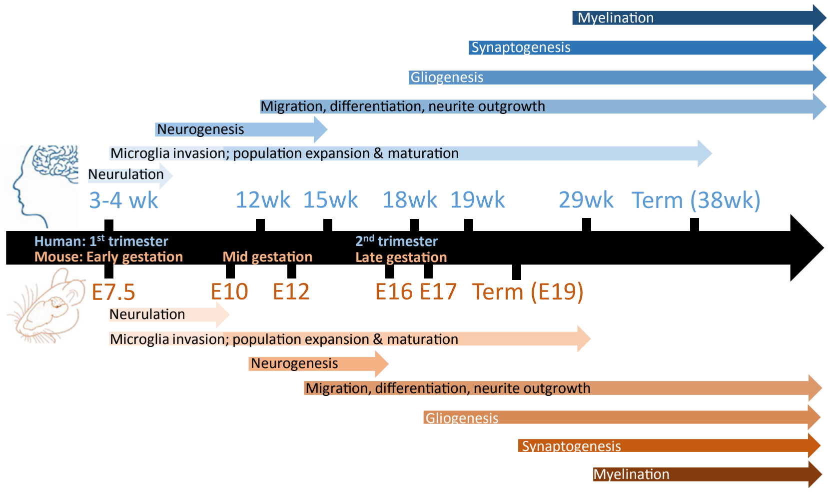

Figure 1. The timing of neurodevelopmental processes differs between mice and humans. These processes include formation of a neural tube and invasion of microglia (from approximately embryonic day [E] 7.5–10 in mouse and 3–4 weeks gestation age [WGA] in human), neural progenitor pool expansion and neurogenesis (from approximately E11–E16 in mouse and 4–15 WGA in human), migration, differentiation, and neurite outgrowth (from approximately E12 onward in mouse and 12 WGA onward in human), further parenchymal microglial population expansion and maturation (from approximately E10 to postpartum day (P) 15 in the mouse and 4 WGA until early in the postpartum period in the human), gliogenesis (beginning at E17 in mouse and 18 WGA in human), and neural patterning throughout these periods.

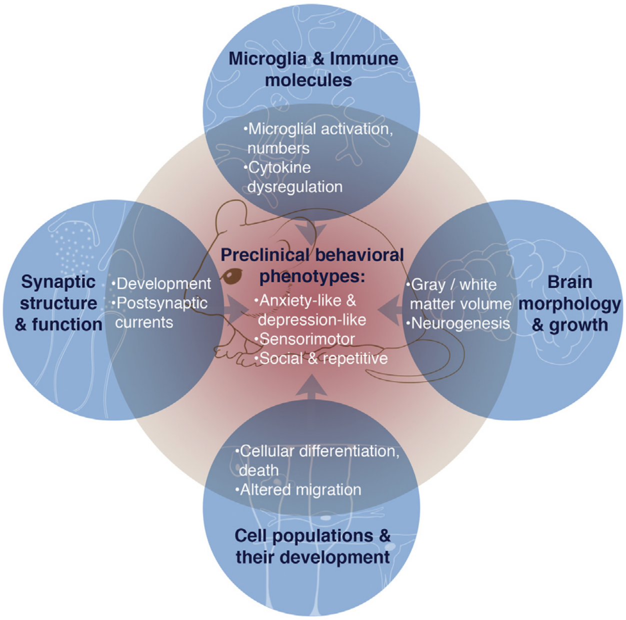

Figure 2. Mechanisms by which prenatal maternal immune perturbation influences animal neurodevelopment and behavior. Peripheral circles depict dimensions of neurodevelopment that are potentially altered by maternal immune perturbation. The central region depicts a zone of interaction, wherein multiple mechanisms may act to alter offspring behavior.

cytokines IL-6 and IL-1β, which are produced during viral and bacterial immune response and are among the most studied MIA outcomes, alter synapse formation and function (31) and drive neural progenitors from neurogenic to gliogenic fate (32). It is unclear whether all maternal cytokines pass to the fetus and have direct effects. Physiological factors induced independently in the fetal compartment after MIA that could communicate between placenta and fetal brain are only beginning to be comprehensively characterized (33). However, given the maternal route of preventive intervention during pregnancy (i.e., folate supplementation) (34,35) that could be applied to MIA, identifying maternal physiological mechanisms or factors may have high translational yield.

NEUROBIOLOGICAL OUTCOMES

Several categories of neurobiological disruption have been consistently investigated across MIA studies (Table 1), including microglia (brain immune cells), overall brain structure, neural cell populations and processes, and synaptic changes, all of which have been invoked as components of psychiatric pathology in humans (36–40) and demonstrated to play roles in critical mood, cognitive, and social functions (41–43).

Immune Molecules and Microglia

Reported outcomes of MIA often include changes to immune molecules (e.g., cytokines) and cells (e.g., microglia) in the offspring brain. Microglia infiltrate the healthy brain in early gestation and maintain a resident pool throughout life, subserving innate and adaptive neuroimmunity and normal neurodevelopmental roles (i.e., regulating progenitor number and projections, synapse refinement) (44–47). However, inflammatory perturbations in the developing brain can drive these cells from physiological to more pathological roles, both short-term and persistently (48,49). Aberrant microglia have been identified postmortem in schizophrenia, depression, Tourette syndrome, and autism spectrum disorder (ASD) (36), and they influence cellular-level pathophysiology related to learning and stress resilience (49).

Despite methodological differences across studies, maternal inflammation generally increases microglial density and/or activation in the offspring brain. These changes begin embryonically, as demonstrated by increased microglia counts and reactivity a few days after mid- or late-gestation LPS administration in sheep (50,51). Administration of LPS during early (52) or late (53) rat gestation also leads to increased active or proliferating microglia densities, respectively, in the postnatal brain. Early gestation (54) and mid-gestation (55) PolyI:C similarly results in increased adult offspring microglia activation in rodents. In Cairo spiny mice (*Acomys cahirinus*), rodents with a longer gestation (39 days) than typical mice or rats (approximately 19 and 21 days, respectively), neonatal but not adult microglia density is also increased after low-dose, midgestation PolyI:C exposure (56).

While still a topic of unclear significance, alterations to fetal microglial numbers and/or activation may underlie pathological brain development and therefore abnormal mature brain function. For example, increased microglia abnormally deplete neural progenitors in the fetal brain and disrupt synaptic development, leading to abnormal neurocircuitry later (57,58). Additionally, microglial and cytokine changes in the adult brain may directly influence adult synaptic plasticity and autocrine/paracrine mechanisms (59–61), processes relevant to multiple psychopathologies.

Furthermore, MIA can prime offspring microglia for decreased (62,63) or increased (52,64,65) reactivity to subsequent immune challenge. For example, adult offspring prenatally exposed to MIA during either early (52) or late (66) gestation and then re-exposed as adults (often called "dual hit" models) demonstrate prolonged proinflammatory cytokine release and increased microglial activation, respectively. These adult changes after fetal disruptions may be highly dependent on critical aspects of microglial development [i.e., early established receptor expression (67)]. Such changes, which may occur immediately after MIA, could be studied in a high-throughput manner to assess many possible pharmacological targets and wide-ranging maternal physiological mechanisms.

Microglial sex differences may underlie additional variance after MIA. Microglia density is similar across sexes prior to the onset of androgen secretion, but microglia morphologies and transcriptomes during early development, as well as number and/or density later, differ (68). The greater impact of prenatal PolyI:C in male offspring compared with that in female offspring on adult brain expression of ionized calcium-binding adapter molecule 1, a common microglia marker, may be due to baseline sex differences [for excellent reviews, see (69–71)]. Despite postnatal sexual differentiation receiving attention in animal studies, sex differences in the placenta and embryonic brain may also mediate MIA effects (72,73).

Specific proinflammatory components of MIA have been examined for their effects on microglia and neurodevelopment

Table 1. Examples of Studies on Selected Neurobiological Outcomes and Their Methods

Model	Timing	Host/Strain	Offspring Age; Sex[a]	Effect in Exposed Offspring	Reference
Immune Molecules and Microglia					
IV LPS, 200 ng	GD102.5 ± 0.5 day (preterm human equivalent)	Sheep	E112; NR	Increased microglia/macrophage activation by morphology (intragyral, periventricular white matter)	Dean *et al.*, 2011 (50)
Uterine artery LPS, 30 or 60 μg	GD134–GD 136	Merino/Border-Leicester sheep	E137–E139; pooled	Increased microglia activation by morphology	Hutton *et al.*, 2008 (51)
IP LPS, 200 μg/kg	GD17 to birth, every 12 hours	Lewis rats	P9; NR	Increased microglia density, proliferation (forebrain white matter); rescued by maternal IL-1R antagonist	Girard *et al.*, 2010 (53)
IP PolyI:C, 20 mg/kg	GD9	BALB/c mice	P30; NR	Increased microglia activation by morphology and microglial density (hippocampus and striatum but not frontal cortex)	Juckel *et al.*, 2011 (54)
IV PolyI:C, 4 mg/kg	GD15	Sprague Dawley rats	P180; M and F	Increased microglia number, intensity, and activation by morphology	Van den Eynde *et al.*, 2014 (55)
SQ PolyI:C, 0.5 mg	GD20	Spiny mice (*Acomys cahirinus*)	P1, P100; M and F	Increased microglia number at P1 (hippocampus) but not P100	Ratnayake *et al.*, 2012 (56)
Dual hit: in vivo IV LPS (400 ng/fetus/day); in vitro LPS (100 ng/mL) for 6 hours	GD130 ± 1.3 days (term 145 dGA), once daily ×2 days	Sheep	E133; pooled (in vivo studies); NR (in vitro studies)	MIA alone changed ion transporter, GABA, and second messenger gene expression in cultured microglia; dual hit (first in vivo, second in vitro) caused differential fructose and iron metabolism gene expression	Cao *et al.*, 2015 (62)
Dual hit: prenatal IP LPS, 0.25, 0.10, and 0.05 mg/kg; postnatal LPS, 0.25 mg/kg	GD15–GD17 and at 8 weeks	C57BL/6J-OlaHsd mice	8 weeks; M	Microglia proinflammatory activation after MIA; lower induction of IL-1β, TNFα, and IL-6 mRNA after dual hit	Schaafsma *et al.*, 2017 (63)
Dual hit: in vivo IP LPS, 120 μg/kg); in vitro LPS, 1 μg/mL	GD17 and at P1–P3 cultured microglia	C57BL/6J mice	P1–P3; M	Primary CNS cultures from LPS-treated group produced more IL-6 and IL-1β and less IL-10 after dual hit	Zager *et al.*, 2015 (64)
Dual hit: prenatal IV PolyI:C, 1 mg/kg; postnatal chronic variable stress	GD9 and P30–P40 or P50–P60 (every other day)	C57BL/6 mice	P41; pooled	Dual hit increased microglia activation markers (CD68 and CD11b; hippocampus and prefrontal cortex); elevated IL-1β, TNFα	Giovanoli *et al.*, 2013 (65)
Dual hit: prenatal IP LPS, 10,000 U/kg; postnatal supranigral LPS infusion, 0.02 μg/hour	GD10.5 and 7 mo for 14 days	Sprague Dawley rats	Adult; M	Dual hit increased activated microglia number and prolonged cytokine response	Ling *et al.*, 2006 (52)
Dual hit: prenatal and postnatal IV PolyI:C, 5 mg/kg	GD17 and at 15 mo	C57BL/6J mice	Adult; NR	Dual hit increased CD68+ cells and microglia activation by morphology	Krstic *et al.*, 2012 (66)
IP IL-1β, 100 ng/200 μL	GD12, 13, 3× daily	CD1 mice	E14; NR	IL-1β increased total, amoeboid, and multivacuolated microglia density in the cortical plate	Bittle and Stevens 2018 (74)
IP IL-6 100 ng or restraint stress; with IP anti-IL-6 antibody, 10 μg	GD12–13 or until birth, 3× daily	CD1 mice	E14 balanced for sex; adult M	IL-6 blockade rescued prenatal stress changes to E14 and adult cortical microglia morphology	Gumusoglu *et al.*, 2017 (77)
IP PolyI:C, 20 mg/kg	GD11.5, or GD11.5 and GD15.5	CX3CR1-eGFP knock-in mice	Single dose: E11.5, E12.5, single/double dose: E17.5; NR	No changes to microglial density or IL-1β expression (cortex at all ages, hippocampus at E17.5)	Smolders *et al.*, 2015 (78)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6J mice	P0, P7, P14, P30, P60; M and F	Cytokine changes (23 analyzed; hippocampus, cingulate and frontal cortex, serum); increased pro- and anti-inflammatory cytokines early, lower in adolescence, and some increased in adult; no microglial morphology and/or density changes	Garay *et al.*, 2013 (80)

Table 1. Continued

Model	Timing	Host/Strain	Offspring Age; Sex[a]	Effect in Exposed Offspring	Reference
Brain Morphology and Growth					
IN human influenza virus, dilution of 10–4.5 of 6.5 log 10 (CCID$_{50}$)/0.1 mL	GD18	C57BL/6J mice	P0, P14, P35, P56; M	Reduced brain and white matter volume (P35)	Fatemi *et al.*, 2008 (86)
IN H1N1 influenza virus, 90 μg	GD9	C57BL/6 mice[b]	14 weeks; NR	Decreased ventricle to brain ratio; increased brain weight, size	Fatemi *et al.*, 2002 (87)
IP PolyI:C, 5 mg/kg	GD10–GD14 or GD14–GD18	CD1 mice	P0; NR	Increased cell density (all cortical layers); increased cortical thickness	Smith *et al.*, 2012 (88)
IP LPS, 0.008 mg/kg	GD9	CD1 mice	P0, P20, P60; pooled	Increased brain weight at P0, P20	Le Belle *et al.*, 2014 (89)
IV PolyI:C, 4 mg/kg	GD15	Wistar rats	P35, P46, P56, P70, P90; M and F	Decreased brain volume (all ages except P35; hippocampus, striatum, prefrontal cortex); increased ventricular volume; deficit delayed in F rats compared with that in M rats	Piontkewitz *et al.*, 2011 (90)
IV 15–20 mg purified IgG (with fetal brain reactivity to 37- and 73-kDa proteins) from mothers of children with ASD	GD30, GD44, GD58, GD72, GD86, and GD100 (normal gestation is 165 days)	Rhesus macaques (*Macaca mulatta*)	1 week, 1 mo, 3 mo, 6 mo, 1 year, 2 years; M and F	Faster rate of growth (M macaques); total brain volume diverged at 3–6 mo, greater at 2 years across white and gray matter; no changes in F macaques	Bauman *et al.*, 2013 (92)
IN influenza virus (A/Sydney/5/97 [H3N2]), 1 mL	Gestational week 17 (normal gestation is 24 weeks)	Rhesus macaques (*Macaca mulatta*)	Approx 1 year; pooled	Reduced gray matter, cerebellar white matter, total brain volume	Short *et al.*, 2010 (93)
Cell Populations and Their Development					
IP LPS, 0.12 μg/g	GD17	C57BL/6 mice[b]	P270; NR	Increased pyramidal cell density, decreased cell size (CA); Increased granular cell layer thickness (dentate gyrus)	Golan *et al.*, 2005 (79)
IN influenza virus H1N1, 90 μg	GD9	C57BL/6 mice[b]	P0, 14 weeks; NR	Increased pyramidal cell density, decreased cell nuclear size (P0; hippocampus); increased pyramidal and nonpyramidal cell density (14 weeks; hippocampus)	Fatemi *et al.*, 2002 (87)
IP PolyI:C, 60 mg/kg	GD9.5	FVB/NJNarl mice	6–8 weeks; M	Decreased neurogenesis; no change in differentiation or cell death (olfactory bulb)	Liu *et al.*, 2013 (95)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6N mice	Adult; M	Decreased neurogenesis (subgranular zone hippocampal DG)	Khan *et al.*, 2014 (96)
IP PolyI:C, 20 mg/kg	GD13–GD15	C57BL/6 mice[b]	P18, P120; pooled	Increased Purkinje cell number (P18, P120); no sex differences	Aavani *et al.*, 2015 (97)
Uterine lumen (at junction), *Escherichia coli,* 1 × 105 CFU	GD17	Sprague Dawley rats	P16, P65; M	Decreased Purkinje cell packing density, sectional area volume, calbindin expression (P16; cerebellum); decreased Purkinje cell packing density (P65; cerebellum)	Wallace *et al.*, 2010 (98)
IP LPS, 100 μg/kg	GD15, GD16	Wistar rats	Adult; M and F	Decreased parvalbumin expression (mPFC, hippocampus; M rats); decreased myelination (OFC, BLA, hippocampal CA1 and DG; M rats); Decreased myelination (BLA and DG; F rats)	Wischhof *et al.*, 2015 (99)
IV PolyI:C, 4.0 mg/kg	GD15	Wistar rats	Adult; balanced M and F	Decreased cell density with increased pyknotic cells (hippocampal CA1 region most affected)	Zuckerman *et al.*, 2003 (23)
LPS, 300 μg/kg	GD19, GD20	Wistar rats	P1 and P7; NR	Increased cell death (P1; subventricular striatal zone) (P7; periventricular striatum and white matter and germinative ventricular zone)	Rousset et *al.*, 2006 (100)
IN influenza virus A/NWS/33, 90 mL (10^{-5} dilution)	GD9	C57BL/6 mice[b]	P0; NR	Decreased Cajal–Retzius cell reelin expression (cortical layer 1); decreased neocortical and hippocampal thickness	Fatemi *et al.*, 1999 (102)
IV PolyI:C, 5 mg/kg	GD9 or GD17	C57BL/6J mice	P24; pooled	Decreased Reelin-immunoreactive cells (GD9; hippocampus, dentate gyrus)	Meyer *et al.*, 2006 (103)
IP LPS, 0.25 mg/kg	GD15	Sprague Dawley rats	E15, E16; 4, 24 hours post maternal LPS administration; NR	Increased cellular stress/death gene expression; decreased developmentally regulated, brain-specific gene expression, specifically interneuron migration pathways (4h: 3285 genes)	Oskvig *et al.*, 2012 (104)

Table 1. Continued

Model	Timing	Host/Strain	Offspring Age; Sex[a]	Effect in Exposed Offspring	Reference
IP IL-6 100 ng or restraint stress; with anti-IL-6 antibody, 10 μg	GD12, 13; 3× daily	GAD67-GFP +/− (CD1) mice	E14; balanced M and F	Decreased migration of GABAergic progenitors with IL-6 or prenatal stress; persists despite IL-6 blockade	Gumusoglu *et al.*, 2017 (77)
IP PolyI:C	GD9	C57BL/6 mice[b]; IL-1R KO mice	P20, P90; M	Decreased cortical KCC2 mRNA (P20) and protein (P20, P90). Prevented by IL-1R KO in offspring	Corradini *et al.*, 2017 (105)
IP PolyI:C, 8 mg/kg	GD14	Sprague Dawley rats	P14, P30, P60; M	Increased GAD67 mRNA (multiple regions, adults); increased GAD67 mRNA (dentate granule cell layer, CA2 pyramidal cell layer, thalamic reticular nucleus; P30); decreased GAD67 mRNA (hippocampal CA2; P30)	Cassella *et al.*, 2016 (106)
IV PolyI:C, 4 mg/kg	GD15	Long-Evans rats	P7, P21, P35, P90; pooled	Decreased PNNs (mPFC; P90); decreased percent PV+ cells with PNN (prelimbic cortex; P90); decreased PNNs (BLA; P35)	Paylor *et al.*, 2016 (107)
Synaptic Structure and Function					
PolyI:C, 20 mg/kg	GD12.5	YFP-H C57BL/6J mice	P17–P19, P30; NR	Decreased apical dendritic spine density (layer 1 somatosensory cortex; P17–P19); decreased basal spine density (layer 1 somatosensory cortex; P30); decreased dendritic spine turnover; deficits in excitatory and inhibitory synaptic transmission	Coiro *et al.*, 2015 (111)
PolyI:C, 20 mg/kg	GD12.5	FVB/N Tg(Pcp2-EGFP) BT153Gsat/Mmmh mice	P1, 7, 14, 30; pooled	Decreased Purkinje cell glutamatergic synapse density (cerebellum; P1); altered expression of synaptic organizing proteins (cerebellum; P14); decreased Purkinje cell synapse number (cerebellum; P1); increased IL-6, TNFα level	Pendyala *et al.*, 2017 (112)
PolyI:C, 20 mg/kg	GD12.5	C56BL/6 mice[b]	P0–P2; pooled	Increased MHCI and MEF2 levels (regulate cortical connections); decreased total and excitatory synapse density (cortical neurons)	Elmer *et al.*, 2013 (113)
IP LPS, 100 μg/kg	GD15	C57BL/6 mice[b]	P15; M and F	Increased granule cell spines, decreased CXCR1 mRNA (hippocampus; M mice only)	Fernandez de Cossio *et al.*, 2017 (114)
IP LPS, 0.12 mg/kg	GD15	Swiss mice	P18–P25; NR	Increased relative contribution of AMPAR to evoked EPSCs (hippocampal slices)	Roumier *et al.*, 2008 (31)
IP LPS, 500 μg/kg	GD19	Sprague Dawley rats	P4–P11, P12–P15, P16–P25, P26–P50, P50+; M	Decreased NMDARs and NMDA/AMPA ratio (hippocampus); altered LTD and NMDAR-mediated excitatory synaptic transmission (hippocampal CA1)	Escobar *et al.*, 2011 (118)
IV PolyI:C, 5 mg/kg	GD12.5	C57BL/6J mice	7–15 weeks; balanced by sex	Decreased functional excitatory synapses, decreased frequency and increased amplitude mEPSCs (CA1 pyramidal neurons)	Ito *et al.*, 2010 (119)
IV PolyI:C, 4.0 mg/kg	GD15	Wistar rats	P18–P20, P34, P70, P90; pooled	Decreased excitatory transmission (hippocampus juvenile M rats, adult F rats); abnormal EPSPs (all M rats; adult F rats)	Patrich *et al.*, 2016 (120)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6N mice	Adult; F	Increased mineralocorticoid and glucocorticoid receptor mRNA expression (hippocampus)	Ronovsky *et al.*, 2017 (122)

Only those outcomes that illustrate the categories discussed here are included.

AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; ASD, autism spectrum disorder; BLA, basolateral amygdala; CA, cornu ammonis; CCID$_{50}$, 50% cell culture infectious dose; CD, cluster of differentiation; CFU, colony-forming unit; CNS, central nervous system; CXCR1, C-X-C chemokine receptor type 1; DG, dentate gyrus; dGA, days gestational age; E, embryonic day; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; F, female; GABA, gamma-aminobutyric acid; GAD67, glutamic acid decarboxylase-67; GD, gestational day; IgG, immunoglobulin G; IL, interleukin; IN, intranasal; IP, intraperitoneal; IV, intravenous; KCC2, potassium chloride transporter 2; KO, knockout; LPS, lipopolysaccharide; LTD, long-term depression; M, male; MEF2, myocyte enhancer factor 2; mEPSC, miniature excitatory postsynaptic current; MHCI, major histocompatibility complex class I; MIA, maternal immune activation; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NMDAR, *N*-methyl-D-aspartate receptor; NR, not reported; OFC, orbitofrontal cortex; P, postnatal day; PolyI:C, polyinosinic:polycytidylic acid; PNN, perineuronal net; PV, parvalbumin; PV+, parvalbumin positive; SQ, subcutaneous; TNFα, tumor necrosis factor alpha.

[a] If results are sex-specific, "pooled" indicates that sexes were combined.

[b] C57BL/6 mouse strain is listed if this was the information reported in the study.

more broadly. In the context of prenatal immune activity, IL-1 signaling increases embryonic microglia number (74) and is necessary for MIA effects on neonatal offspring proliferating and total forebrain white matter microglia (53). Maternal prenatal restraint stress may elicit cytokine and microglial dysregulation in male and female offspring (75,76) and has IL-6–dependent effects on fetal and adult microglia morphology (77). Further examination of cytokines and their combinations in maternal circulation, particularly with respect to downstream acute molecular and cellular impacts on the fetal brain, may reveal crucial mechanistic pivot points within maternal-fetal signaling networks.

Despite a rich literature suggesting that MIA elicits proneuroinflammatory effects in offspring, microglial and cytokine phenotypes across studies are not entirely consistent. For example, fetal offspring exhibit no immediate changes to cortical or hippocampal microglia density or activation, as indicated by microglial IL-1β expression, despite robust maternal immune activation by PolyI:C (78). Similarly, fetal brain levels of IL-1β are unchanged by short-term late-gestation LPS administration (79). A comprehensive analysis across multiple postnatal ages demonstrated that PolyI:C-induced changes to offspring proinflammatory cytokines occurred across multiple brain regions despite a lack of changes to microglial density (80). Offspring behaviors altered by MIA have also been uncoupled from microglial activation and brain cytokine levels in both mice (81,82) and pigs (83). These inconsistent results highlight the importance of MIA effects on other targets as mechanisms of risk during fetal development. However, robust evidence of MIA effects on microglia suggests that treatment for MIA-linked psychiatric disorders could target these immune components (84).

Brain Morphology and Growth

Changes at the level of offspring brain morphology may occur after maternal inflammation, either directly, through changing neuronal and glial progenitors, or indirectly, for example through microglial effects on neurodevelopmental processes such as neuronal survival and synaptic pruning (49,57,58,85). MIA results in brain over- and undergrowth, neurodevelopmental outcomes that are particularly relevant to psychiatric disorders (e.g., ASD and schizophrenia, respectively). Influenza infection in early or late mouse gestation increases (86) or decreases (87), respectively, the volume of the adult offspring brain. Also in mice, PolyI:C repeatedly administered over several days throughout mid- or late gestation significantly increases neonatal cortical thickness and cell density (88). Similarly, LPS (single, early injection) causes subtle neonatal and juvenile macrocephaly (89). In rats, maternal administration of PolyI:C in late gestation influences cerebral vasculature, reduces brain volume in some regions, and increases ventricular size, with some effects delayed in female rats relative to male rats (90). The timing of MIA relative to brain developmental processes in each species, including the switches from neural stem cell expansion to neurogenesis (91) and then to gliogenesis (Figure 1), may be critical in the eventual impact on brain growth.

Rhesus monkeys have a gestation length comparable to that of humans. Monkeys treated in the first two trimesters with immunoglobulin G isolated from individuals with ASD have increased brain volume, especially in frontal lobes, driven mostly by white matter increases (92). However, further rhesus monkey work also found that another maternal immune manipulation, prenatal H3N2 influenza infection in the last trimester, results in the opposite—decreased total brain volume and regionally specific reductions in gray and white matter (93). These results again demonstrate that even broad offspring brain growth outcomes after maternal immune manipulation depend on manipulation timing, with earlier manipulations generally resulting in enhanced growth. Brain over- or undergrowth is a pathology that may inform both diagnosis and treatment (94). To further clarify mechanisms that underlie MIA's effects and focus on well-defined outcomes of translational value (e.g., cortical thickness), it may be useful to manipulate single maternal cytokines or define broad manipulations in terms of maternal cytokine profiles.

Cell Populations and Their Development

Specific cell populations and their developmental processes (e.g., proliferation, survival, and migration) are modified by maternal immune activation, with potentially lasting effects on offspring neurodevelopment and disruptions to psychiatrically relevant circuits and structures (e.g., excitatory-inhibitory imbalance, reduced substrates for learning). For example, maternal administration of LPS in late gestation in mice increases pyramidal and granular cell numbers in postnatal hippocampus (79). H1N1 influenza infection during early mouse gestation similarly results in increased neonatal and adult offspring pyramidal and adult-only nonpyramidal cell densities (87).

Further evidence suggests that entirely postnatal neural cell processes may be altered by MIA—for example, reduced neurogenesis in olfactory bulb (95) and hippocampal dentate gyrus (96). Later-developing brain structures such as the cerebellum are also disrupted by prenatal inflammatory perturbation. The gestational maternal administration of PolyI:C results in adult offspring cerebellar hyperplasia, while prenatal maternal *Escherichia coli* bacterial infection results in decreased juvenile, but not adult, offspring cerebellar Purkinje cell volume (97,98). These findings were not paired with cytokines or other maternal or fetal immune profile markers, so immunologic mechanisms implicated are unclear. These findings follow the pattern that some prenatal immune challenges may increase embryonic neuronal cell survival and/or proliferation but reduce postnatal proliferation and/or survival.

The loss of specific cellular subsets may also result from prenatal immune manipulation. Repetitive LPS exposure in late gestation leads to male-specific decreases to parvalbumin-expressing cell densities in the entorhinal and medial prefrontal cortices and hippocampus, as well as myelination deficits across sexes; these pathologies are associated with schizophrenia (99). Cell death is increased in hippocampal and entorhinal cortex neurons in adult rats after midgestation maternal administration of PolyI:C (23) and in neonatal proliferative zones after repetitive administration of LPS in late gestation (100). Inflammatory factor effects on neuronal survival, which decrease in vitro with proinflammatory cytokine exposure, may underlie some of these results (101).

Table 2. Examples of Studies on Selected Behavioral Outcomes and Their Methods

Model	Timing	Host/Strain	Offspring Age[a]; Sex[b]	Effect In Exposed Offspring	Citation
Anxiety-like and Depression-like Behaviors					
IV PolyI:C, 5 mg/kg	GD9 or GD17	C57BL/6J mice	14–16 weeks; pooled	Reduced OF exploration (GD9 MIA); perseverative T-maze behavior (GD17 MIA)	Meyer *et al.*, 2006 (103)
IP LPS, 25 μg/kg	GD9	C57BL/6J mice	8–10 weeks; M	Increased anxiety-related behavior (EPM and OF); increased depression-related behavior (forced swim and tail suspension)	Depino, 2015 (124)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6N mice	Adult; M	Increased anxiety-related behavior (EPM, OF, light/dark box); increased depression-related behavior (forced swim and tail suspension)	Khan *et al.*, 2014 (96)
IP PolyI:C, 20 mg/kg	GD12	C57BL/6 mice[c]	P87, P89; M and F	Increased anxiety-related behavior (EPM, M and F mice; light-zone time, M mice); increased depression-related behavior (forced swim and tail suspension tests)	Majidi-Zolbanin *et al.*, 2015 (125)
IP PolyI:C, 5 mg/kg	GD15	C57BL/6J mice	3 mo; M	Increased depression-related behavior (tail suspension test)	Zhang and van Praag, 2015 (126)
IP LPS, 66 μg/kg	GD10.5	Sprague Dawley rats	P90; M and F	Increased depression-related behavior (forced swim test, both sexes)	Lin and Wang, 2014 (128)
IP IL-6, 5 μg; PolyI:C, 20 mg/kg; anti-IL-6, rat IgG1, 100 μg	GD12.5	C57BL/6J mice and IL-6 KO (C57 strain) mice	Adult; NR	Anti-IL-6 or IL-6R KO rescue of MIA-linked OF reduced locomotion, center avoidance	Smith *et al.*, 2007 (129)
IV PolyI:C, 2 mg/kg	GD9	MacIL-10tg FVB mice	14–16 weeks; pooled	Decreased exploratory behavior (OF) reversed in macIL-10tg mice	Meyer *et al.*, 2008 (130)
Sensorimotor Deficits					
IV PolyI:C, 4.0 mg/kg	GD15	Wistar rats	P35 or 3 mo; balanced M and F	LI deficits in adults, not juveniles	Zuckerman *et al.*, 2003 (23)
SQ LPS, 1 mg/kg	Alternate days throughout pregnancy	Wistar rats	P55–P65, P100–P115, P290–P310; M and F	PPI deficits (M rats, all ages; F rats at P100, P300); increased serum IL-6 (M rats and F rats at P100); increased IL-2 (M rats at P100, P300; F rats at P300); IL-1β unchanged	Borrell *et al.*, 2002 (133)
IN human influenza A/NWS/33CHINI virus, 6 × 103 PFU	GD9.5	BALB/c mice and C57BL/6 mice[c]	9–10 mo; pooled	PPI deficits in both strains	Shi *et al.*, 2003 (134)
IV PolyI:C, 5 mg/kg	GD17	C57BL/6 mice[c]	P80; pooled	LI deficits, increased locomotion and apomorphine-induced climbing time (M and F mice)	Bitanihirwe *et al.*, 2010 (131)
IV PolyI:C, 4.0 mg/kg	GD10 or GD19	Wistar rats	10 weeks; M and F	PPI deficits (M rats only) from P10 and 19 MIA	Meehan *et al.*, 2017 (135)
IP IL-6, 5 μg; PolyI:C, 20 mg/kg; anti-IL-6, rat IgG1, 100 μg	GD12.5	C57BL/6J mice and IL-6 KO (C57 strain) mice	Adult; NR	Anti-IL-6 or IL-6R KO rescue of PolyI:C-linked PPI deficits; anti-IL-6 rescue of LI deficits	Smith *et al.*, 2007 (129)
IV PolyI:C, 2.5 mg/kg, 5.0 mg/kg, 10.0 mg/kg	GD9	C57BL/6 mice[c]	Cytokines: E16; behavior: 14–16 weeks or 28–30 weeks; balanced M and F	No change IL-1β and IL-10 (fetal brain); PPI deficits (5 and 10 mg/kg doses); LI abolished (any dose); dose-dependent increase in amphetamine-induced locomotion	Meyer *et al.*, 2005 (136)
IV PolyI:C, 2 mg/kg	GD9	MacIL-10tg (FVB background) mice	14–16 weeks; pooled	Reversal with macIL-10tg mice of LI and PPI deficits but not of locomotor sensitivity to amphetamine	Meyer *et al.*, 2008 (130)

Table 2. Continued

Model	Timing	Host/Strain	Offspring Age[a]; Sex[b]	Effect In Exposed Offspring	Citation
Social Deficits and Repetitive Behaviors					
IP PolyI:C, 5 mg/kg	GD10.5, GD12.5, GD14.5	C57BL/6J mice	USV: P10 and 8–10 weeks; M; sociability: 10 weeks; M; grooming: 13 weeks; NR; marble burying: 12 weeks; M	Fewer harmonic syllables, more short and complex syllables (juvenile USV); decreased sociability, reduced adult USV in encounters; increased grooming and marble burying	Malkova *et al.*, 2012 (138)
IP LPS, 75 mg/kg	GD11.5, E12	C57BL/6 mice[c]	Social test, grooming: 7–8 weeks; marble burying: 9–10 weeks; M and F	Abnormal social behavior (only F mice); increased stereotyped behaviors (M and F mice) and marble burying (only M mice)	Xuan and Hampson, 2014 (139)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6 mice[c]	7–10 weeks; M and F	No sociability deficits; nonsignificant increased grooming (M and F mice); marble burying abnormality (only M mice)	Xuan and Hampson, 2014 (139)
IN human influenza A/NWS/33CHINI virus, 6 × 103 pfu	GD9.5	BALB/c mice	9–10 mo; pooled	Social deficits (less contact)	Shi *et al.*, 2003 (134)
in utero inoculation, Asian-lineage ZIKV strain PRVABC59 (Zika virus)	GD50 (normal gestation is 114–115 days)	Pigs	P0–P21; pooled	Increased aggression, fighting	Antonson *et al.*, 2017 (83)
IV 15–20 mg purified IgG (with fetal brain reactivity to 37- and 73-kDa proteins) from mothers of children with ASD	GD30, GD44, GD58, GD72, GD86, GD100 (normal gestation is 165 days)	Rhesus macaques (*Macaca mulatta*)	0–6, 6–12, 12–18 mo; pooled	No peer interaction change (0–6 mo); increased frequency peer approach (6–12 mo); increased approach initiation and physical contact, decreased approaches received (12–18 mo)	Bauman *et al.*, 2013 (92)
IV PolyI:C, 25 mg/kg	GD43, GD44, and GD46 (MIA1), or GD100, GD101, and GD103 (MIA2)	Rhesus macaques (*Macaca mulatta*)	10, 17, 22 mo; pooled	Increased repetitive behaviors (MIA2 at 10 mo; MIA2 at 17 mo; both at 22 mo); decreased affiliative vocalization, inappropriate social approach, increased unreciprocated interactions	Bauman *et al.*, 2014 (141)
IV 15–20 mg purified IgG (with fetal brain reactivity to 37- and 73-kDa proteins) from mothers of children with ASD	GD27, GD41, GD55	Rhesus macaques (*Macaca mulatta*)	8.5 mo, 1 year; pooled	Increased pacing, frequency, duration of bouts of extended stereotypy (8.5 mo); increased activity at 1 year	Martin *et al.*, 2008 (142)
IP IL-6, 5 μg; PolyI:C, 20 mg/kg; anti-IL-6, rat IgG1, 100 μg	GD12.5	C57BL/6J mice and IL-6 KO (C57 strain) mice	Adult; NR	Anti-IL-6 rescue of sociability deficit	Smith *et al.*, 2007 (129)
IP PolyI:C, 20 mg/kg	GD12.5	C57BL/6[c] and RORγt KO mice	8–12 weeks; M	Social interaction deficits rescued with IL-17a blocking antibody pretreatment, maternal RORγt deletion	Choi *et al.*, 2016 (144)

ASD, autism spectrum disorder; E, embryonic day; EPM, elevated plus maze; F, female; GD, gestational day; IgG, immunoglobulin G; IL, interleukin; IN, intranasal; IP, intraperitoneal; IV, intravenous; KO, knockout; LI, latent inhibition; LPS, lipopolysaccharide; M, male; MIA, maternal immune activation; NR, not reported; OF, open field; P, postnatal day; PFU, plaque-forming unit; PNN, perineuronal net; PolyI:C, polyinosinic:polycytidylic acid; PPI, prepulse inhibition; RORγt, retinoic acid receptor–related orphan receptor gamma; SQ, subcutaneous; USV, ultrasonic vocalization.

[a] In cases of behavior outcomes, age indicates animal age at commencement of behavioral testing.

[b] If results are sex-specific, "pooled" indicates that results of both sexes were combined.

[c] C57BL/6 mouse strain is listed if this was the information reported in the study.

Altered migration of neural precursors and newly born neurons may contribute to long-lasting brain changes through altered mitogen levels, such as decreased neonatal hippocampal reelin expression after influenza infection in early gestation (102) or PolyI:C (103). Intrinsic gene expression profiles that underlie migration processes are also disrupted by LPS exposure in mice (104). IL-6 exposure, specifically, in mice delays cortical interneuron migration, but immunologic IL-6 blockade does not prevent comparable delays caused by prenatal stress (77). Interneuron development is sensitive to more complex shifts in prenatal stress–induced physiology than accounted for by IL-6 alone.

As cells migrate, they continue to differentiate, a process also hindered by maternal immune manipulation. For example, the excitatory-to-inhibitory switch of gamma-aminobutyric acid signaling, mediated by the neuronal cotransporter potassium chloride transporter 2, is delayed after early PolyI:C exposure in mice (105). MIA also leads to altered expression of glutamic acid decarboxylase-67, an enzyme critical to gamma-aminobutyric acid production (106). One possible intermediate mechanism for disruptions to development of this system may be altered extracellular perineuronal nets, which provide a scaffold for the synapses and neurites around parvalbumin cells and are diminished after prenatal exposure to PolyI:C (107). Such changes may be a critical component of psychopathology, as evidenced by similar findings in postmortem examinations of brains of persons with schizophrenia (108). Broadly, findings that MIA affects gamma-aminobutyric acidergic development and postnatal neurogenesis point to mechanisms that may be treatment targets.

While not considered in detail here, epigenetics may underlie specific disrupted cellular processes after MIA. Altered methylation of genes in the embryonic brain during MIA can persist and affect adult neurons (109). For example, neuronal differentiation pathway genes exhibit greater methylation than those in neurogenesis or myeloid cell differentiation pathways in the brain of MIA-affected offspring (110). This finding suggests that epigenetic mechanisms may serve as an additional mechanism by which MIA alters neurodevelopmental processes. Broader assessments of brain changes via data-rich methods (i.e., epigenetic or transcriptomic approaches) may yield critical insights into MIA's influence on distinct neurodevelopmental processes.

Synaptic Structure and Function

Alterations in synapse formation and dendritic development are core aspects of psychiatric pathophysiology that may mechanistically link prenatal immune disruption to psychiatric risk. Studies have shown that midgestation PolyI:C leads to persistently reduced cortical dendritic spine density, turnover, and connectivity, as well as altered excitatory and inhibitory synaptic transmission (111). In the same model, cerebellar synapses and their function are also disrupted after MIA, as are levels of proinflammatory cerebellar cytokines, including those of IL-6 and tumor necrosis factor alpha (112). Others report similar synaptic dysregulation (113).

The well-documented role of microglia in synaptic development (48,58), which may be altered by maternal immune manipulation (114), suggests one potential mechanism for these effects. Specific cytokines and chemokines, such as IL-1β, IL-6, and tumor necrosis factor alpha, have direct roles in neurite developmental processes, including altering synaptic efficacy, truncating dendrites (115,116), regulating neuronal migration, and pathfinding via C-X-C chemokine receptor type 4 (117).

The dynamic and highly conserved hippocampus provides an excellent model for understanding synaptic physiology changes after MIA. Late-gestation exposure to LPS increases the ratio of excitatory α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor–to–*N*-methyl-D-aspartate receptor currents in adult hippocampal slices (31) and impairs *N*-methyl-D-aspartate receptor function and development in hippocampal CA1 (118). CA1 synaptic physiology is similarly perturbed after MIA via PolyI:C (119,120). When injected directly into the neonatal rat hippocampus to mirror MIA exposure in late human gestation, LPS induces local dysregulation of tumor necrosis factor alpha, IL-1, and IL-2 at short- and long-term time points (121). MIA also disproportionately impedes hippocampal development and impairs its role in regulating stress reactivity (122), learning, and memory (96), core functions that, as with synaptic disruptions that may result from MIA, are also disrupted in many psychiatric disorders. While specific immune factors have yet to be causally implicated in synaptic and hippocampal dysfunction after MIA, a cascade of events beginning with changes to embryonic neuronal differentiation and microglia likely underlie these dysfunctions.

BEHAVIORAL OUTCOMES

Prenatal maternal immune manipulations result in a broad array of offspring behavioral phenotypes relevant to psychiatric disorders. Below we review the most robust and reliable that are also of greatest translational interest (Table 2).

Anxiety-like and Depression-like Behaviors

Depression- and anxiety-like behaviors in preclinical models are among the most widely studied and replicated outcomes in the MIA field. Commonly examined behaviors include locomotor inhibition, sucrose preference, forced swim, and elevated plus maze performance (123). Offspring changes in these behaviors arise after MIA at embryonic day 9 (103,124), embryonic day 12 (96,125), or later gestation (126). Animal genetic strain is a critical factor in the effects of MIA on offspring behaviors (127)—this may parallel the genetic variability in humans that differentially influences risk susceptibility. Higher rates of anxiety and depressive disorders in women have not been observed in rodent depressive- and anxiety-like outcomes after MIA. For example, increased immobility in the forced swim test, an assay of antidepressant efficacy, increases in male mouse offspring (96,125) or in rat offspring of both sexes (128) who were exposed to MIA. To adequately address sex differences, however, more studies must include both sexes. Additionally, evaluating specific maternal stress factors will be valuable. Prenatal immune factors including IL-6 (129) and IL-10 (130) may mediate some effects of MIA on offspring depressive- and anxiety-like behaviors, although others have not been ruled out.

Sensorimotor Deficits

A cluster of sensory and motor phenotypes, including exploratory behavior, PPI, LI, and altered responsiveness to psychoactive drugs are often considered endophenotypes of schizophrenia in animal models. Maternal PolyI:C robustly impairs LI in male mice and increases postpubertal offspring locomotor sensitivity to apomorphine across sexes in mice (131). PPI-measured sensorimotor gating, which is disrupted in individuals with schizophrenia, measures the ability to filter sensory information (55,132). The presence of maternal PolyI:C (23), LPS (133), or influenza infection (134) alters PPI and LI performance. PPI deficits are further associated with increased levels of adult serum IL-6 and IL-2, but not IL-1β, after LPS exposure throughout gestation (133), and they may be male specific (135).

Specific inflammatory mediators may underlie some sensorimotor behavioral programming. A single PolyI:C or IL-6 dose at embryonic day 12 yields PPI and LI deficits in adult mouse offspring, as well as proinflammatory transcriptional changes—effects that can be rescued by immunologic or genetic amelioration of maternal IL-6 action (129). Deficits in PPI and LI, as well as increased locomotor responsivity to amphetamine after embryonic day 9 PolyI:C exposure, are associated with moderately increased proinflammatory fetal brain IL-1β (136). PPI and LI are further directly dependent on fetal IL-10, an anti-inflammatory cytokine that, when overexpressed in macrophages, prevents these PolyI:C-induced offspring behaviors (130).

Social Deficits and Repetitive Behaviors

Rodent behaviors used in autism model work (137) include neonatal ultrasonic vocalizations, animal sociability, and stereotyped behaviors including grooming. These behaviors are sensitive to the maternal gestational administration of PolyI:C and LPS in rodents (138,139). Maternal manipulations involving complex immunologic perturbations, such as human influenza or Zika virus infection, further result in abnormal social behavior in immune-suppressed (BALB/c) mice (134) and pigs (83), respectively.

As with other MIA-induced phenotypes, autism-like behaviors also depend on animal strain (29), genetics (140), and experimental protocol. However, commonalities with nonhuman primate work further support a role for maternal immune exposure in driving social deficits in offspring. PolyI:C exposure alters repetitive and social behaviors, including decreased affiliative vocalization, inappropriate social approach, and increased unreciprocated social interactions, in macaque offspring (141). Also in macaques, maternal treatment with immunoglobulin G extracted from individuals with ASD leads to offspring whole-body stereotypies and hyperactivity, including back-flipping and cage-pacing (142), increased inappropriate social approach (without affiliative behaviors such as grooming or playing), and unreciprocated social interactions. These behaviors intensified throughout development, unlike stable rates seen in control macaques (92,142).

Mediation of offspring social and repetitive behaviors by specific cytokines including maternal IL-6 (129,143) or IL-17a has also been demonstrated. For example, blockade of IL-17a activity in the context of PolyI:C via ameliorating antibody or maternal knockout of the IL-17a pathway regulator retinoic acid receptor–related orphan receptor gamma rescues prenatal offspring cortical disorganization and adult autism-like phenotypes (144). Determining the changes in the developing brain that are required for these outcomes, particularly sex-specifically, would contribute significantly to the autism research field.

CONCLUSIONS

Maternal-to-fetal immune programming of the offspring brain in model systems demonstrates the relevance of these mechanisms to psychopathology. Changes in adult brain and behavior (Figure 2) resemble those found in individuals with major psychiatric illnesses. Much less is known about how alterations to embryonic brain processes after MIA underlie later dysfunction, a period increasingly recognized as relevant to later-onset psychiatric illness. The timing of MIA relative to neurodevelopmental events and later phenotypes has suggested some mechanisms. For translating this work to preventive science, broad models of immune activation are relevant, as multiple immune molecules change together. However, larger advances will be made by identifying distinct molecules or critical immune profiles through unbiased, high-throughput approaches. Such approaches have been successfully employed in recent years in toxicology, microbiology, and genetics. For example, see work on the exposome (145), network-based analyses of the microbiome (146), and polygenic approaches to assessing psychiatric disease risk (147–149). Adopting an immunome approach (150) would allow for greater insight into mechanisms underlying maternal immune manipulation and for exploration of other specific differences of relevance to clinical domains, including offspring sex and the developmental timing of disruptions.

Determining mechanisms that underlie psychiatric outcomes, often separated by years or decades from early developmental disruptions, poses significant challenges. Advances in developmental neuroscience that link subsequent brain-development events to prenatal processes provide a foundation on which pathophysiology can be better understood. In addition, recognition of the important role of the placenta and immune shifts during pregnancy, which are not intuitively linked to psychiatric risk, is essential to this mechanistic work. Despite limitations, animal models provide critical data supporting prenatal inflammation programming of the brain and will be fundamentally involved as immunome-level analyses and other innovative methods are developed.

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