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Maternal Immune Activation in Neurodevelopmental Disorders

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Converging lines of evidence from basic science and clinical studies suggest a relationship between maternal immune activation (MIA) and neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia. The mechanisms through which MIA increases the risk of neurodevelopmental disorders have become a subject of intensive research. This review aims to describe how dysregulation of microglial function and immune mechanisms may link MIA and neurodevelopmental pathologies. We also summarize the current evidence in animal models of MIA. ***Developmental Dynamics 247:588–619, 2018.*** **© 2017 Wiley Periodicals, Inc.**

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Introduction

In the past few decades, epidemiological studies have generated a growing interest in the relationship between maternal immune activation (MIA) and neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia. After the 1964 rubella epidemic, it was found that an unanticipated 18 out of the 243 children studied with congenital rubella had developed characteristics associated with ASD (Chess, 1971). It was later observed in a New York City cohort that 20% of subjects who were born to mothers with clinical rubella were diagnosed with adult schizophrenia (Brown, 2006), whereas this disorder is prevalent in less than 1% of the general population (Saha et al., 2005). In addition to rubella, maternal infections with influenza (Mednick et al., 1988; Brown et al., 2004), toxoplasma gondii (Mortensen et al., 2007; Yolken et al., 2009), cytomegalovirus (Hyman et al., 2005), and the Borna disease virus (Rott et al., 1985) have been reported to increase the incidence of neurodevelopmental disorders. This suggests that immune activation in general, rather than a specific pathogen, disrupts normal brain development. In 2010, an influential study utilized the Danish health registry to examine the records of more than 1.6 million children born between 1980 and 2005. It demonstrated a significant association between ASD and maternal viral infection during the first trimester of pregnancy (hazard ratio: 2.98) and bacterial infection during the second trimester of pregnancy (hazard ratio: 1.42) (Atladóttir et al., 2010). More recently, a study of the Kaiser Permanente database for Northern California reported that maternal infection requiring hospital admission was associated with an increased risk of delivering a child who would develop ASD, and that bacterial infection during pregnancy engendered the highest risk with an odds ratio of 1.58 (Zerbo et al., 2015). Since the placenta is one source of hematopoietic stem cells for the fetus (Gekas et al., 2005), it has been suggested that maternal infection may permanently alter the immune system of the offspring and consequently alter the immune status of the fetal brain (Patterson, 2009).

Epidemiological and preclinical studies are beginning to elucidate some of the mechanisms that may be involved: neuroimmune interaction is increasingly implicated in the etiology of neuropsychiatric disorders (Khandaker et al., 2015; Müller et al., 2015; Stuart et al., 2015; García-Bueno et al., 2016; Leboyer et al., 2016; Mottahedin et al., 2017). Microglia, the resident immune cells of the central nervous system (CNS), are now thought to play roles in normal brain development and maturation, including the refinement of neural circuitry, the promotion of developmental apoptosis, and synaptic pruning (Paolicelli et al., 2011; Wu et al., 2013; Nayak et al., 2014; Hong and Stevens, 2016; Mosser et al., 2017). Since cellular and molecular components of the immune system have important functions in normal neurodevelopment, it has been hypothesized that their abnormal activation can lead to a variety of CNS disorders (Deverman and Patterson, 2009; Mosser et al., 2017; Salter and Stevens, 2017; Sarlus and Heneka, 2017; Tiwari and Pal, 2017; Yang et al., 2017). Dysregulation of microglial function specifically has been proposed to contribute to the pathogenesis of neurodevelopmental disorders (Monji et al., 2009; Petrelli et al., 2016; Hanamsagar and Bilbo, 2017). Furthermore, it has been suggested that MIA may prime microglia to drive inflammatory

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processes in the CNS during postnatal development (Knuesel et al., 2014). This suggests that microglia may mediate long-lasting neuroimmune dysregulation induced by MIA. Here we will discuss how MIA may disrupt neurodevelopment by altering cellular and molecular functions of microglia.

Evidence of a Role for the Immune System in Neurodevelopmental Disorders

Autism spectrum disorder

ASD is used to describe a heterogeneous group of developmental neuropsychiatric disorders characterized by impaired social interaction and communication, as well as restricted and repetitive interests and behaviors (Lord et al., 2000; American Psychiatric Association, 2013). Symptoms of ASD first appear between 12 months and 18 months of age and persist throughout adulthood (Johnson et al., 2007). Recent reports have estimated the prevalence of ASD in the United States at approximately 1 in 68 children, with a higher prevalence in boys at 1 in 42 (Christensen et al., 2016). These data suggest a seven-fold increase in ASD since 1992, when the prevalence of ASD as a disorder was reported to occur in roughly 1 in 500 children (Estes and McAllister, 2015). Given that public awareness, loosening of the diagnostic criteria, improvements in screening programs, and altered reporting practices may account for some of the increase in ASD prevalence (Hansen et al., 2015), it is unclear whether the continued rise in ASD diagnoses can be attributed to a true increase in the occurrence of autism (Hertz-Picciotto and Delwiche, 2009).

Although the exact etiology of autism remains to be elucidated, it is thought to result from a complex interaction between genetic, environmental, and immunological factors (Persico and Bourgeron, 2006). Genetic contributions to ASD have been extensively studied. For instance, early familial and twin studies demonstrated that ASD may have a heritability index (the ratio of the variance due to genetic factors to the total variance in a population) ranging from 0.5 to 0.9 (Sandin et al., 2014). Genetic variants that have been suggested to contribute to the broad clinical spectrum of ASD include autosomal recessive, autosomal dominant, X-linked and additive risk variants, and chromosomal translocations, as well as triplet repeats. Rare genetic syndromes with high penetrance may account for around 5% of individuals with ASD (de la Torre-Ubieta et al., 2016). There is also increasing evidence suggesting a relationship between an aberrant immune system and ASD pathogenesis. Atopic autoimmune and allergic disorders (psoriasis, asthma, and type 1 diabetes) or a family history of such disorders have been associated with ASD (Pardo et al., 2005; Keil et al., 2010; Xu et al., 2014). Likewise, individuals with ASD are also more likely than the general population to suffer from a concurrent autoimmune disorder (Kohane et al., 2012; McDougle et al., 2015).

Postmortem brain studies have reported pathological features consistent with aberrant CNS inflammation or immune activation in the brains of ASD individuals. Microglia respond to infection or injury in CNS through phagocytosis of cellular debris and release of inflammatory cytokines and other mediators of inflammation (Kettenmann et al., 2011). It is commonly understood that under physiological conditions, surveilling microglia display a highly ramified morphology, and that upon inflammatory activation they typically adopt an amoeboid shape, characterized by a larger somal volume with retracted and thickened processes (Ransohoff and Perry, 2009; Tremblay et al., 2010; Franco and Fernández-Suárez, 2015). Microglial activation has been implicated in the etiology of ASD (Rodriguez and Kern, 2011; Takano, 2015). Microglial density was found to be higher and displayed a more amoeboid morphology in the postmortem brains of individuals with autism between 3 and 41 years of age compared to age-matched controls (Morgan et al., 2010; Tetreault et al., 2012). Moreover, microglia in the dorsolateral prefrontal cortex (dlPFC), an area associated with complex cognitive processing and behavior, displayed distributions that were abnormally closely associated with neuronal somata in ASD postmortem samples when compared with age-matched (1 to 44 years of age) controls, suggesting an increase in microglia-neuron interaction and potential neuronal loss (Morgan et al., 2012). Increased microglial activation, inferred in part from elevated expression of Major Histocompatibility Complex class II markers, was observed in the cerebellum of postmortem brains of ASD patients ages 5 to 44 years compared to age-matched controls (Vargas et al., 2005). Other reported histological abnormalities include astrocytic dysregulation with an increased number of astrocytes, decreased astrocytic branching, increased glial fibrillary acid protein (GFAP) expression, and increased natural killer and macrophage activity (Goines and Van de Water, 2010; Edmonson et al., 2014). In vivo evidence of microglial activation was also presented in a study that used positron emission tomography (PET) imaging (Suzuki et al., 2013), although this method has been mainly used to study schizophrenia (see below).

Additional evidence of immune system dysregulation in ASD includes up-regulation of cytokines and their downstream signaling pathways in the CNS of affected individuals (Pardo et al., 2005). This study further reported elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6) and macrophage chemoattractant protein-1 (MCP-1), as well as anti-inflammatory transforming growth factor-ß (TGF-ß). A similar increase in cytokines and proinflammatory markers was not observed in the cerebrospinal fluid (CSF) of a small cohort of young (2.7 to 10 years old) ASD patients compared with age-matched patients with other CNS diseases (Zimmerman et al., 2005). Expression profiling in a small number of autistic and control brain specimens revealed increased transcript levels of many immune related genes, including many components of the IL-1ß and IL-6 pathways (Garbett et al., 2008). A larger study using microarray and RNA-seq to assess differential transcription regulation in ASD likewise reported increased expression of many genes associated with immune and inflammatory responses in samples from autistic individuals (Voineagu et al., 2011).

Immune profiling has also been performed on living ASD patients and their families. Such studies have reported respectively increased and decreased levels of proinflammatory and anti-inflammatory cytokines in the serum or plasma of individuals with ASD (Estes and McAllister, 2015). A marked up-regulation of tumor necrosis factor alpha (TNF-α) was observed in the CSF of autistic children (Chez et al., 2007), as were lowered

immunoglobulin (IgG and IgM) plasma levels (Heuer et al., 2008), corroborating previous findings suggesting a dysfunction of the immune system in these patients. Individuals with ASD also have an increased number of circulating blood monocytes relative to controls (Sweeten et al., 2003). Stimulation of peripheral blood monocytes (PBMC) from ASD individuals was shown to produce higher levels of proinflammatory cytokines in comparison to PBMCs of unaffected controls, suggesting a degree of immune "priming" (Molloy et al., 2006; Enstrom et al., 2010). Elevated levels of interleukins IL-1β, IL-6, IL-8, and IL12p40 were detected in the peripheral blood plasma of individuals with ASD (Ashwood et al., 2011). A recent meta-analysis of studies comparing blood and serum levels of 19 cytokines revealed significantly elevated levels of IL-1β, IL-6, IL-8, interferon-γ (IFN-γ), eotaxin, and MCP-1, and significantly lower levels of the anti-inflammatory TGF-β1 in individuals with ASD, compared with healthy controls (Masi et al., 2015). Interestingly this finding contradicted the increase in TGF-β1 observed in the postmortem tissue from ASD individuals (Vargas et al., 2005) and may reflect differences in inflammatory responses between CNS parenchyma and systemic circulation. No significant change was demonstrated for several other cytokines, including TNF-α, IL-10, and IL-17, while the strongest effects were observed for IFN-γ and TGF-β1 (Masi et al., 2015). Finally, cytokine expression levels have been correlated with the clinical severity of ASD symptoms, as individuals with higher levels of plasma cytokine expression are more likely to have severe forms of ASD (Masi et al., 2015).

In addition to infection, environmental factors may trigger immune activation. Pollutants, food additives, and cosmetic ingredients have been proposed to interact with genetic predispositions to increase the incidence of ASD partly through inflammatory pathways (Carter and Blizard, 2016). Respiratory irritants in environmental pollution can induce an infection-free MIA response that may contribute to ASD-like behavioral dysfunction and other neurodevelopmental defects (Bilbo et al., 2018).

Schizophrenia

Schizophrenia is increasingly considered to have neurodevelopmental origins, though symptoms typically appear in late adolescence or early adulthood (Rapoport et al., 2012). The disorder affects approximately 1% of the population (Rössler et al., 2005). Symptoms include delusions, hallucinations, and cognitive deficits (Green, 1996). Although the mechanisms underlying schizophrenia are incompletely understood, they are likely to involve complex interactions between genetic/epigenetic and environmental factors, particularly in the perinatal period (Brown, 2011). Nutrition, cannabis use, and stress are among some of the environmental factors proposed to hasten or increase the likelihood of psychosis in genetically susceptible individuals (Davis et al., 2016). Intriguingly, an analysis in a relatively small cohort of the interaction between polymorphism in sialyltransferase (ST8SIA2), a susceptibility gene for schizophrenia, and the incidence of stressful life events showed a trend toward a certain amount of stress being protective against the disorder (Mandelli et al., 2016). A recent study showed a genetic association of schizophrenia with allelic variants of complement component C4, a protein involved in an innate immune system pathway that rapidly recognizes and eliminates pathogens and cellular debris (Sekar et al., 2016). An increasing number of human and animal studies have found interacting effects of genetic mutations and environmental factors (including MIA) on the manifestation of schizophrenia-like symptoms (Ayhan et al., 2016).

Although the relationship between abnormal microglia function and schizophrenia has been explored in the context of neurodevelopment, other lines of evidence point to a possible role of microglia in the neurodegeneration associated with schizophrenia. Magnetic resonance imaging studies in patients suggest that neurodegeneration is involved in the development of schizophrenia, including evidence of cortical gray matter loss associated with childhood onset of schizophrenia (Thompson et al., 2001). It has been suggested that the neurodegeneration observed in schizophrenia may be attributable to dysregulation of microglial function (Block and Hong, 2005). Although early studies of the contribution of the immune system to the etiology of schizophrenia gave contradicting results, in part due to confounding factors such as disease onset and severity, drug treatment, and sex and age differences in patient cohorts, it is becoming increasingly clear that immune mechanisms and MIA contribute to the pathogenesis of schizophrenia (Brown and Derkits, 2010; Müller and Schwarz, 2010; Volk, 2017). Activated microglia release proinflammatory cytokines and free radicals, which may cause neuronal degeneration and thus contribute to the pathophysiology of schizophrenia (Pérez-Neri et al., 2006; Monji et al., 2009; Miller et al., 2011; Laskaris et al., 2016). For instance, fetal exposure to elevated levels of maternal IL-8 gives rise to significant neuroanatomic alterations (as visualized by T1-weighted magnetic resonance imaging) that have been consistently linked to schizophrenia in adult patients (Ellman et al., 2010). There is also some indication that the inflammatory profile of patients varies across the spectrum of the disorder, with different levels of inflammation detected among those with paranoid vs. residual schizophrenia (Busse et al., 2012).

Several lines of evidence from postmortem studies suggest the presence of immune dysregulation in individuals with schizophrenia. However, these findings have at times provided conflicting results. Although there have been multiple postmortem studies suggesting an increase in microglial density, upregulation of the expression of human leukocyte antigen-DR (HLA-DR), a marker of microglia activation, and morphological changes suggestive of microglial activation in several brain regions of individuals with schizophrenia (Bayer et al., 1999; Radewicz et al., 2000; Wierzba-Bobrowicz et al., 2005; Fillman et al., 2013), other studies found no difference (Steiner et al., 2006; Steiner et al., 2008; Busse et al., 2012). There is nonetheless a considerable body of research pointing toward the implication of the immune system in schizophrenia, encompassing multiple immune mechanisms. Alterations in B-lymphocyte populations, increased antibody production, and differential T-lymphocyte activation have also been reported in individuals with schizophrenia (Busse et al., 2012; Richard and Brahm, 2012). The relationship between microglial activation and cytokines in neurodevelopmental abnormalities has led to the suggestion that anti-inflammatory treatments be used as novel adjuvant

therapies for schizophrenia patients (Na et al., 2014). Relatively small trial studies adding anti-inflammatory drugs to patients' treatments yielded some positive results, including improvement of positive and negative symptoms (Fineberg and Ellman, 2013).

Gene expression profiling studies in postmortem human samples have uncovered a wide array of cellular processes disrupted in schizophrenia patients (Horváth and Mirnics, 2014; Bergon et al., 2015), including immune mechanisms (Arion et al., 2007; Saetre et al., 2007; Fillman et al., 2013). A recent meta-analysis of long-term antipsychotic monotherapy–stabilized patients (61.6% male, average age 50.5 years, and sex- and age-matched controls) examined blood and serum cytokine transcript levels and found elevated expression of numerous genes involved in inflammatory and wound response (Bergon et al., 2015). Some studies have reported elevated levels of proinflammatory cytokines, including IL-6 and TNF-α in the blood or CSF of individuals with schizophrenia (Sperner-Unterweger, 2005), although contradicting findings were obtained in many studies due to different-size cohorts, level of psychosis, and medication status of the patients (Potvin et al., 2008; Brown and Derkits, 2010; Miller et al., 2011). A recent systematic review of cytokines in the serum of medication-naïve first-episode psychosis patients found a significant elevation in IL-1ß, IL-6, sIL-2r, and TNF-α (Upthegrove et al., 2014).

Radioactive tracers that bind to peripheral-type benzodiazepine receptors (PBR), which are associated with glial cells in the brain, can be detected at higher levels by PET in activated astrocytes and microglia during inflammation (Doorduin et al., 2008). The main source of lesion-induced increases in PBR expression signal in the brain is from microglia (Banati et al., 1997). Most human studies investigating brain inflammation have used the PBR ligand (R)-N-^{11}C-methyl-N-(1-methylpropyl)-1-(2-chloro- phenyl)isoquinoline-3-carboxamide (^{11}C-(R)-PK11195), despite it having a fairly low signal-to-noise ratio, which is likely due to its relatively poor ability to cross the blood-brain barrier (Doorduin et al., 2008). PET studies using ^{11}C-(R)-PK11195 reported an increase in microglial activity in the frontotemporal brain regions of schizophrenic patients (van Berckel et al., 2008; Doorduin et al., 2009). Van Berckel and colleagues show that activated microglia are present in the white matter of schizophrenic patients within the first 5 years after the onset of the disease (van Berckel et al., 2008). A number of new PET tracers for PBR imaging have been developed, each with different uptake and binding kinetics (Doorduin et al., 2008). [^{11}C]-labeled N-(2,5-dimethoxybenzyl)-N-(5-fluoro-2- phenoxyphenyl)acetamide ([^{11}C]DAA1106) has been used in very few human studies but was shown to have higher uptake and to allow reliable detection of inflammation in several rodent models and nonhuman primates. The only study to use [^{11}C]DAA1106 PET imaging in schizophrenia patients found a correlation between PBR binding and severity of the symptoms and disease duration, although they detected no significant difference in PBR binding in patients vs. healthy controls (Takano et al., 2010). Another PET study using N-acetyl-N-(2-[^{18}F]fluoroethoxybenzyl)-2-phenoxy-5-pyridinamine ([^{18}F]-FEPPA, also a second-generation tracer) likewise did not observe significantly different ligand binding between healthy controls and schizophrenia patients (Kenk et al., 2015). It is clear that more live imaging studies are needed, with larger patient and control cohorts and carefully controlled variables, ideally comparing the ability of radioactive tracers to detect changes in microglia activation in schizophrenia.

Taken together, these results suggest that dysregulation in the immune system, including abnormalities in microglial structure and function, is disproportionately present in individuals with schizophrenia and ASD. Given reports of MIA inducing microglial dysregulation, microglia are likely a key factor in MIA-induced neurodevelopmental disorders. In the following sections, we present evidence from preclinical studies of MIA in animal models exploring the cellular and molecular mechanisms that give rise to defects in circuit formation.

Animal Models of MIA

Preclinical studies in animal models have explored the relationship between MIA and neurodevelopment by inducing inflammation in pregnant mice, rats, and nonhuman primates (primarily rhesus macaques). The pioneering contributions of the late Paul Patterson (1943–2014) at the California Institute of Technology should be particularly noted in this regard (Patterson, 2009; Patterson, 2011). Although a few studies induced MIA via exposure of pregnant mice to the influenza virus (Fatemi et al., 1999; Fatemi et al., 2002a; Fatemi et al., 2002b), the need for increased safety measures to adequately protect the experimenters makes the use of infection-mimicking immunogenic substances more convenient. The two most commonly used approaches are the injection of synthetic viral RNA polyinosinic:polycytidylic acid (Poly(I:C)) and bacterial endotoxin lipopolysaccharide (LPS) to evoke antiviral or antibacterial innate immune responses, respectively. Poly(I:C) interacts with toll-like receptor (TLR) 3 and induces the production of antiviral interferons and inflammatory cytokines (Reisinger et al., 2015). LPS, a gram-negative bacterial cell wall component, binds to TLR4, activating parallel and overlapping inflammatory signaling to that of Poly(I:C) (Reisinger et al., 2015). It is important to note that components of the TLR signal transduction machinery have been implicated in the etiology of neuropsychiatric disorders (Reisinger et al., 2015).

Effect of MIA on behavior

Treatment of animals (primarily rodents) with LPS, Poly(I:C), or other agents capable of inducing a substantial maternal immune response has been demonstrated to elicit behaviors in the offspring that are reminiscent of ASD and schizophrenia (Boksa, 2010; Patterson, 2011; Kneeland and Fatemi, 2013; Meyer, 2013; Meyer, 2014). These include deficits in communication and social interaction, elevated anxiety, reduced sensorimotor gating (a measure of the ability of the brain to filter out extraneous information), deficits in cognitive flexibility and working memory, and enhanced sensitivity to amphetamines (Meyer et al., 2009a; Patterson, 2009; Meyer, 2013; Meyer, 2014). These behaviors have been described to correlate with neurological defects observed in patients suffering from schizophrenia and ASD.

Assessment of anxiety-like behaviors are often performed in rodents using open field locomotion monitoring, where an animal is placed in a wide, well-lit box and left to explore. A decrease in the amount of time spent in the center (more vulnerable area) is

recorded as a measure of increased anxiety. Elevated-plus maze and zero maze assessments use a similar paradigm, where a decrease in time spent in the open parts of the maze vs. the safer, covered areas implies an increase in anxiety. MIA induced with LPS and Poly(I:C) results in increased anxiety in the adult animal, although some MIA treatments caused no difference in anxiety levels (Table 1). Social interaction is measured by monitoring time spent exploring an object or another animal or preference between a familiar and unfamiliar animal. Decreased social interest is observed often in MIA animals (Table 1), however some instances of LPS treatment resulted in little to no effect (Xuan and Hampson, 2014; Batinić et al., 2016) or an increase in social preference (Harvey and Boksa, 2014).

Prepulse inhibition (PPI) is a neurological phenomenon described by the attenuation of the startle response to a strong (usually acoustic) stimulus by a preceding weaker stimulus. Deficits in PPI are linked to abnormalities in sensorimotor gating and have been observed in schizophrenia patients (Swerdlow et al., 2016). A vast number of MIA protocols have resulted in PPI deficits in model animals, while some conditions produced no significant effect on PPI or the basal startle response (Table 1).

Other cognitive deficits, including impairments in learning and memory, have been described in schizophrenia and ASD patients (Paulsen et al., 1995; Goh and Peterson, 2012). Several behavioral tests are used in rodents to assess similar aspects of cognitive function, using a variety of aversive, appetitive, or innate stimuli, including the novel object recognition (NOR) test, the Morris Water Maze (MWM), and the Odor Span Task (OST) (Young et al., 2009). Many LPS or Poly(I:C) MIA protocols result in significant learning and memory deficits in rodents (Table 1), and these effects can be reversed with antipsychotic medications such as risperidone (Piontkewitz et al., 2011) or clozapine (Zuckerman and Weiner, 2005), or antioxidants such as N-acetyl-cysteine (Lanté et al., 2007; Lanté et al., 2008). One study using LPS-induced MIA (200 μg/kg on gestational day [GD]15 and GD16) in rats detected no difference in spatial learning (Yin et al., 2015).

Anhedonia is another common symptom of schizophrenia. It can be readily assessed in rodents by the simple measure of sucrose preference, where animals are offered regular or sweet water and the intake ratio is an estimate of the level of disinterest. MIA induction in rodents, using either LPS or Poly(I:C), has been shown to decrease sucrose preference, suggesting that anhedonia is induced in these MIA models (Bitanihirwe et al., 2010; Lin and Wang, 2014; da Silveira et al., 2017).

One of the core symptoms of ASD is repetitive behaviors, which include motor stereotypies, compulsions and rituals, repetitive use of objects, and unusual or very narrow restricted interests (American Psychiatric Association, 1994). These behaviors can be observed in rodents through evaluation of repetitive self-grooming and compulsive marble-burying tasks, among others (Silverman et al., 2010). Many MIA studies attempting to model ASD specifically have investigated these types of behaviors; so far, all have reported an increase in these stereotypies, consistent with the pathology observed in autistic patients (Table 1). Ultrasonic vocalizations (USVs) in isolated mouse pups are thought to represent distress calls to elicit maternal intervention. They can be affected in a number of complex ways, which may indicate altered emotional or social behavior and communication (Moy and Nadler, 2008). The effects of MIA on USVs vary greatly (Table 1), with identical protocols (4 mg/kg Poly(I:C) in rat on GD15) yielding opposite effects on the frequency of the calls (Yee et al., 2012; Chou et al., 2015). These differences might be due in part to the different methodologies used to record the USVs (Hahn and Lavooy, 2005).

An enhanced locomotor activity (LMA) reaction to low doses of amphetamine is interpreted as an indication of a functional imbalance in dopaminergic transmission underlying a subset of schizophrenia symptoms (Schmidt et al., 2010). MK-801 and ketamine, antagonists of the N-methyl-D-aspartate (NMDA) receptor, are also used to mimic psychosis in animal models, a logical approach given the perturbations in NMDA receptor signaling reported in schizophrenia (Kristiansen et al., 2007). MIA most often induces an increase in the LMA response to these psychomimetics (Table 1), but some LPS and Poly(I:C) protocols instead revealed an attenuation of this behavior (Richtand et al., 2011), sometimes specific to male (Howland et al., 2012) or female (Batinić et al., 2016; Batinić et al., 2017) offspring. As with other behavioral assays, some MIA studies report no change in LMA response to amphetamine or MK-801 (Holloway et al., 2013; Meehan et al., 2017). This behavior is also dependent on weight gain or loss of the mother following Poly(I:C) treatment (Vorhees et al., 2012; Vorhees et al., 2015).

From the variability in observed behavioral outcome in rodent offspring from MIA protocols, it is becoming increasingly apparent that the type of immunogen that is used, the timing of application during gestation, and the approaches used for behavior analysis all can lead to differing conclusions about the effects of maternal immune challenge on the developing brains of offspring (Knuesel et al., 2014; Meyer, 2014). Few studies have compared the effects of different doses or timing of treatment within a single experiment. One of the earliest studies to evaluate the effects of Poly(I:C) in comparison with influenza virus infection showed that a dose of 20 mg/kg injected intraperitoneally (i.p.) on GD9.5 was sufficient to induce a deficit in PPI, whereas a lower dose (10 mg/kg) failed to do so (Shi et al., 2003). Thorough analysis of the difference between injecting a single dose of Poly(I:C) (5 mg/kg) at mid or late gestation (GD9 or GD17, respectively) revealed significant differences in maternal serum and fetal brain cytokine levels shortly after treatment, along with a more pronounced deficit in exploratory behavior in open field tests in GD9-treated offspring, as well as a greater deficit in discrimination-reversal learning tasks in GD17 MIA animals (Meyer, 2006). Dose-response analysis of cytokine mRNA levels in maternal blood and fetal CNS from Poly(I:C) treatment at two different stages of pregnancy (2, 4, and 8 mg/kg on GD9 and GD15) showed that the largest overall proinflammatory response was obtained at GD15 with 4 mg/kg (Missault et al., 2014). Comparison of LPS injection (100 μg/kg) at GD10–11 and GD18–19 revealed motor impairments in MIA induced at mid-gestation, while altered reward-seeking behavior was apparent only in late-gestation MIA offspring (Straley et al., 2017). A large comparative analysis examined three separate MIA agents (LPS, Poly(I:C), and turpentine) at varying doses (25, 50, and 100 μg/kg LPS; 0.75 and 1 mg/kg Poly(I:C) at three stages of pregnancy (GD10–11, GD15–16, and

TABLE 1. Behavior alterations in MIA model animals

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated animals versus control	Disease model	Reference
LPS	25 μg/Kg s.c. GD15 & 25 μg/Kg s.c. GD16 & 50 μg/Kg s.c. GD17	Mouse	F	increased anxiety (open field, elevated plus maze and light/dark boxes)	N/S	Hsueh et al., 2017
LPS	100 μg/kg i.p. GD9.5	Rat	M	increased repetitive self-grooming and stereotypies	ASD	Kirsten and Bernardi, 2017
LPS	2 /4 ng/kg i.v. 3rd trimester	Rhesus macaque	M & F	increased reticence toward examiner, decreased adaptation to prepulse sounds	N/S	Willette et al., 2011
LPS	100 μg/kg i.p. GD15	Mouse	M & F	shorter USVs, decreased social interest, increased stereotypic movements and marble burying	ASD	Fernández de Cossío et al., 2017
LPS	50 μg/kg i.p. GD12/16	Rat	M	MIA timing dependent changes in locomotor activity and amphetamine responsiveness/ reward behavior	N/S	Straley et al., 2017
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	deficits in learning and memory (MWM), no effect on social behavior, diminished response to amphetamine induced LMA (F)	SC	Batinić et al., 2016
LPS	25 μg/kg s.c. GD9	Mouse	M	increased anxiety (open field, elevated plus maze and light/dark boxes), increased depressive-like behavior (forced swim and tail suspension)	N/S	Depino, 2015
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	reduced PPI (M), increased baseline locomotor activity (M&F), impaired NOR (M>F)	SC	Wischhof et al., 2015b
LPS	75 μg/kg i.p. GD11.5-12	Mouse	M & F	decreased social preference (F)	ASD	Xuan and Hampson, 2014
LPS	500 μg/kg i.p. GD17	Mouse (NMRI & C57BL/6 mice)	M	strain dependent increase in anxiety (open field, elevated plus maze, elevated zero maze, light/ dark box) and depression-like (tail suspension and forced swim) behavior	ANX & D	Babri et al., 2014
LPS	120 μg/kg i.p. GD17	Mouse	M	enhanced amphetamine locomotor response	SC	Zager et al., 2012
LPS	100 μg/kg i.p. GD15-16	Rat	M	impaired learning, reduced USVs	ASD & SC	Baharnoori et al., 2012
LPS	25/50/100 μg/kg i.p. GD10-11/ 100 μg/kg i.p. GD15-16/ 50 mg/kg i.p. GD18-19	Rat	M	PPI deficit with LPS 50 μg/kg GD18-19, LPS 100 μg/kg GD15-16 only	SC	Fortier et al., 2007
LPS	200 μg/kg i.p. GD15-16	Rat	M	increased seizure susceptibility, increased anxiety (elevated plus maze), impaired learning and memory (MWM)	SC	Yin et al, 2013

TABLE 1. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated animals versus control	Disease model	Reference
LPS	0.79 mg/kg i.p. GD8,10&12	Rat	M & F	decreased social interaction (adult), worsening with age (3m, 10m, 20m)	N/S	Hao et al., 2010
LPS	100 μg/kg i.p. GD15	Rat	M/F	reduction in juvenile play behavior (M)	N/S	Taylor et al., 2012
LPS	1 mg/kg s.c. chronic from GD7 (every other day)	Rat	M/F	PPI deficit, increased exploratory activity, disturbances in social interactions (M&F)	SC	Basta-Kaim et al., 2015
LPS	50 μg/kg s.c. GD12	Rat	M/F	no difference on juvenile (P33) or adult (P70) social interaction, no effect on NOR	ASD	Foley et al., 2014
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	decreased social interest, increased marble burying	ASD	Onore et al., 2014
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	decreased social interest, increased marble burying, increased anxiety	ASD	Hsiao et al., 2012
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	increased marble burying (M&F), decreased social preference (M&F)	ASD	Xuan and Hampson, 2014
Poly(I:C)	2/4/8 mg/kg s.c. GD9/15	Rat	M	no effect on PPI, modest effect on MK-801 and amphetamine induced LMA, modest effect on sucrose preference	SC	Missault et al., 2014
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M & F	no effect on PPI, decrease in basal startle response, decrease in LMA	SC	Van den Eynde et al., 2014
Poly(I:C)	0/2.5/5/10/20 i.p. mg/kg GD9.5	Mouse	M & F	decreased PPI @ 20 mg/kg	ASD & SC	Shi et al., 2003
Poly(I:C)	20 mg/kg i.p. GD13-15	Mouse	M/F	decreased social preference (M&F P40) no change in social preference (M&F P120)	ASD	Aavani et al., 2015
Poly(I:C)	5 mg/kg i.v. GD9	Mouse	M	decreased PPI (adult), no difference in PPI (pubescent)	ASD & SC	Giovanoli et al., 2015
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M/F	impaired reversal learning (M), no effect on behavior (F)	SC	Zhang et al., 2012
Poly(I:C)	1 mg/kg i.p. GD10-11/15-16/ 0.75 mg/kg i.p. GD18-19	Rat	M	no behavioral deficit	SC	Fortier et al., 2007
Poly(I:C)	4 mg/kg i.p. GD15	Rat	M/F	many, mostly no difference, effect on PPI and LMA response to MK801 depends on maternal weight	SC	Vorhees et al., 2015
Poly(I:C)	8 mg/kg i.p. GD14	Rat	M/F	many, mostly no difference, effect on PPI and LMA response to MK801 and amphetamine depends on maternal weight	SC	Vorhees et al., 2012
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	impaired memory (NOR), deficit in PPI	ASD & SC	Luchicchi et al., 2016
Poly(I:C)	5 mg/kg i.v. GD9	Mouse	M & F	impaired PPI (P70), no change in PPI (P35), impaired locomotor response to apomorphine (P70), increased locomotor response to amphetamine (P35 & P70)	SC	Vuillermot et al., 2010

TABLE 1. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated animals versus control	Disease model	Reference
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	deficits in latent inhibition, open field and NOR behavior, trend toward deficit in PPI	ASD & SC	Shi et al., 2009
Poly(I:C)	4 mg/kg i.v. GD10/19	Rat	M/F	deficit in PPI (M), impaired working memory (GD19), no effect on locomotor response to amphetamine & MK801	SC	Meehan et al., 2017
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M/F	PPI deficit (pre-puberty & adult), decreased response to MK-801 induced LMA, impaired recognition memory (M)	SC	Howland et al., 2012
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	modest PPI deficit (juvenile)	SC	Wolff and Bilkey, 2008
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	PPI deficit (juvenile & adult)	SC	Wolff and Bilkey, 2010
Poly(I:C)	4 mg/kg i.v. GD9/17	Mouse	M/ M & F	PPI deficity (GD9 MIA), impaired working memory (GD17 MIA), increased locomotor response to amphetamine & MK801 (GD9 & GD17 MIA)	ASD & SC	Meyer et al. 2008b
Poly(I:C)	5 mg/kg i.v. GD9/17	Mouse	M	increased anxiety (open field), increased locomotor response to ketamine, decreased sucrose preference (GD17 MIA)	SC	da Silveira et al., 2017
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	impaired working memory (odor span test)	SC	Murray et al., 2017
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	impaired NOR	SC	Vernon et al., 2015
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	F	2nd generation impairment in behavior	N/S	Ronovsky et al., 2017
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M/F	strain specific increase in USVs (BTBR) & decrease in sociability (BTBR), increased grooming behavior (M), marble burying,	ASD	Schwartzer et al., 2013
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	no effect on fear conditioning, increased USVs	N/S	Yee et al., 2012
Poly(I:C)	60 mg/kg i.p. GD9.5	Mouse	M	PPI deficit	SC	Makinodan et al., 2008
Poly(I:C)	5 mg/kg i.v. GD17	Mouse	M/F	decreases social preference, sucrose preference, enhanced locomotor response to apomorphine, enhanced latent inhibition (M)	SC	Bitanihirwe et al., 2010
Poly(I:C)	5 mg/kg i.p. GD10.5,12.5&14.5	Mouse	M/F / M & F	decreased USVs, sociability, increased marble burying, self-grooming, deficit in urine induced scent marking (M)	ASD & SC	Malkova et al., 2012

TABLE 1. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated animals versus control	Disease model	Reference
Poly(I:C)	2.5/5/10 mg/kg i.v GD9	Mouse	M/F	increased anxiety (open field), latent inhibition deficit, impaired working memory (MWM), PPI & conditioned avoidance response deficit, increased LMA response to amphetamine (5/10 mg/kg)	SC	Meyer et al., 2005
Poly(I:C)	5 mg/kg i.v. GD9/17	Mouse	M & F	increased anxiety (GD9), deficit in reversal learning (M)	N/S	Meyer et al., 2006
Poly(I:C)	0.5 mg/kg i.p. GD15-18	Rat	M	no change in spatial learning (MWM), modest effect on reversal learning (MWM)	SC	Han et al., 2011
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	decreased novelty preference	SC	Wolff et al., 2011
Poly(I:C)	5 mg/kg i.v. GD12.5/17.5	Mouse	M &F	impaired working memory (T-maze, GD17.5)	SC	Connor et al., 2012
Poly(I:C)	5/20 mg/kg i.v. GD12.5	Mouse	N/S	impaired reversal learning (MWM), higher sensitivity to novel object	SC	Ito et al., 2010
Poly(I:C-LC)	0.25 mg/kg i.v. 1st or 2nd trimester	Rhesus macaque	M & F	increased stereotyped behaviors	ASD & SC	Rose et al., 2017
Poly(I:C-LC)	0.25 mg/kg i.v. 1st or 2nd trimester	Rhesus macaque	M & F	increased distress to maternal separation (2nd trimester MIA), repetitive behaviors (mostly 2nd trimester), inappropriate social interactions with unfamiliar animals	ASD & SC	Bauman et al., 2014
Poly(I:C-LC)	0.25 mg/kg i.v. 1st trimester	Rhesus macaque	M	gaze tracking response to neutral, fear, lip smack or aggressive facial expression	ASD & SC	Machado et al., 2015
Poly(I:C-LC)	0.25, 0.5 and i.v. 1 mg/kg 1st trimester	Rhesus macaque	M & F	increased whole body stereotypies	N/S	Weir et al., 2015
PRRSV	5×10^5 $TCID_{50}$ i.n. 3rd trimester	Pig	M & F	decreased sociability and social interest, no change in learning and memory	N/S	Antonson et al., 2017
turpentine	10 μL i.m. GD10/15/18	Rat	M	PPI deficit with turpentine on GD15 only	SC	Fortier et al., 2007
turpentine	100 μL i.m. GD15/18	Rat	M	deficit in PPI and decreased motivation, increased locomotor response to amphetamine (GD15 MIA), enhanced conditioned fear response (GD15&18 MIA)	SC	Aguilar-Valles and Luheshi, 2011
E. coli	1×10^5 CFUs i.u. GD17	Rat	M	deficit in sensorimotor development	ASD & SC	Wallace et al., 2010
H1N1	6×10^3 PFU i.n. GD9.5	Mouse	M & F	deficits in latent inhibition, open field and NOR behavior, trend toward deficit in PPI	ASD & SC	Shi et al., 2009
IL-1β/IL-6/IL-1β+IL-6	20 mg/kg total i.p. GD12-14	Mouse	N/S	decreased sociability (IL-6 & IL-6+IL-1β)	ASD	Pineda et al., 2013
IL-6	5 μg i.p. GD12.5	Mouse	N/S	decreased PPI	ASD & SC	Smith et al., 2007
IL-6	9 μg/kg i.p. GD8,10&12 or GD16,18&20	Rat	M/F	working memory deficit (MWM - F, GD16,18&20 IL-6)	N/S	Samuelsson et al., 2006

TABLE 1. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated animals versus control	Disease model	Reference
IFN-γ	5 μg i.p. GD12.5	Mouse	N/S	no effect on PPI	ASD & SC	Smith et al., 2007

Abbreviations: ANX: anxiety; ASD: autism spectrum disorder; D: depression; GD: gestational day; IFN: interferon; i.m.: intra-muscular; i.n.: intra-nasal; i.p.: intra-peritoneal; i.u.: intra-uterine; i.v.: intra-venous; LPS: lipopolysaccharide; LMA: locomotor activity; MWM: Morris water maze; NOR: novel object recognition; N/S: not specified; PFU: plaque forming units; Poly(I:C-LC): polyinosinic:polycytidylic acid stabilized with poly-L-lysine; Poly(I:C): polyinosinic:polycytidylic acid; PPA: propionic acid; PPI: pre-pulse inhibition; PRRSV: porcine reproductive and respiratory syndrome virus; s.c.: subcutaneous; SC: schizophrenia; TCID: tissue culture infectious dose; USV: ultrasonic vocalization

GD18–19) and found MIA-associated deficits in PPI in only a few conditions: LPS (100 μg/kg GD15–16 or 100 μg/kg GD 18–19) and turpentine (10 μL GD15) (Fortier et al., 2007). Additional systematic comparisons of different MIA protocols may contribute to resolve issues of reproducibility between laboratories.

The use of rodent models to characterize human psychiatric disorders is also somewhat controversial, since the brain regions underlying the complex behaviors of social cognition involved in the pathologies of ASD and schizophrenia are not as well developed in the rodent (Careaga et al., 2017). A way to bridge the gap between rodents and human pathologies is to induce MIA in nonhuman primate models, most commonly the rhesus macaque (Careaga et al., 2017). Stereotypies relevant to ASD (impaired social interactions and repetitive behaviors) have been observed in the offspring of macaques treated with Poly(I:C) or with human IgG purified from mothers of children with autism (Martin et al., 2008; Bauman et al., 2013; Bauman et al., 2014; Machado et al., 2015). Other studies have shown a long-term (up to 4 years) elevation in plasma cytokine and chemokine concentrations in MIA offspring (Rose et al., 2017), as well as a significant difference in dendritic morphology of layer III pyramidal neurons in the dlPFC (Weir et al., 2015), strengthening the relevance of the rhesus macaque model to neurodevelopmental disorders. There are however considerable time and monetary costs associated with the use of nonhuman primates. By contrast, rodents have a relatively short generation time and low housing costs, and therefore will continue to provide valuable insight into the mechanisms involved in MIA and neurodevelopmental disorders. Moreover, mouse models are genetically tractable, which permits the investigation of interactions between genetic and environmental factors. In an effort to mitigate the relative limitations of these model systems, there has been increasing interest in the use of the marmoset, a nonhuman primate model that breeds rapidly and is therefore suitable for transgenic studies (Drenzek et al., 2008; Sasaki et al., 2014). Nonetheless, rodent models constitute the vast majority of animal studies on neurodevelopmental disorders performed to date. Moreover, available data on the ability of antipsychotic drugs to alleviate some other MIA-induced behaviors and brain abnormalities (Shi et al., 2003; Moreno et al., 2011; Meyer, 2014; Reisinger et al., 2015) support the predictive validity of the current preclinical models.

Effect of MIA on microglial activation and morphology

Effects on microglial cell number and activation state (characterized by amoeboid morphology and elevated expression of immune markers such as CD11b and Iba-1) have also been observed in preclinical models of MIA (Table 2). These findings parallel those from human ASD and schizophrenia postmortem studies. However, some studies report behavioral and synaptic deficits characteristic of neuropsychiatric disorders without concurrent morphological activation of microglia or increase in their number (Pineda et al., 2013; Missault et al., 2014; Giovanoli et al., 2015; Smolders et al., 2015; Manitz et al., 2016; Hsueh et al., 2017). These discrepancies are most likely due to a combination of factors, including the different animal models and MIA protocols, the different times of assessment of microglial activation, and the experimental variance in the determination of "activation."

Nevertheless, many lines of experimental evidence support the hypothesis that activation of microglia is implicated in the

TABLE 2. Effect of MIA on cytokine levels and microglia density and activation

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
LPS	500 μg/kg i.p. GD17	Mouse	M	increased IL-6 (maternal blood , GD17)	-	ANX & D	Babri et al., 2014
LPS	1 mg/kg s.c. chronic from GD7 (every 2 days)	Rat	M	increased IL-1β, IL-2, IL-6,TNF-α in cultured, no change in IL-10 (ConA treated splenocytes)	-	SC	Basta-Kaim et al., 2012
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	increased TNF-α, IL-6 in maternal plasma	-	SC	Batinić et al., 2016
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	increased TNF-α, IL-6 in maternal blood, placenta & amniotic fluid	-	SC	Batinić et al., 2017
LPS	500 μg/kg i.p. GD18	Rat	N/S	decreased IL-1β, IL-6, IL-10, TNF-α in offspring plasma 4h post MIA	-	N/S	Beloosesky et al., 2010
LPS	0.5 mg/kg s.c. GD16	Mouse	N/S	increase in number of TNF-α expressing cells (IHC on sections, 2d post MIA)		N/S	Chua et al., 2012
LPS	100 μg/kg i.p. GD15-16 or 50 μg/kg i.p. GD 18-19	Rat	M	increased TNF-a, IL-6, IL-1ra and corticosterone in maternal plasma soon after MIA	-	SC	Cui et al., 2009
LPS	100 μg/kg i.p. GD15-16	Rat	N/S	increase in number of IL-1β expressing cells (IHC on sections)	no change in Iba-1 positive cell morphology, increase in number of iNOS expressing cells	ASD (& SC)	Cunningham et al., 2013
LPS	500 μg/kg i.p. GD18-19	Rat	M & F	increased levels of S100B (M cortex, P30, F cortex, P60, M hippocampus P60)	-	N/S	de Souza et al., 2015
LPS	1 mg/kg i.p. GD19	Rat	N/S	increased CCL2, IL-6, TNF-α (protein and mRNA in placenta 4h post MIA)	-	N/S	Dowling et al., 2012
LPS	100 μg/kg i.p. GD15	Mouse	M & F	-	decreased CX3CR1 mRNA (males)	ASD	Fernández de Cossío et al., 2017
LPS	50 μg/kg i.p. GD 18-19	Rat	M	increased maternal plasma IL-6 in parallel animals (3h post MIA)	-	SC	Fortier et al., 2004
LPS	200 μg/kg s.c. GD16&18&20	Rat	M & F	no increase in IL-1β, TNF-α in 2nd LPS immune challenge (P19) MIA offspring serum	-	N/S	Hodyl et al., 2007
LPS	25 μg/kg s.c. GD15 & 25 μg/kg s.c. GD16 & 50 μg/kg s.c. GD17	Mouse	F	-	no change in morphology, number and immunoreactive densities	N/S	Hsueh et al., 2017
LPS	100 μg/kg i.p. GD9.5	Rat	M	increase in IL-1β, no change in TNF-α in 2nd LPS immune challenge (P60-67) MIA offspring serum	-	ASD	Kirsten et al., 2013
LPS	2 or 4 ng/kg i.v. 3rd trimester	Rhesus macaque	M & F	increased IL-6 in maternal serum, increased IL-6 production in PHA stimulated blood monocytes	-	N/S	Willette et al., 2011

TABLE 2. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
LPS	120 μg/kg i.p. GD17	Mouse	M	no change in IL-2, IL-4, IL-6, IFN-γ, TFN-α, IL-17, IL-10 in non-adherent LPS treated splenocytes; decrease in IL-10, no change in IL-6, TNF-α in adherent splenocytes, increased IL-12 in adherent LPS treated splenocytes,	-	N/S	Zager et al., 2013
LPS	120 μg/kg i.p. GD17	Mouse	M/F	increased expression of IL-6, IL-1β? decreased IL-10, no change in TNF-a in LPS stimulated neuron x glia cultures; increased IL-6, IL-1β, TNF-α, IL-17 mRNA in cerebellum (F EAE)	-	EAE	Zager et al., 2015
LPS	500 μg/kg i.p. GD18	Rat	N/S	increased IL-1β, IL-6 mRNA pre and post-2nd LPS immune challenge (P21) MIA offspring cerebellum, hippocampus, PFC, brainstem	-	N/S	Zhou, 2015
Poly(I:C)	5 mg/kg i.v. GD9	Mouse	M	increased IL-1β, IL-4, IL-5, no change in IL-2, IL-6, IL-10, IL-12, TNF-α	-	N/S	Abazyan et al., 2010
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	increased IL-1β, TNF-α, CXCL1, no change in IL-6, IFN-γ, IL-1, IL-10, IL4, IL-2 in maternal serum 3h post-MIA	-	SC	Ballendine et al., 2015
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M	increased IL-6, IL-17a, TNF-α, IFN-β, IL-1β in maternal serum, increased IL-17ra mRNA in placenta and fetal brain	-	ASD	Choi et al., 2016
Poly(I:C)	5 mg/kg i.v. GD12.5/17.5	Mouse	M &F	increased IL-6, increased TNF-α (GD12.5), no change IFN-γ, IL-1β in maternal serum, increased IL-6 in fetal brain 3h post-MIA	-	SC	Connor et al., 2012
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	increased IL-6, TNF-α, corticosterone in maternal serum (2h post MIA)	-	N/S	Dalton et al., 2012
Poly(I:C)	10 mg/kg i.p. GD14,16&18	Rat	N/S	no change in IL-1β, TNF-α, increase in MCP-1 in maternal blood 5h post-MIA	-	SC	Forrest et al., 2012
Poly(I:C)	5 mg/kg i.v. GD9	Mouse	M	no change in IL-4, IL-6, TNF-α, IL-1β in plasma and hippocampus (adult and pubescent) except increased IL-1β level in hippocampus of MIA adult mice	no change in number of Iba-1 positive cells, amoeboid morphology or CD68 expression in hippocampus of pubescent and adult MIA mice	ASD & SC	Giovanoli et al., 2015

TABLE 2. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
Poly(I:C)	1 mg/kg i.v. GD9	Mouse	M & F	-	increased amoeboid shape, no change in number of Iba-1 & IL-1β positive cells in Poly(I:C)	SC	Giovanoli et al., 2016b
Poly(I:C)	0.5 mg/kg i.p. GD15-18	Rat	M	increased TNF-α in adolescent serum	-	SC	Han et al., 2011
Poly(I:C)	21 mg/kg i.p. GD12.5	Mouse	M & F	increased IL-6, IL-17 no change in TNF-α in PMA/ionomycin stimulated splenocytes	-	ASD	Hsiao et al., 2012
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	N/S	increased IL-6, IL-17, no change in TNF-α in stimulated, cultured CD4 + splenocytes from adult MIA offspring	-	ASD	Hsiao et al., 2013
Poly(I:C)	20 mg/kg i.p. GD9	Mouse	N/S	-	increased number of microglia in striatum, hippocampus, no change in microglia number in cortex, fewer processes	SC	Juckel et al., 2011
Poly(I:C)	20 mg/kg i.p. GD9	Mouse	M/F	-	deceased CD11b (M&F P100) and CD45 (M P100) expression	SC	Manitz et al., 2016
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	increased IL-1β, TNF-α mRNA in hippocampus, no change in cerebellum	decreased Iba-1 immunoreactivity with no change in microglial density in cerebellum and nucleus accumbens	SC	Mattei et al., 2014
Poly(I:C)	2.5/5/10 mg/kg i.v GD9	Mouse	M/F	poly(I:C) dose dependent increase in IL-10 3h post-MIA and 6h post-MIA (5 &10 mg/kg significant only), no change in fetal brain IL-1β and IL-10 12h post MIA	-	SC	Meyer et al., 2005
Poly(I:C)	5 mg/kg i.v. GD9/17	Mouse	M & F	increased IL-1β, IL-6, IL-10, TNF-α 3h post-MIA, increased IL-6, IL-10 6h post-MIA in maternal serum (GD 9 + 17); increased IL-6 (GD9), IL-1β? IL-10 (GD17), decreased IL-1β, IL-10 (GD9) 3h post-MIA, increased IL-1β, IL-6 (GD9), increased IL-6 (GD17) 6h post-MIA in fetal brain	-	N/S	Meyer et al., 2006

TABLE 2. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
Poly(I:C)	2 mg/kg i.v. GD9	Mouse	M & F	increased IL-10, IL-6, TNF-α, no change in IL-1β in maternal serum 1.5h post MIA, increased IL-6, no change in IL-10, IL-1β, TNF-α in maternal serum 5h post MIA; increased IL-1b, TNF-a, IL-6, no change in IL-10 in fetal brain; no change in IL-1β, IL-10 in adult brain	-	SC	Meyer et al., 2008a
Poly(I:C)	2/4/8 mg/kg i.v. GD9/15	Rat	M	increased IL-1β, 4 mg/kg GD15; increased TNF-a, 8 mg/kg GD9 in maternal blood; no other significant change in IL-1b, TNF-a, no change in IL-10, IL-6 in maternal blood and fetal CNS	-	SC	Missault et al., 2014
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	increased IL-12p40 in 2nd LPS immune challenge, increased CCL3 with or without 2nd LPS challenge, increased CCL4 without 2nd LPS challenge; no change in IL-1β, IL-6, IL-10, TNF-α, and CCL4 in BMDM (P70)	-	ASD	Onore et al., 2014
Poly(I:C)	5 mg/kg i.v. GD15	Rat	M & F	-	no change in Iba-1 positive cell density, nuclei density in MIA	SC	Paylor et al., 2016
Poly(I:C)	2.5 mg/kg i.p. GD12-16	Mouse	N/S	increased IL-6, IL-1β in maternal plasma	no change in microglia activation	ASD	Pineda et al., 2013
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	N/S	increased IL-6, IL-1α, IL-4, IL-9, GM-CSF, M-CSF, eotaxin, MIP-1β, LIX, rantes mRNA in E16.5 CD11b expressing microglia	-	ASD	Pratt et al., 2013
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M/F	increased IL-17, IL-10, TNF-α in splenocytes from MIA offspring (higher in BTBR)	-	ASD	Schwartzer et al., 2013
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	N/S	increased IL-1β, IL-6 in maternal serum	-	ASD & SC	Smith et al., 2007
Poly(I:C)	20 mg/kg i.p. GD11.5/ 11.5-15.5	Mouse	N/S	-	no difference in microglial cell density in cortex E11.5, E12.5 & E17.5 and hippocampus E17.5, no increase in iNOS, IL-1β & MAC-2 expression (IHC)	ASD & SC	Smolders et al., 2015

TABLE 2. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
Poly(I:C)	1/4/20 mg/kg i.p. GD12.5	Rat	N/S	dose dependent increase of IL-6 in maternal serum 3h post-MIA	-	ASD & SC	Tsukada et al., 2015
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M & F	-	increased CD11b in thalamus, corpus callosum and hippocampus, no change in CD11b in striatum, no difference in CD68	SC	Van den Eynde et al., 2014
Poly(I:C)	2 mg/kg i.v. GD17	Mouse	M	increased IL-6, TNF-α, IL-10 in maternal serum 2h post-MIA	-	SC & ADHD	Vuillermot et al., 2012
Poly(I:C)	20 mg/kg i.p. GD9	Mouse	N/S	-	increased Iba-1 immunoreactive cell number, more amoeboid morphology	SC	Zhu et al., 2014
Poly(I:C-LC)	0.25 mg/kg i.v. 1st or 2nd trimester	Rhesus macaque	M & F	IL-1β, IL-6, IL-12p40, increased TNF-α, IL-2, IFN-γ, IL-13, G-CSF in 1 year old MIA offspring plasma; increased IL-6, IFN-γ, IL-10, CXCL8, CCL2 in 4 year old MIA offspring plasma; no other significant change (IL-1β, IL-12p40, IL-4, IL-5, IL-17, GM-CSF, CCL3, CCL4)	-	ASD & SC	Rose et al., 2017
Poly(I:C-LC)	0.25, 0.5 & 1 mg/kg i.v. 1st trimester	Rhesus macaque	M & F	increased IL-6 in maternal serum 3h post MIA (GD43 & GD50)	-	N/S	Weir et al., 2015
IL-17a/IL-6	1.2 ng i.p. E14.5	Mouse	M	increased IL-17a in maternal serum (IL-6 MIA)	-	ASD	Choi et al., 2016
IL-1β/IL-6/IL-1β+IL-6	20 mg/kg total i.p. GD12-14	Mouse	N/S	increased IL-6, IL-1β in maternal plasma	no change in microglia activation	ASD	Pineda et al., 2013
IL-6	9 μg/kg i.p. GD8,10&12/GD16,18&20	Rat	M/F	increased IL-6 mRNA in hippocampus (4wk, 24wk offspring), complex fluctuations of IL-6 in serum of offspring (4wk, 8wk, 24wk)	-	N/S	Samuelsson et al., 2006
PRRSV	5×10^5 $TCID_{50}$ i.n. 3rd trimester	Pig	M & F	increased TNF-α 7, 14, 21 days post-MIA, IL-6 below detectable threshold (in separate animals)	no effect on MHCII or stimulation with LPS	N/S	Antonson et al., 2017
turpentine	100 μL i.m. GD15/18	Rat	M	increased IL-6, IL-1ra in maternal blood, increased IL-6, no change in IL-1ra, TNF-α, decreased IL-1β mRNA in placenta 10-11h post treatment	-	SC	Aguilar-Valles and Luheshi, 2011

TABLE 2. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Cytokine assessment	Microglial assessment	Disease model	Reference
turpentine	100 μL i.m. GD15	Rat	M	increased IL-6, IL-1ra in maternal serum 10h post treatment	-	SC	Aguilar-Valles et al., 2010

Abbreviations: EAE: experimental autoimmune encephalomyelitis; GD: gestational day; IFN: interferon; IL: interleukin; i.m.: intra-muscular; i.n.: intra-nasal; i.p.: intra-peritoneal; i.v.: intra-venous; LPS: lipopolysaccharide; N/S: not specified; PFC: prefrontal cortex; PFU: plaque forming units; PHA: phytohemagglutinin; PMA: phorbol 12-myristate 13-acetate; Poly(I:C-LC): polyinosinic:polycytidylic acid stabilized with poly-L-lysine; Poly(I:C): polyinosinic:polycytidylic acid; PRRSV: porcine reproductive and respiratory syndrome virus; s.c.: subcutaneous; SC: schizophrenia; TCID: tissue culture infectious dose; TNF: tumor necrosis factor

etiology of neurodevelopmental disorders. Microglia are a major source of inflammatory cytokines in the CNS (Deverman and Patterson, 2009; Perry and Holmes, 2014). A wide range of cytokines are increased in the fetal brain hours after MIA in pregnant rodents, including IL-1ß, IL-6, and TNF-α, following treatment with varying doses of LPS or Poly(I:C) in mouse or rat (Table 2) (Patterson, 2009; Boksa, 2010). In a study using Poly(I:C) treatment in mice at GD16, a very large panel of different cytokines and other signaling factors were shown to have highly dynamic expression levels when comparing maternal prenatal serum, prenatal, and postnatal brain homogenates (Arrode-Brusés and Brusés, 2012). Measurement of the levels of 23 separate cytokines in frontal cortex, cingulate cortex, hippocampus, and serum of MIA offspring at birth (P0) and postnatal day (P)7, P14, P30, and P60 showed up- and down-regulation patterns relative to control mice that varied with time and by brain region (Garay et al., 2013). Moreover, MIA does not elicit behavioral deficits in an IL-6 knockout background and can be prevented either by a blockade of IL-6 or IL-1 pathways (Smith et al., 2007) or through the overexpression of the anti-inflammatory cytokine IL-10 (Meyer et al., 2008a). Maternal IL-17a signaling was found to be both necessary and sufficient to produce neurobehavioral deficits in a mouse model of MIA (Choi et al., 2016). These data further support a causative role for microglia-derived cytokines in the psychiatric behaviors associated with MIA.

Effect of MIA on neurogenesis and neuronal development

MIA offspring exhibit many of the typical neuropathologies associated with neurodevelopmental disorders, such as reduced cortical thickness and hippocampal volume and increased ventricular size, as well as cerebellar aberrations (Estes and McAllister, 2016). Patches of disorganized cortex were observed in embryonic day 14.5 embryos from poly(I:C)- or IL-17a-injected mothers (Choi et al., 2016), in accordance with similar malformations observed in postmortem samples of ASD patients (Casanova et al., 2013; Stoner et al., 2014). The number of proliferative neural stem or progenitor cells and cerebral cortex volume are reduced in late-gestation (E18.5) embryos from Poly(I:C)-injected litters (4 or 20 mg/kg on GD12.5) (Tsukada et al., 2015). These defects may be due in part to microglial dysfunction, since microglia were shown to directly phagocytose neural precursor cells in the cerebral cortex of mouse and macaque (Cunningham et al., 2013). Activation of microglia through MIA (LPS, 100 μg/kg i.p. on GD15–16) or inhibition of microglial function with minocycline (in vitro organotypic slices) or by ablation with liposomal clodronate in vivo can respectively decrease or increase the size of the progenitor and precursor pools in cerebral cortex (Cunningham et al., 2013). Indeed, cortical precursors isolated from PU.$1^{-/-}$ mice, which are devoid of microglia, show reduced proliferation and survival in culture, while addition of microglia into depleted cultures rescues precursor proliferation (Antony et al., 2011).

The effect of MIA on cell proliferation was evaluated in a rat model and showed that LPS injection (100 μg/kg i.p. on GD15–16 or 50 μg/kg i.p. on GD18–19) caused a reduction of proliferative cells labeled with BrdU in the dentate gyrus (DG) during fetal development and in the early postnatal stage (P14) (Cui et al., 2009). Other MIA protocols have also resulted in decreased numbers of BrdU-positive, proliferating cells giving rise primarily to neurons in the hippocampus (Piontkewitz et al., 2012; Lin and

Wang, 2014; Mattei et al., 2014). However, treatment with LPS earlier in gestation (25 μg/kg on GD9) did not affect neurogenesis in the mouse DG (Depino, 2015). A reduction in the number of reelin-positive cells was observed in the same animals, however, suggesting a potential defect in cell migration and morphogenesis of the DG (Depino, 2015). In vitro assays using DG neural progenitor cells treated with Poly(I:C) showed that direct TLR3 activation in these cells could increase proliferation; however, a decrease in the number of cells immunoreactive for the proliferation marker Ki67 was observed in the DG of adult MIA animals (Melnik et al., 2012). Further in vitro evidence suggests that IL-1ß signaling may contribute to the decrease in proliferation of neural progenitor cells isolated from ventral mesencephalon (Crampton et al., 2012). An increase in the number of Caspase-3-positive, apoptotic cells was also observed in hippocampus of P24 mouse MIA offspring (Meyer, 2006), indicating a possible imbalance of both proliferative and survival signals caused by inflammation during development.

The effect of MIA in mid-gestation (Poly(I:C) on GD9.5) on adult neurogenesis was also assessed in the olfactory system of the mouse; a reduced number of neural stem cells and neuroblasts was observed in the subventricular zone (SVZ), resulting in fewer adult newborn neurons and a deficit in olfactory discrimination (Liu et al., 2013), a phenomenon relevant to the pathology of schizophrenia (Atanasova et al., 2008). A recent study showed that maternally administered IL-6 (on GD13.5) causes increased proliferation of neural precursors in the SVZ and disrupts the calretinin subpopulation of adult-born olfactory neurons (Gallagher et al., 2013). These differences may reflect an effect of the timing of MIA or of the more complex inflammatory reaction triggered by Poly(I:C) vs. a single cytokine injection.

Developmental defects in other types of neurons have also been observed in MIA animal models. A reduction in Purkinje cell number was detected after induction of MIA with influenza virus or Poly(I:C) at GD9.5 in mice (Shi et al., 2009) and with *Escherichia coli* injections in rats (GD17) (Wallace et al., 2010), similar to the cerebellar Purkinje cell defects observed in postmortem samples of patients with ASD (Amaral et al., 2008). In contrast, MIA induction in mid-gestation (GD13–15) with Poly(I:C) results in an increase in Purkinje cell numbers in juvenile and adult mice (Aavani et al., 2015). This may represent a narrow window in which inflammatory cytokines enhance proliferation or inhibit apoptosis of Purkinje cell precursors. Defects in the development and function of interneurons have been implicated in a number of psychiatric disorders (Marín, 2012). There have been several observations of a decrease in parvalbumin (PV)-positive cell number in medial prefrontal cortex (mPFC) and a decrease or no significant difference in the number of these GABAergic neurons in the hippocampus of adult MIA offspring (Meyer et al., 2008b; Piontkewitz et al., 2012; Dickerson et al., 2014; Wischhof et al., 2015b; Zhang and van Praag, 2015). This is in contrast to a recent observation that reported an increase in the number of PV immunoreactive cells in the dlPFC of adolescent male rats from LPS-treated dams (50 μg/kg i.p. on GD15/16) (Boksa et al., 2017). Other neuronal deficiencies, including in dopaminergic and serotonergic neurons, have been described in MIA models (Meyer et al., 2009b; Boksa, 2010; Vuillermot et al., 2012; Pratt et al., 2013; Smith et al., 2014; Squarzoni et al., 2014; Depino, 2015; Reisinger et al., 2015). Imbalances in dopamine, serotonin, and other neurotransmitters have also been implicated in the neuropathology of schizophrenia (Yang and Tsai, 2017) and ASD (Fernández et al., 2017).

Effect of MIA on synaptic properties and synapse number

Given the proposed role of microglia in synaptic pruning during normal development (Paolicelli et al., 2011; Zhan et al., 2014; Hong et al., 2016) and the abnormal activation of microglial cells in MIA offspring, it is tempting to infer defects in pruning as a cause of neurodevelopmental defects. LPS injection on P9 in mice was sufficient to up-regulate mRNA expression of several genes involved in the synaptic pruning process (Bolouri et al., 2014; Mottahedin et al., 2017), lending support to this hypothesis. Recently, spine density and molecular pruning signals were investigated in an LPS mouse model of MIA (100 μg/kg i.p. on GD15) (Fernández de Cossío et al., 2017). Increased spine density was observed on granule cells of the hippocampus from juvenile male offspring of LPS-treated mice, while no equivalent change was observed in the female offspring (Fernández de Cossío et al., 2017). This phenotype was accompanied by reduced CX3CR1 mRNA expression in hippocampus of male pups prenatally treated with LPS, with no concurrent effect of LPS treatment on C3 or C1q mRNA levels. CX3CR1 is important for synaptic pruning during normal brain development (Paolicelli et al., 2011), therefore decreased expression of this chemokine receptor may contribute to the abnormality in spine density in MIA animals. A Poly(I:C) protocol for MIA, also in mouse (20 mg/kg i.p. on GD12.5), likewise revealed a decrease in spine density on layer 5 pyramidal neurons of the somatosensory cortex from juvenile (P17) and adult (P90) animals, as well as reduced spine dynamics, observed in vivo by multiphoton imaging through a thinned skull window (Coiro et al., 2015). LPS-driven MIA in a rat model (100 μg/kg i.p. on GD15–16) showed variability in neuronal morphology with age and in different brain regions, with reductions in spine density in layer 5 PFC pyramidal neurons in adult (P60) animals, but no change in layer 3 PFC or in hippocampal neurons (P10, P35, or P60) (Baharnoori et al., 2009). Dendritic length was significantly reduced or trended toward a decrease in all conditions examined. In the rat, spine density was increased in hippocampal neurons of juvenile (P21) MIA offspring, but decreased in adults (P90) (Lin and Wang, 2014). Further analysis is required to characterize the potential significance of this transient increase in spine number in the hippocampus.

Adult reduction in the expression of presynaptic (synaptophysin) and postsynaptic (PSD-95) proteins was also reported in models of MIA (Hao et al., 2010; Meyer, 2013; Giovanoli et al., 2016b), both neuropathological hallmarks of disorders such as ASD and schizophrenia (Penzes et al., 2011; Varghese et al., 2017). Vesicle-associated membrane protein (VAMP)-1 levels are higher in brain tissue from Poly(I:C)-treated juvenile (P21) animals, but synaptotagmin and synaptophysin levels are unchanged (Forrest et al., 2012). Increased levels of VAMP-1 are also detected in the brain of schizophrenia patients (Halim et al., 2003). Western blot analysis of NMDA receptor–associated proteins in the brain of juvenile animals from Poly(I:C)-treated mothers revealed a decrease in the critical GluN1 subunit but no change in GluN2A, GluN2B, or PSD-95 (Forrest et al., 2012). This implies a hypofunction of NMDA receptors in these animals, with potential associated disruptions in synaptic plasticity during brain development.

TABLE 3. Treatment and second hit models of MIA

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
Poly(I:C)	5 mg/kg i.p. GD12-17	Mouse		PPI deficit, impaired novel object recognition	-	7,8-DHF reversed effect of MIA on behavior	SC	Han et al., 2016
Poly(I:C)	5 mg/kg i.p. GD12-17	Mouse	M	impaired novel object recognition	-	7,8-DHF reversed effect of MIA on behavior	ASD & SC	Han et al., 2017
Poly(I:C)	2.5 mg/kg i.p. GD12-16	Mouse	N/S	decreased sociability	-	anti-IL-6/ anti-IL-1β antibody GD12-17, anti-IL-6 antibody reversed effect of MIA on behavior	ASD	Pineda et al., 2013
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	N/S	increased marble burying, anxiety, decreased social preference	-	bone marrow transplant, reversed effect of MIA on marble burying and anxiety, but not social preference	ASD	Hsiao et al., 2013
Poly(I:C)	4 mg/kg i.v. GD15/17	Rat	N/S	impaired latent inhibition, increased reversal learning, increased locomotor response to MK-801	-	clozapine reversed effect of MIA on behavior	SC	Zuckerman and Weiner, 2005
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M & F	impaired latent inhibition in juvenile and adult	-	clozapine, haloperidol reversed effect of MIA on behavior	SC	Zuckerman et al., 2003
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	modest PPI deficit (P35 & P56), deficit in associative & crossmodal memory (object in place test), impaired visual cue learning and set-shifting (lever press)	-	G31P (a synthetic, mutated form of human IL-8 that binds CXCR1/R2 with high affinity) did not reverse effect of MIA on behavior	SC	Ballendine et al., 2015
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M & F	increased marble burying	-	Ibudilast (anti-inflammatory drug) reversed effect of MIA on behavior	ASD	Coiro et al., 2015

TABLE 3. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	M	increased ultrasonic vocalizations, decreased social interest, increased marble burying	-	IL-17a antibody (GD12) & IL-17Ra KO prevent elevation of cytokine level and reversed effects of MIA on behavior	ASD	Choi et al., 2016
Poly(I:C)	5 mg/kg i.p. GD10.5, 12.5&14.5	Mouse	M	enhanced DOI induced stereotypic behavior	-	ketanserine reduced DOI induced stereotypic behavior	SC	Malkova et al., 2014
Poly(I:C)	5 mg/kg i.p. GD10.5, 12.5&14.5	Mouse	M/F	decreased sociability (M) and social interest (M&F), increased grooming behavior (M)	-	ketogenic diet reversed effect of MIA on behavior	ASD	Ruskin et al., 2017
Poly(I:C)	5 mg/kg i.p. GD9.5	Mouse	M	increased effect of DOI hallucinogen, no effect on locomotor response to MK801, deficit in working memory	-	LY379268 (mGlu2/3 receptor agonist) decreased locomotor response to MK801, no effect on working memory deficit induced by MIA	SC	Holloway et al., 2013
Poly(I:C)	2 mg/kg i.v. GD9	Mouse	M & F	increased PPI	-	macIL-10*tg* (IL-10 overexpression) reversed effects of MIA on PPI	SC	Meyer et al., 2008a
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	PPI deficit	-	minocycline reversed effect of MIA on behavior and cytokine expression levels, no rescue of Iba-1 immunoreactivity	SC	Mattei et al., 2014
Poly(I:C)	20 mg/kg GD9	Mouse	N/S	increased LMA, decreased social interaction, decreased PPI	-	minocycline, reversed behavioral and microglial effects of Poly(I:C)	SC	Zhu et al., 2014
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	impaired latent inhibition, increased reversal learning, increased locomotor response to amphetamine	-	risperidone reversed effect of MIA on behavior	SC	Piontkewitz et al., 2011

TABLE 3. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
Poly(I:C)	8 mg/kg i.p. GD14	Rat	M & F	decreased response to low dose amphetamine locomotor response	-	risperidone, paliperidone reversed effect of MIA on behavior	SC	Richtand et al., 2011
Poly(I:C)	3 mg/kg i.p. GD12.5 & 1.5 mg/kg i.p. GD17.5	Mouse	M	reduced sociability, decreased novelty preference (T maze), no change in anxiety levels	-	suramin reversed effect of MIA on behavior	ASD & SC	Naviaux et al., 2014
Poly(I:C)	2 mg/kg i.p. GD12.5/ 3 mg/kg i.p. GD12.5 & 1.5 mg/kg i.p. GD17.5	Mouse	M/F	reduced sociability, decreased sensorimotor coordination (rotarod)	-	suramin reversed effect of MIA on behavior and restored Purkinje cell numbers	ASD	Naviaux et al., 2013
LPS	1 mg/kg s.c. chronic from GD7 (every 2 days)	Rat	M	deficit in PPI at P90	-	clozapine, chlorpromazine, reduced effect of MIA on PPI	SC	Basta-Kaim et al., 2012
LPS	100 μg/kg i.p. GD15	Rat	M	decreased spatial discrimination	-	environmental enrichment and colony nesting reversed or trend toward reversal of MIA effect on behavior	ASD & SC	Kentner et al., 2016
LPS	66 μg/kg i.p. GD10.5	Rat	M/F	increased anxiety (open field, elevated plus maze), increased response to stress, increased novelty-induced hypophagia	-	fluoxetine reversed effect on MIA induced anxiety behavior	N/S	Lin et al., 2012
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	PPI deficit, exacerbated by DOI	-	LY379268 (mGlu2/3 receptor agonist) attenuated effect of DOI on PPI	SC	Wischhof et al., 2015a
LPS	100 μg/kg i.p. GD15-16	Rat	M & F	decreased baseline LMA & response to amphetamine (F)	-	MP-III-022 (selective positive allosteric modulator of a5GABAARs) @ 4th post-natal week reversed effect of MIA on behavior	SC	Batinić et al., 2017

TABLE 3. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
LPS	500 μg/kg i.p. GD19	Rat	M/F	impaired spatial learning (M, MWM)	-	NAC reversed effect of MIA on behavior	SC	Lanté et al, 2007
LPS	500 μg/kg i.p. GD19	Rat	M	spatial learning and memory deficit (water maze)	-	NAC reversed effect of MIA on behavior, a-tocopherol	SC	Lanté et al, 2008
LPS	800 μg/kg i.p. GD15&17	Mouse	M&F	increased anxiety (P35 & P85), partially rescued by PAL treatment (M)	-	paliperidone (PAL, GD15)	SC	Kumar and Mohanty 2015
LPS	100 μg/kg i.p. GD9.5	Rat	F	no effect of LPS treatment on stress response	-	Zinc (GD9.5) decreased overall stress response	N/S	Galvão et al., 2015
LPS	100 μg/kg i.p. GD9.5	Rat	M & F	decreased USVs	-	Zinc (GD9.5) rescued USVs	ASD	Kirsten et al., 2015
IL-17a/IL-6	1.2 ng i.p. E14.5	Mouse	M	increased ultrasonic vocalizations (IL-6 & IL-17a), decreased social interest, increased marble burying (IL-17a)	-	IL-17a antibody (GD12) & IL-17Ra KO reversed effects of MIA on behavior	ASD	Choi et al., 2016
H1N1	6×10^3 PFU i.n. GD9.5	Mouse	M & F	increased anxiety, decreased PPI	-	clozapine, chlorpromazine increased PPI	ASD & SC	Shi et al., 2003
turpentine	100 μL i.m. GD15	Rat	M	increased locomotor response to amphetamine	-	anti-IL-6 or anti-leptin antibodies reversed effect of MIA on behavior	SC	Aguilar-Valles et al., 2012
turpentine	100 μL i.m. GD15	Rat	M	increased locomotor response to amphetamine	-	Iron (GD15-18) reversed MIA effect on behavior but increased locomotor response to amphetamine without MIA	SC	Aguilar-Valles et al., 2010
Poly(I:C)	20 mg/kg i.p. GD12.5	Mouse	N/S	PPI deficit, increased anxiety (open field test), decreased social preference	IL-6 KO background negated effect of MIA on PPI, anxiety and social preference	anti-IL-6, IFN-γ or IL-1β antibodies (GD12.5) reversed effect of MIA on PPI, anti-IL6 antibodies reversed effect of MIA on anxiety and social preference	ASD & SC	Smith et al., 2007

TABLE 3. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
Poly(I:C)	1 mg/kg i.v. GD9	Mouse	M & F	subtle to no change in PPI, anxiety and increased LMA response to MK-801 & amphetamine	peripubertal stress caused increased anxiety (elevated plus maze), decreased PPI, increased LMA response to MK-801 & amphetamine in MIA animals	minocycline, reversed behavioral and microglial effects of Poly(I:C) + stress	SC	Giovanoli et al., 2016a
Poly(I:C)	5 mg/kg i.v. GD17	Mouse	M/F	no difference in anxiety (elevated plus maze and open field), enhanced fear conditioning (F adolescent & adult, M adult)	cross-fostering, no interaction with Poly(I:C) induced MIA on behavior	-	N/S	Schwendener et al., 2009
Poly(I:C)	2.5/5 mg/kg i.v. GD9	Mouse	M	no effect on anxiety (elevated plus maze), no effect on PPI (high dose MIA, 8wk), impaired PPI (high dose MIA, 16wk), impaired novel object recognition & sociability	DISC1 Q31L, causes impaired PPI, novel object recognition, sociability with low dose MIA	-	SC	Lipina et al., 2013
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M	impaired PPI (P68), increased anxiety (elevated plus maze, P61)	juvenile stress, increased anxiety (without MIA), no increase in PPI deficit over MIA	-	N/S	Yee et al., 2011
Poly(I:C)	2 mg/kg i.v. GD17	Mouse	M	increased basal LMA, PPI deficit, impairments of attention (LI & 2-CVDT) only in Nurr1+/-, impaired working memory (dry maze)	Nurr1+/- genotype restores cytokine levels to non-MIA levels, further increases LMA	-	SC & ADHD	Vuillermot et al., 2012
Poly(I:C)	4 mg/kg i.v. GD15	Rat	M/ M & F	decreased ultrasonic vocalizations, modest increase in locomotor response to amphetamine, no change in conditioned avoidance response (M), PPI	olanzapine sensitization, decreased conditioned avoidance response, independent of MIA (M)	-	SC	Chou et al., 2015

TABLE 3. *Continued*

MIA induction agent	Dose and timing	Animal model	Gender	Behavior assessment of MIA treated vs control	Second hit or genetic interaction	Treatment attempt to rescue MIA phenotype	Disease model	Reference
LPS	50 μg/kg GD i.p. 18-19	Rat	M	increased locomotor response to amphetamine, increased startle acoustic response (adult)	anoxia, no interaction with LPS induced MIA on behavior	-	SC	Fortier et al., 2004
LPS	66 μg/kg i.p. GD10.5	Rat	M/F	decreased performance in forced swim test (M&F), no change in sucrose preference	decreased sucrose preference in chronic mild stress (CMS) MIA animals	-	D	Lin and Wang, 2014
LPS	200 μg/kg i.p. GD15-16	Rat	M	increased seizure susceptibility, no difference in anxiety (elevated plus maze), impaired spatial learning (Y maze)	no further increase in anxiety but greater impairment of spatial learning with kainic acid (P21)	-	N/S	Yin et al., 2015
LPS	50 μg/kg i.p. GD15/16	Rat	M	no change in PPI, LMA response to amphetamine & MK-801, increased social interaction	PPI deficit in MIA animals with maternal iron deficiency (ID)	-	ASD & SC	Harvey and Boksa, 2014

Abbreviations: ADHD: attention deficit hyperactivity disorder; CVDT: choice visual discrimination test; D: depression; DHF: 7-8-dihydroxyflavone; depression; EAE: experimental autoimmune encephalomyelitis; DOI: 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; GD: gestational day; ID: iron deficiency; IFN: interferon; IL: interleukin; i.m.: intramuscular; i.n.: intra-nasal; i.p.: intra-peritoneal; i.v.: intra-venous; LI: latent inhibition; LMA: locomotor activity; LPS: lipopolysaccharide; NAC: N-acetylcysteine; N/S: not specified; PFU: plaque forming units; Poly(I:C): polyinosinic:polycytidylic acid; PPI: pre-pulse inhibition; s.c.: subcutaneous; SC: schizophrenia; USV: ultrasonic vocalization

In a mouse model of MIA (Poly(I:C) on GD9), functional deficits in synaptic release probability by PV interneurons in the mPFC were observed, concurrent with an increase in anxiety-like behavior, without any alteration in the total number of PV-expressing cells (Canetta et al., 2016). Synapses are altered in neurons from animals treated with Poly(I:C) during development, as a decrease in miniature excitatory postsynaptic current (mEPSC) frequency was observed in pyramidal neurons of the somatosensory cortex (Coiro et al., 2015) and in CA1 hippocampal neurons, where an accompanying increase in mEPSC amplitude was also recorded (Ito et al., 2010). Cultured hippocampal neurons isolated from neonatal rats from Poly(I:C)-treated mothers display several abnormal neurophysiological properties, including lower intrinsic excitability and stronger spike frequency adaptation, lower frequency of spontaneous firing, and larger amplitude of miniature inhibitory postsynaptic currents (mIPSCs) (Patrich et al., 2016). Animals from LPS-treated mothers (100 μg/kg i.p. on GD15–16) display an enhancement in excitatory synaptic transmission of CA1 pyramidal neurons, as evidenced by larger excitatory postsynaptic field potentials, accompanied by a decrease in paired-pulse facilitation (Lowe et al., 2008). An increase in the intrinsic excitability of dentate granule cells (lower threshold for action potentials) was observed in both adult-born and more mature neurons from animals in a Poly(I:C) model of MIA (5 mg/kg i.p. on GD15) (Zhang and van Praag, 2015). A reduction in GABAergic inhibitory input was also observed in mature neurons only, reflected by a decrease in frequency of mIPSCs, with no change in frequency or amplitude of mEPSCs (Zhang and van Praag, 2015), suggestive of an alteration of the excitatory-inhibitory balance in the DG. Hippocampal place cell activity is also affected in adult MIA offspring (Wolff and Bilkey, 2015). These changes potentially alter the encoding of spatial context by these cells and may contribute to the memory dysfunction associated with MIA. These data suggest that neuronal defects caused by MIA on cortical and hippocampal development extend beyond neurogenesis and regulation of apoptosis and affect synaptic properties of at least a subset of neurons in patients with ASD, schizophrenia, and other neurodevelopmental disorders.

Effect of suppression of inflammatory programs and "second hit" factors on MIA

Suppression of microglial activation by minocycline, a tetracycline antibiotic, has wide-ranging effects on neuronal development (Table 3) (Inta et al., 2017). Injection of minocycline to suppress microglial activation in a rodent model of MIA (Poly(I:C) on GD15) attenuated the inflammatory response in hippocampus-derived microglia and consequently rescued the PPI deficit (Mattei et al., 2014). A separate study likewise observed a normalization of PPI and social interaction behaviors, as well as of the number of Iba-1 + cells in the hippocampus with treatment of minocycline in adolescent mice from mothers treated with Poly(I:C) on GD9 (Zhu et al., 2014). Other compounds that modulate microglial function, such as anti-inflammatory cyclo-oxygenase-2 (COX-2) inhibitors, have been found to restore normal LMA response to MK-801 in adolescence in a mouse model of MIA (Zavitsanou et al., 2014) in agreement with early beneficial effects of COX-2 inhibitors in clinical trials (Müller and Schwarz, 2010).

It is widely agreed that MIA-induced activation of microglia alone is generally not sufficient to cause neurodevelopmental defects resulting in psychiatric symptoms. A "second hit" in the form of a genetic predisposition or another environmental challenge such as stress or pollutants is often needed to trigger symptom onset (Table 3) (Davis et al., 2016). It has been demonstrated that following prenatal or neonatal exposure to Poly(I:C), a second insult to the immune system such as stress or hypoxia resulted in a significant increase of hyperactive CD68 + microglia and a decreased reparative CD11b + microglia (Giovanoli et al., 2013; Stridh et al., 2013), suggesting that MIA and subsequent insults to the immune system during postnatal development may be important to alter microglial distribution and function. Indeed, it has been suggested that microglia are "primed" during MIA and thereby are more susceptible to produce an exaggerated response to a subsequent inflammatory insult (Perry and Holmes, 2014). A recent study showed an increase in microglial activation markers (Iba-1-, CD68-, and IL-1ß-expressing cell number) accompanied by an increased LMA response to MK-801 and amphetamine, as well as a deficit in PPI only in low-dose Poly(I:C)-treated MIA animals subjected to stress around puberty (P30 and P40) (Giovanoli et al., 2016a). Minocycline administered in the drinking water during the stress period was able to reverse these behavioral perturbations and prevent microglial activation (Giovanoli et al., 2016a).

Interactions of genetic predispositions with MIA are likely to be involved in many cases (Knuesel et al., 2014; Estes and McAllister, 2016). For instance, a reduction in spine density on hippocampal neurons and behavioral abnormalities in PPI, anxiety (elevated-plus maze), and depression (forced swim test) were observed only in MIA offspring from a mutant disrupted-in-schizophrenia (DISC1) genetic background (Abazyan et al., 2010; Lipina et al., 2013). Disc1 is one of two genes involved in a chromosomal translocation originally identified in a large family with a history of schizophrenia (Millar, 2000) and is now associated with ASD, bipolar disorder, and depression as well (Chubb et al., 2008). Nuclear receptor related protein 1 (Nurr1), a transcription factor essential for normal dopaminergic development and implicated in dopamine-associated brain disorders, has also been shown to interact with MIA (Poly(I:C) on GD17) in mice heterozygotic for the *Nurr1* gene to exacerbate PPI deficits and spontaneous locomotor hyperactivity (Vuillermot et al., 2012).

The evidence from the currently available MIA preclinical studies points to a role for microglia and cytokines in the etiology of neurodevelopmental disorders. However, much like the complications encountered in clinical studies, which arise from the wide spectrum of behavioral and physiological manifestations, achieving a consensus from MIA animal models will require further investigation. The use of different animals and immunogens and the variability in dosage and timing of administration make comparisons between studies difficult. Moreover, studies of MIA as an interacting factor with environmental or genetic elements add yet another layer of complexity to the field. Nevertheless, findings from these studies have already provided avenues for the development of new immunomodulating therapies for the treatment of ASD and schizophrenia patients.

Perspectives and Conclusion

Taken together, the evidence reviewed here strongly suggests a causal relationship between MIA and neurodevelopmental

disorders such as ASD and schizophrenia. Microglia may be one of the critical mediators of MIA-induced disruption of brain development and maturation. These CNS-resident cells respond to peripheral and local immune challenges, elaborate neurotrophic, inflammatory, and anti-inflammatory factors, and engage in physical interactions with neurons. They regulate neuronal birth, structure, function, and death in brain circuits. A better understanding of the relationship between microglial activity and brain development offers great promise for novel intervention strategies to prevent, mitigate, or treat neurodevelopmental disorders.

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