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Brain changes in a maternal Immune activation model of neurodevelopmental brain disorders

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Abstract

The developing brain is sensitive to a variety of insults. Epidemiological studies have identified prenatal exposure to infection as a risk factor for a range of neurological disorders, including autism spectrum disorder and schizophrenia. Animal models corroborate this association and have been used to probe the contribution of gene-environment interactions to the etiology of neurodevelopmental disorders. Here we review the behavior and brain phenotypes that have been characterized in MIA offspring, including the studies that have looked at the interaction between maternal immune activation and genetic risk factors for autism spectrum disorder or schizophrenia. These phenotypes include behaviors relevant to autism, schizophrenia, and other neurological disorders, alterations in brain anatomy, and structural and functional neuronal impairments. The link between maternal infection and these phenotypic changes is not fully understood, but there is increasing evidence that maternal immune activation induces prolonged immune alterations in the offspring's brain which could underlie epigenetic alterations which in turn may mediate the behavior and brain changes. These concepts will be discussed followed by a summary of the pharmacological interventions that have been tested in the maternal immune activation model.

1. Introduction

Brain development is a complex organization of processes under genetic, environmental, and immune regulation, and consequently is vulnerable to a variety of insults (Garay and McAllister, 2010; Stiles and Jernigan, 2010). Insults during specific windows of development can alter the normal trajectory of brain development, leading to disorders that have developmental origins, including autism spectrum disorder (ASD) and schizophrenia (Bale, 2015; Ploeger *et al.*, 2010; Rapoport *et al.*, 2012). One such insult is maternal infection, which is particularly detrimental to neurodevelopment when it occurs early in gestation (Estes and McAllister, 2016; Knuesel *et al.*, 2014; Meyer, 2014; Meyer *et al.*, 2007; Reisinger *et al.*, 2015). Numerous epidemiological reports suggest an association

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between ASD or schizophrenia and prenatal exposure to viral or bacterial pathogens (Atladottir *et al.*, 2010; Brown and Derkits, 2010; Brown, 2012; Hagberg *et al.*, 2012; Jiang *et al.*, 2016; Patterson, 2009; Zerbo *et al.*, 2013; Zerbo *et al.*, 2015). Maternal infection has also been associated with increased risk for bipolar disorder, major depression, epilepsy, and cerebral palsy in the offspring (Brown and Derkits, 2010; Knuesel *et al.*, 2014; Reisinger *et al.*, 2015). Maternal infection disrupts the delicate immune balance between the maternal and fetal environments, resulting in an altered immune profile in the developing brain. Under normal conditions, immune molecules have regulatory roles throughout neurodevelopment, beginning with neural induction (Deverman and Patterson, 2009). They are also involved in the proper formation of neural circuits through their regulation of synaptic refinement, transmission, and plasticity (Garay and McAllister, 2010).

Animal models have helped to further establish the relationship between maternal infection and neurodevelopmental disorders. It is well established that it is the maternal immune response, not a specific pathogen, which is a risk factor for neurodevelopmental disorders (Hagberg *et al.*, 2012). Likewise, different agents have been used to induce maternal immune response during gestation in animal models of maternal immune activation (MIA) (Meyer, 2014). The most commonly used agents are polyinosinic-polycytidylic acid (Poly (I:C)) and lipopolysaccharide (LPS), which mimic viral and bacterial maternal infections by activating the Toll-like receptor 3 and Toll-like receptor 4 pathways, respectively (Meyer, 2014; Smith *et al.*, 2010). A side-by-side comparison demonstrated that certain MIA-induced phenotypes are observed with either agent, while other phenotypes appear to be specific to the immunogen used (Arsenault *et al.*, 2014). Strains of influenza have also been used, with the main advantage being that they elicit a full spectrum of immune responses (Meyer, 2014; Smith *et al.*, 2010). Poly (I:C) and LPS, on the other hand, induce a limited, well-defined immune response, and allow the time and intensity of MIA to be more precisely controlled (Meyer and Feldon, 2012). The ability to restrict the immune response to a specific time point in gestation is important because different phenotypes emerge in the offspring depending on which developmental processes were disrupted by MIA (Fortier *et al.*, 2007; Meyer *et al.*, 2006b; Meyer *et al.*, 2008c).

It has been suggested that the etiology of neurodevelopmental disorders is a combination of environmental factors and genetic predisposition (Clarke *et al.*, 2009). MIA may be one of two hits that together result in ASD or schizophrenia. The other hits may be genetic, for example, mutations in ASD or schizophrenia risk genes (Abazyan *et al.*, 2010; Ehninger *et al.*, 2012; Lipina *et al.*, 2013), or environmental, such as gestational diabetes mellitus (Money *et al.*, 2017), maternal iron deficiency (Boksa *et al.*, 2016; Li *et al.*, 2018), or stress around the time of puberty (Giovanoli *et al.*, 2016a; Giovanoli *et al.*, 2013). The synergism of gene-environment or environment-environment risk factors has been evaluated in multiple studies using either a full dose of Poly (I:C) or a physiologically relevant, subthreshold dose of Poly (I:C), such that MIA alone does not produce disease phenotypes in the offspring, but offspring exposed to a second hit (genetic or environmental) display disease-relevant behavioral abnormalities (Abazyan *et al.*, 2010; Giovanoli *et al.*, 2013; Lipina *et al.*, 2013). These studies offer valuable insight into the complex etiology of neurodevelopmental disorders.

With MIA being used as a model for multiple disorders, MIA paradigms are quite heterogeneous. As such, there is variation in experimental parameters including the time of immune insult, the age of the offspring, and the brain regions studied, each having an effect on the phenotypes observed (e.g. Garay *et al.*, 2013; Meyer *et al.*, 2006b; Patrich *et al.*, 2016b; Shin Yim *et al.*, 2017). Additional factors such as the caging system (Mueller *et al.*, 2018) or the mouse strain (Babri *et al.*, 2014; Morais *et al.*, 2018; Schwartzer *et al.*, 2013) also influence experimental outcomes.

In this review, we present the major alterations in MIA offspring, including, behavioral impairments, alterations in brain structure, impairments in synaptic function and transmission, and immune alterations in the developing brain. We propose that such diverse effects could be mediated by epigenetic alterations that occur following exposure to MIA (Figure 1). Increasing evidence suggests an association between prenatal exposure to environmental insults, epigenetic modifications, and neurodevelopmental disorders (reviewed by Kundakovic and Jaric, 2017). During normal neurodevelopment, gene expression is regulated by a pattern of epigenetic changes including histone modifications, DNA methylation, and microRNA expression. Acetylation of histones induces a looser chromatin structure and facilitates transcription (Eberharter and Becker, 2002). In contrast, DNA methylation within the gene promoter represses transcription while DNA methylation in the gene body is associated with transcription (Jones, 2012). Gene expression can also be regulated by microRNAs, short noncoding nucleic acids that bind to mRNA and either block translation or facilitate degradation of the target mRNA. All of these epigenetic mechanisms have been implicated in regulating proper neuronal migration, neurite outgrowth, dendritic development (Mehler, 2008; Sun and Shi, 2015; Trakhtenberg and Goldberg, 2012; Zibetti *et al.*, 2010), and synapse formation and function (Nelson *et al.*, 2008; Sando *et al.*, 2012). Epigenetic modifications are also associated with many of the behavior changes that have been observed in MIA offspring including social deficits, impairments in learning and memory, and anxiety- and depression-like behaviors (Allan *et al.*, 2008; Guan *et al.*, 2015; Sun *et al.*, 2013). The timing of epigenetic changes may be related to certain developmental windows of susceptibility, time periods during which offspring are particularly vulnerable to environmental insults (Bale, 2015). Epigenetic studies are emerging in attempts to provide a link between prenatal exposure to maternal immune activation and the phenotypic changes in MIA offspring. These studies address how epigenetic alterations in MIA offspring affect gene expression and behavior and the plausible relationship between the two.

2. Behavioral changes

Behavior tests are key in determining the face validity of animal models of CNS diseases, especially disorders for which behavioral symptoms are an important component of the diagnosis. MIA offspring exhibit several behavioral alterations that are relevant for ASD and schizophrenia. The core symptoms of ASD fit into three main categories: abnormal social interactions, communication deficits, and repetitive behavior while schizophrenia symptoms are often classified as positive (behaviors not seen in healthy people, such as hallucinations or racing thoughts), negative (disrupted normal emotions or behaviors), or cognitive (e.g. poor executive functioning or trouble focusing; https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml). In addition to the core symptoms of ASD, there are several

associated symptoms that are present in a subset of ASD patients including seizures, anxiety, intellectual disability, and hyperreactivity or hyporeactivity to sensory stimuli (Silverman *et al.*, 2010). Some of these symptoms overlap with symptoms of schizophrenia.

Maternal separation-induced production of ultrasonic vocalizations (USVs), which is often interpreted in the context of communicative ability (Scattoni *et al.*, 2009), but can also be an indication of stress response, altered bonding with the mother (Malkova *et al.*, 2012), or anxiety (Kessler *et al.*, 2011), is the earliest ASD-like behavior that can be tested in rodents. Abnormalities in USV production by MIA offspring emerged within the first two postnatal weeks, a period that is typically characterized by a peak in USV production between P8 and P10 and a decline towards no USVs produced on P14 (Scattoni *et al.*, 2009). Both rats and mice exposed to MIA, induced either by Poly (I:C) or LPS, exhibited abnormalities in USV production, but the exact differences observed in independent studies varied. Several studies reported a decrease in the number or duration of USVs (Baharnoori *et al.*, 2012; Fernandez de Cossio *et al.*, 2017; Malkova *et al.*, 2012; Pendyala *et al.*, 2017) while some found an increase in the number of USVs produced (Choi *et al.*, 2016; Pendyala *et al.*, 2017; Shin Yim *et al.*, 2017). A number of factors may contribute to these differences including species (rat or mouse), immunogen used, timing of immune insult, and pup age during testing. Altered USV production was not observed when a single Poly (I:C) injection was administered later than E12.5 (Shin Yim *et al.*, 2017), but LPS administration later in gestation resulted in defects in mice and rats (Baharnoori *et al.*, 2012; Fernandez de Cossio *et al.*, 2017). Repeated testing of pups revealed age-dependent effects of MIA on USV production (Baharnoori *et al.*, 2012; Malkova *et al.*, 2012; Pendyala *et al.*, 2017). The type of USV syllables was also altered in MIA offspring, although different syllable types were altered when Poly (I:C) was administered once compared to a milder dose three times on alternate days (Malkova *et al.*, 2012; Shin Yim *et al.*, 2017). MIA offspring that were tested for both USVs and reflex development had normal reflexes at this time, suggesting that the USV deficit is not due to general developmental delays (Fernandez de Cossio *et al.*, 2017; Malkova *et al.*, 2012). However, others reported modest reflex impairments in LPS-induced MIA offspring and larger impairments in Poly (I:C)-induced MIA offspring when the immunogen was administered daily for three days near the end of gestation (Arsenault *et al.*, 2014). USVs produced by adult animals in social contexts have also been used as indication of communication capabilities. Adult male MIA offspring produced a smaller number and altered type of USVs in the presence of either an unfamiliar male or female (Malkova *et al.*, 2012). In addition, male MIA offspring exhibited a deficit in chemical communication, as seen in their tendency to leave fewer urinary scent marks in response to female urine in the absence of disrupted olfactory sensitivity (Ehninger *et al.*, 2012; Malkova *et al.*, 2012).

A behavior tested in many MIA studies that is relevant to both ASD and schizophrenia is social interaction. Social interaction deficits are a key phenotype of ASD and are one of the negative symptoms of schizophrenia. The following tests take advantage of the natural sociability of mice to assess abnormal social interactions in the MIA model. One indication of a deficit in social interaction, specifically social affiliation, is an obvious preference for a novel object or empty cage over a novel conspecific in a three-chamber apparatus. MIA offspring often spent more or equal time in the chamber with the object compared to the chamber with the conspecific (Bitanihirwe *et al.*, 2010a; Choi *et al.*, 2016; Fernandez de

Cossio *et al.*, 2017; Labouesse *et al.*, 2015; Malkova *et al.*, 2012; Mattei *et al.*, 2017; Shin Yim *et al.*, 2017; Smith *et al.*, 2007). This social deficit was not observed in adolescent mice (O'Leary *et al.*, 2014). MIA did not exacerbate the social interaction deficits observed in mice heterozygous for *Nrg1*, a candidate gene for schizophrenia (O'Leary *et al.*, 2014). Subthreshold MIA combined with expression of mutant *Tsc2* or *Disc1*, genes implicated in ASD and schizophrenia respectively, led to reduced preference for the conspecific (Abazyan *et al.*, 2010; Ehninger *et al.*, 2012; Lipina *et al.*, 2013).

There is also a social recognition deficit in MIA offspring. Mice tend to spend more time near a novel mouse than a familiar mouse, but given the choice between a novel mouse and a familiar mouse, MIA offspring will spend more time with the familiar mouse or equal amounts of time with both mice (O'Leary *et al.*, 2014). Abnormal social interactions are also seen when MIA offspring are allowed to interact directly with a novel mouse (Hava *et al.*, 2006; Pendyala *et al.*, 2017; Zhu *et al.*, 2014), but not when a cage prevented direct interaction with the novel mouse (Li *et al.*, 2018). MIA in rhesus monkeys did not affect social interaction as measured by time spent with the novel conspecific, but they did show abnormal social behaviors such as increased cooing and interactions with the novel monkey (Bauman *et al.*, 2014). In addition, they showed abnormal patterns of eye fixation, preferring to fixate on the mouth, rather than the eyes, in a picture of a grimacing monkey (Machado *et al.*, 2015).

ASD is also characterized by repetitive or stereotypic behaviors or an insistence on sameness. Marble burying is commonly used to test repetitive behaviors. Increased digging results in an increased number of buried marbles. MIA offspring consistently buried more marbles (Choi *et al.*, 2016; Coiro *et al.*, 2015; Fernandez de Cossio *et al.*, 2017; Malkova *et al.*, 2012; Pendyala *et al.*, 2017; Shin Yim *et al.*, 2017; Wu *et al.*, 2015). Other repetitive/stereotypic behaviors in MIA offspring include excessive grooming or head bobbing (Fernandez de Cossio *et al.*, 2017; Kirsten and Bernardi, 2017; Malkova *et al.*, 2012). Non-human primates also exhibited stereotypic behaviors such as repetitive pacing, spinning, and bouncing (Bauman *et al.*, 2014).

When given the choice between a familiar object and a novel object or displaced and nondisplaced objects, MIA offspring showed a preference for the familiar or nondisplaced object (Coyle *et al.*, 2009; Li *et al.*, 2014; Lipina *et al.*, 2013; Ozawa *et al.*, 2006; Wischhof *et al.*, 2015b), in contrast to the typical response in which a rodent will spend more time exploring the novel object. Novel object recognition was impaired by an interaction of subthreshold MIA and a point mutation in *Disc1* (Lipina *et al.*, 2013). This test is often interpreted in the context of working memory or cognitive impairment (Leger *et al.*, 2013), but preference for the familiar object could also indicate restricted interests, which are observed in patients with ASD (Silverman *et al.*, 2010). Both interpretations are corroborated by other tests for repetitive behavior or cognitive ability in MIA offspring as described above and in the following paragraphs.

In maze tests (T maze, Y maze, Morris water maze, and dry maze) for working and/or spatial memory MIA offspring were found to have impaired memory (Giovanoli *et al.*, 2015; Labouesse *et al.*, 2015; MacDowell *et al.*, 2017; O'Leary *et al.*, 2014; Vuillermot *et al.*,

2012; Zhang and van Praag, 2015). However, in the Morris water maze, memory deficits only emerged following a longer interval between trials (Meyer *et al.*, 2005; Meyer *et al.*, 2008c) or in adult males (Batinic *et al.*, 2016) while others found no cognitive deficits in MIA offspring (Abazyan *et al.*, 2010). The timing of the prenatal immune insult and the caging system were both found to affect performance in the Y-maze (Mueller *et al.*, 2018). MIA offspring were further shown to have impaired working memory capacity in the odor span test (Murray *et al.*, 2017).

Latent inhibition, another measure of cognitive ability, was abolished in adult MIA offspring (Garay *et al.*, 2013; Giovanoli *et al.*, 2013; Lipina *et al.*, 2013; Meyer *et al.*, 2005; Meyer *et al.*, 2008a; Meyer *et al.*, 2006c; Smith *et al.*, 2007), except when MIA occurred late in prenatal development (Meyer *et al.*, 2006a). This emerged in adult, but not young mice, regardless of the conditioning paradigm used (Meyer *et al.*, 2006c; Zuckerman *et al.*, 2003) which is appropriate because latent inhibition pertains to the cognitive symptoms of schizophrenia which tend to manifest in adulthood in humans. Rearing conditions also appear to impact the presence or absence of latent inhibition. Mice that were not prenatally exposed to immune activation, but were cross-fostered to surrogate mothers who had an immune activation during pregnancy also lacked latent inhibition which would suggest that both prenatal and postnatal events can affect the emergence of latent inhibition (Meyer *et al.*, 2006c). Additional indicators of cognitive ability including temporal perception and set-shifting were also impaired in MIA offspring (Canetta *et al.*, 2016; Deane *et al.*, 2017; Zhang *et al.*, 2012). Optogenetic inhibition of parvalbumin (PV) interneurons in non-immune challenged mice recapitulated the set-shifting impairments (Canetta *et al.*, 2016), while transplantation of stem cell-derived PV interneurons into the mPFC improved cognitive flexibility (Donegan *et al.*, 2018), suggesting that loss or dysfunction of PV interneurons contributes to cognitive impairments in MIA offspring.

Another schizophrenia relevant behavior observed in MIA offspring is increased locomotor activity induced by amphetamine, an indirect dopamine receptor agonist, or dizocilpine (MK-801), an NMDA receptor antagonist (Luan *et al.*, 2018; Meyer *et al.*, 2005; Meyer *et al.*, 2008c; Ozawa *et al.*, 2006; Zuckerman *et al.*, 2003). The sensitivity to MK-801 is age dependent (Meyer *et al.*, 2008b). Subthreshold MIA combined with peripubertal stress also elicited this response (Giovanoli *et al.*, 2016a; Giovanoli *et al.*, 2013).

A widely used test in the MIA model is a test for prepulse inhibition (PPI). A decrease in the percent PPI is indicative of deficits in sensorimotor gating, a characteristic of patients with schizophrenia. The majority of studies demonstrated PPI deficits in MIA offspring (Garay *et al.*, 2013; Giovanoli *et al.*, 2016b; Hadar *et al.*, 2017; Lipina *et al.*, 2013; Mattei *et al.*, 2017; Meehan *et al.*, 2017; Meyer *et al.*, 2005; Meyer *et al.*, 2008c; Ozawa *et al.*, 2006; Smith *et al.*, 2007; Wischhof *et al.*, 2015a; Wischhof *et al.*, 2015b; Wu *et al.*, 2015; Zhang and van Praag, 2015; Zhu *et al.*, 2014). However, the emergence of PPI deficits depends on the caging system used and the timing of the prenatal insult (Mueller *et al.*, 2018). In addition, young MIA offspring (Lipina *et al.*, 2013; Ozawa *et al.*, 2006; Wischhof *et al.*, 2015b), MIA offspring that overexpress IL-10 in macrophages (Meyer *et al.*, 2008a) and MIA offspring exposed to inflammation near the end of gestation (Meyer *et al.*, 2006b) did not exhibit PPI deficits. Variability also arose between males and females (Meehan *et al.*, 2017; Wischhof *et*

al., 2015b), with different prepulse intensities (Missault *et al.*, 2014), and with different interstimulus intervals (Wischhof *et al.*, 2015a). A low dose of Poly(I:C) did not cause deficits in PPI (Abazyan *et al.*, 2010), but a deficit emerged when a mild immune activation was combined with peripubertal stress (Giovanoli *et al.*, 2016a; Giovanoli *et al.*, 2013) or mutations in candidate schizophrenia genes including *Disc1* and *Nurr1* (Lipina *et al.*, 2013; Vuillermot *et al.*, 2011; Vuillermot *et al.*, 2012).

MIA offspring exhibit some depressive-like behaviors in a strain-specific manner. MIA offspring from the NMRI strain, an outbred strain of mice, were immobile for a greater period of time in the forced swim and tail suspension tests but inbred C57BL6 mice exposed to MIA did not exhibit behavioral alterations in these tests (Babri *et al.*, 2014). However, MIA offspring expressing mutant human DISC1 on a C57BL6 background spent more time immobile in the forced swim and tail suspension tests (Abazyan *et al.*, 2010). Reduced sucrose preference, an indicator of anhedonia and depressive-like behavior, was consistently observed in MIA offspring (Bitanihirwe *et al.*, 2010a; Missault *et al.*, 2014; Reisinger *et al.*, 2016). In addition to the behaviors mentioned above, other behaviors that are not specifically related to ASD or schizophrenia have been observed in MIA offspring (Table 1). These other behaviors suggest that prenatal infection causes diverse neurological dysfunctions and may be risk factor for other neurological disorders (reviewed by Knuesel *et al.*, 2014).

3. Structural and functional brain changes

3.1 Anatomical abnormalities

Given the abundance and diversity of atypical behaviors observed in MIA offspring, an important question is: what are the underlying brain abnormalities and how do they relate to brain function?

MRI studies have identified enlarged ventricles and reductions in the volume of several brain regions in adult rodent and nonhuman primate MIA offspring (da Silveira *et al.*, 2017; Fatemi *et al.*, 2008; Patrich *et al.*, 2016b; Piontkewitz *et al.*, 2011; Short *et al.*, 2010) although a longitudinal study found that a decrease in ventricle volume emerged in older mice (Crum *et al.*, 2017). Another study found no change in total brain volume, but the relative volume of several regions was increased or decreased unilaterally (Richetto *et al.*, 2017a). Subthreshold MIA combined with low or high expression of mutant human DISC1 also reduced brain volume and increased ventricular volume (Abazyan *et al.*, 2010). Full MIA also decreased the volume of the central nucleus of the amygdala in P14 MIA offspring (O'Loughlin *et al.*, 2017). The extent of these changes in volume is correlated with the maternal immune response to influenza (Short *et al.*, 2010).

Histological experiments suggest that underlying the overall decrease in brain volume is a change in neuronal density. In a porcine model of MIA, the total neuron density was decreased in the dentate gyrus and subiculum of fetal MIA offspring (Antonson *et al.*, 2018). In contrast, MIA induced late in gestation caused a slight increase in the density of neurons in the corpus callosum of MIA offspring, accompanied by an increase in the density of somatostatin interneurons (Duchatel *et al.*, 2016). A common finding is a decrease in the density of GABAergic neurons, specifically Purkinje cells in the cerebellum (Naviaux *et al.*,

2013; Shi *et al.*, 2009) and PV-positive and reelin-positive neurons in the hippocampus and cortex (Donegan *et al.*, 2018; Fatemi *et al.*, 1999; Matsuura *et al.*, 2018; Meyer *et al.*, 2008c; Wischhof *et al.*, 2015b; Zhang and van Praag, 2015). The Purkinje cell deficit was restricted to lobule VII and some Purkinje cells in this lobule were also heterotopic (Naviaux *et al.*, 2013; Shi *et al.*, 2009). However, the timing of MIA is critical. When mice were exposed to MIA after the height of mitosis in Purkinje precursor cells (Miale and Sidman, 1961), an increase in cerebellum size and number of Purkinje cells was observed (Aavani *et al.*, 2015). Similar to Purkinje cells, the loss of PV-positive cells appears to depend on the time of MIA. Interneurons begin to migrate from the ganglionic eminence at E12.5 in rodents (Corbin and Butt, 2011) and only MIA after this time consistently resulted in loss of PV-positive neurons in adult offspring (Canetta *et al.*, 2016; Matsuura *et al.*, 2018; Meyer *et al.*, 2008c; Wischhof *et al.*, 2015b). However, in young MIA offspring an increase in the number of PV interneurons was observed in the dorsolateral PFC, mPFC, and ventral subiculum at P14, but the number of PV neurons normalized by P28 (Boksa *et al.*, 2016). Interestingly, this increase in PV neuron density was abolished when the mother had iron deficiency. One study reported a significant main effect of prenatal treatment on the density of PV neurons across multiple time points in the frontal association cortex and amygdala (Paylor *et al.*, 2016). In the same study, the proportion of PV neurons ensheathed by perineuronal nets was evaluated. While there was no significant effect of MIA on the percentage of PV neurons surrounded by perineuronal nets in the regions with fewer PV neurons, a smaller proportion of PV neurons were surrounded by perineuronal nets in the medial prelimbic cortex (Paylor *et al.*, 2016). In support of impaired neuronal migration in MIA offspring, gene expression of several proteins involved in tangential migration of interneurons was reduced in the fetal brain four hours after LPS administration (Oskvig *et al.*, 2012). GABAergic neurons may be particularly susceptible to MIA given that DNA methylation patterns are altered in MIA offspring (Basil *et al.*, 2014; Basil *et al.*, 2018; Labouesse *et al.*, 2015; Richetto *et al.*, 2017b) and the DNA of GABAergic neurons is more highly methylated compared to that of glutamatergic neurons or glia (Jang *et al.*, 2017).

Migration of pyramidal neurons may also be impaired by MIA. Reduced production of reelin, a glycoprotein involved in the migration of both embryonic-born and adult-born neurons (Fatemi *et al.*, 2008; Teixeira *et al.*, 2012), was observed in the neonatal (Fatemi *et al.*, 1999), developing (Harvey and Boksa, 2012; Nouel *et al.*, 2012), and adult (Meyer *et al.*, 2008c) brain of MIA offspring. Abnormalities in cortical neurons have been reported as early as E14.5, two days after MIA induction with Poly (I:C), or E18.5, four days after MIA induction with LPS. These abnormalities were characterized by loss of neurons expressing special AT-rich sequence binding protein 2 (SATB2) and later by disorganized expression of the layer-specific neuronal markers SATB2 and T-brain-1 (TBR1) (Choi *et al.*, 2016; Wu *et al.*, 2018). In Poly (I:C) offspring, patches of cortical disorganization were observed throughout the cortex of adult MIA offspring, but the majority of patches were located in the primary somatosensory cortex, secondary motor cortex, and temporal association cortex (Shin Yim *et al.*, 2017). These patches were sensitive to the time of MIA and the size of patches in the primary somatosensory cortex was correlated with behaviors characteristic of MIA offspring. These studies suggest that MIA at discrete developmental stages impairs neuronal migration.

While the number of inhibitory neurons is affected by MIA, the dendritic structure and synaptic formation of excitatory neurons is altered (Figure 3). The length and complexity of dendrites were reduced in an age-specific manner in the cortex and hippocampus of rodents (Baharnoori *et al.*, 2009; Fernandez de Cossio *et al.*, 2017; Li *et al.*, 2014; Zhang and van Praag, 2015), but dendrite complexity in the basolateral amygdala was not altered by MIA (Li *et al.*, 2018). However, in rhesus monkeys, no change in dendrite complexity was observed, but the apical dendrites were thinner in MIA offspring (Weir *et al.*, 2015). In addition, the density of dendritic spines on pyramidal neurons in the cortex (Baharnoori *et al.*, 2009; Coiro *et al.*, 2015; Li *et al.*, 2014) and granule cells in the DG (Abazyan *et al.*, 2010; Li *et al.*, 2014) was reduced in MIA offspring. Subthreshold MIA combined with expression of mutant human DISC1 also caused spine deficits on granule cells (Abazyan *et al.*, 2010). On apical dendrites in the medial prefrontal cortex (mPFC), the decreased spine density was limited to dendrite segments proximal to the soma but the spine deficit was observed on first, second, and third order basilar dendrites (Li *et al.*, 2014). The spine density on cortical neurons at 3 months was inversely correlated with marble burying behavior (Coiro *et al.*, 2015). *In vivo* time-lapse imaging of dendritic spines in P17 mice demonstrated reduced rate of spine turnover in MIA offspring, due to a lower rate of both spine gain and spine loss, suggesting an impairment in the normal dynamic properties of dynamic spines (Coiro *et al.*, 2015). Reduced synapse density on cultured cortical neurons was shown to be caused by increased expression of MEF2 transcription factors and surface MHC1 (Elmer *et al.*, 2013). However, one group reported an increase in the number of spines on granule cells at the peak of synaptic pruning, accompanied by decreased expression of CX3CR1, the microglial fractalkine receptor, which is involved in synaptic pruning (Fernandez de Cossio *et al.*, 2017). A reduction in spine density was not observed in primates (Weir *et al.*, 2015). Dendritic spines are often an appropriate proxy for synapses, but spine density alone is insufficient to fully describe synaptic alterations in MIA offspring. In the cortex, although there are fewer spines, there is a greater percentage of spines that are contacted by excitatory or inhibitory presynaptic input (Coiro *et al.*, 2015). On the other hand, fewer spines on Purkinje cells form structural synapses (Pendyala *et al.*, 2017).

Consistent with the reduction in the structural unit of synapses, there is a reduction in the expression of presynaptic proteins (cerebellin-1, bassoon, and synaptophysin) and post synaptic proteins (GluRδ2, PSD-95, and SynGAP) in the cerebellum and hippocampus of MIA offspring (Giovanoli *et al.*, 2015; Giovanoli *et al.*, 2016b; Pendyala *et al.*, 2017). A decrease in brain-derived neurotrophic factor (BDNF) expression and signaling have also been observed in MIA offspring (Giovanoli *et al.*, 2015; Han *et al.*, 2017b; Schaafsma *et al.*, 2017) and this may contribute to the reduced expression of some synaptic proteins, such as synaptophysin, that are downstream targets of BDNF signaling (Poo, 2001). In the cerebellum, the reduction in expression of synaptic proteins is not necessarily because there are fewer spines. In the case of glutamate receptor delta 2 (GluRδ2) expression on Purkinje cells, the proportion of spines in which GluRδ2 is expressed is lower in MIA offspring compared to controls (Pendyala *et al.*, 2017). Taken together, these data suggest that synaptic function is impaired in MIA offspring. This concept will be further discussed in the following paragraphs.

3.2 Altered neuronal function

The effect of MIA on the excitatory and inhibitory drive of pyramidal cells in cortical and hippocampal slices was investigated by recording miniature excitatory or inhibitory postsynaptic currents (mEPSC and mIPSC). A common finding was reduced mEPSC frequency while the amplitude was either unchanged or increased (Coiro *et al.*, 2015; Ito *et al.*, 2010). Recordings from granule cells in the dentate gyrus of the hippocampus detected no differences in mEPSC frequency or amplitude in either adult-born or embryonic-born granule cells (Zhang and van Praag, 2015). The reduction in mEPSC frequency is unlikely to be due to altered presynaptic release properties as, with the exception of one study (Oh-Nishi *et al.*, 2010), no difference in presynaptic release properties was observed in either brain regions (Ito *et al.*, 2010; Patrich *et al.*, 2016a; Zhang and van Praag, 2015) nor in the mPFC to basolateral amygdala (BLA) projections (Li *et al.*, 2018). The reported effects of MIA on inhibitory drive were also variable. mIPSC frequency was unchanged in the somatosensory cortical neurons (Coiro *et al.*, 2015), hippocampal pyramidal neurons (Inestrosa and Varela-Nallar, 2015; Ito *et al.*, 2010; Patrich *et al.*, 2016a) and in adult born granule cells in the hippocampus while being reduced in embryonically born granule cells (Zhang and van Praag, 2015), mPFC (Canetta *et al.*, 2016) and in cortical patches of the somatosensory cortex (Shin Yim *et al.*, 2017). mIPSC amplitude was found to be unaffected in most studies in the cortex (Canetta *et al.*, 2016; Shin Yim *et al.*, 2017) and the hippocampus (Ito *et al.*, 2010; Zhang and van Praag, 2015) although increases were also reported (Coiro *et al.*, 2015; Patrich *et al.*, 2016a).

Consistent with the findings of unitary synaptic responses, evoked synaptic responses were also found to be altered in MIA offspring. Stimulation of Schaffer collaterals while recording field-EPSPs in CA1 pyramidal neurons revealed reduced excitatory transmission in MIA offspring with female mice exhibiting a delay in the expression of this phenotype (Patrich *et al.*, 2016b). In the mPFC, connectivity between various GABAergic interneurons and pyramidal cells was probed with cell specific expression of the light-activated cation channel, channelrhodopsin2 (Canetta *et al.*, 2016). It was found that in MIA offspring there was reduced light-evoked-IPSCs, suggesting reduced connectivity between pyramidal neurons and PV neurons. This deficit was specific to PV neurons as GABAergic transmission from calretinin or somatostatin interneurons onto pyramidal neurons was unchanged. In this study, the decreased connectivity has been shown not to be mediated by altered number of PV neurons or synaptic contacts but rather by reduced presynaptic release probability (Canetta *et al.*, 2016). This is in contrast to excitatory synaptic inputs where the majority of studies found no change in release properties with MIA (Ito *et al.*, 2010; Patrich *et al.*, 2016a; Zhang and van Praag, 2015). However, analysis of mPFC projections to the amygdala demonstrated an increase in glutamatergic synaptic transmission with MIA on both interneurons and principle neurons (Li *et al.*, 2018).

In addition to the finding of alterations in basic synaptic properties a few studies have examined how synaptic plasticity is impacted by MIA. Measurements of long-term potentiation (LTP), a cellular mechanism of learning and memory has demonstrated that LTP is reduced in the CA1 hippocampal regions when measured in slices (Ito *et al.*, 2010; Oh-Nishi *et al.*, 2010). However, in vivo recordings in MIA offspring demonstrated increased

maintenance of LTP with no discernable difference in magnitude (Savanthrapadian *et al.*, 2013). The effect of MIA on long-term depression has been examined in LPS injected rats demonstrating the acceleration of the normal developmentally regulated reduction of NMDAR mediated long-term depression (LTD) in the hippocampus (Escobar *et al.*, 2011).

Neuronal function is determined not only by synaptic properties but also by the membrane properties that regulate the intrinsic excitability of neurons and thus affect their firing properties. The intrinsic excitability of neurons in the MIA model has not been extensively studied but in hippocampal cultures and in slices, MIA offspring displayed reduced intrinsic excitability manifested as increased current necessary to evoke a single action potential as well as reduced spiking frequency (Patrich *et al.*, 2016a). Together these studies indicate that both synaptic and intrinsic properties of neurons are impaired in MIA offspring.

So far a handful of studies analyzed how MIA affects neuronal activity *in vivo* in awake behaving mice. Recordings of hippocampal place cells (pyramidal neurons that fire in specific locations in the environment) has not detected a difference in basal firing properties such as firing rates but did detect smaller place fields in the MIA offspring which could underlie the spatial memory deficits reported in these mice (Wolff and Bilkey, 2015). In addition the same group has investigated how synchrony in neuronal activity between brain regions was impacted by MIA. Using EEG recordings they found reduced mPFC-hippocampus coherence suggesting reduced long-range functional connectivity in MIA offspring (Dickerson *et al.*, 2010). In future studies it will be critical to examine neuronal activity in the intact brain and in relevant brain regions in order to further understand how altered neuronal activity affects behaviors impaired in MIA offspring.

3.3 Neurotransmitter systems

In line with the altered neuronal function described above, components of neurotransmitter systems (neurotransmitters, receptors, and transporters) are dysregulated in MIA offspring. Affected systems include the glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic systems (see Table 2). Expression of the genes encoding many of the proteins involved in these signaling systems is regulated by microRNA or histone modifications (Shrestha and Offer, 2016; Stadler *et al.*, 2005; Sun and Shi, 2015).

Altered expression of components of the glutamatergic and GABAergic signaling pathways provide a molecular basis for the effect of MIA on excitatory and inhibitory drive as well as behavior impairments described above. Of note is the increased NR2A:NR2B ratio in the hippocampus of MIA offspring (Rahman *et al.*, 2017). The proper balance of these NMDA receptor subunits is critical for activity-dependent plasticity. Additional evidence for impaired NMDA receptor signaling was observed in juvenile and adult offspring (Fujita *et al.*, 2016). Levels of the NMDA receptor agonist glutamate and/or glycine, an NMDA receptor co-agonist, were decreased in multiple brain regions of juvenile MIA offspring while the NMDA receptor co-agonist D-serine and its precursor L-serine were decreased in adult MIA offspring (Fujita *et al.*, 2016).

Another mechanism that affects the excitatory/inhibitory balance is the developmental excitatory-inhibitory switch of GABA. Adult MIA offspring appear to have an immature

GABAergic system. Increased intracellular chloride levels due to reduced expression of the K^+-Cl^- cotransporter 2 (KCC2) and elevated expression of the Na^+-K^+-Cl^- cotransporter 1 results in a delay in the switch of the inhibitory action of GABA and is likely to underlie the increased susceptibility to seizures observed in MIA offspring (Corradini *et al.*, 2018; Richetto *et al.*, 2014). Reduced expression of KCC2 is attributed to increased binding of two transcription factors, RE1-silencing transcription factor and methyl-CpG-binding protein 2, to the *Kcc2* promoter, thus implicating epigenetic modifications in the delayed neuronal inhibition by GABA.

Aberrations in the serotonergic system were observed as early as 48 hours after Poly (I:C) administration. Levels of serotonin were increased in the forebrain of MIA offspring, likely due to elevated serotonin output from the placenta corresponding to an increase in tryptophan hydroxylase activity in the placenta of Poly (I:C)-injected females (Goeden *et al.*, 2016). In addition, the density of serotonergic axons was significantly decreased in the fetal brain (Goeden *et al.*, 2016).

The dopaminergic system has been widely studied in the context of MIA as imbalances in this signaling pathway are pertinent to schizophrenia. Quantification of dopaminergic neurons on the mesencephalon revealed a reduction in the number of dopaminergic precursor cells in the MIA fetus two days following MIA as well as altered positioning of post-mitotic and mature dopaminergic neurons (Luan *et al.*, 2018). In contrast, levels of tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis, were increased in the striatum in an age and region specific manner (Meyer *et al.*, 2008b; Vuillermot *et al.*, 2010). The number of tyrosine hydroxylase-positive neurons, as well as the number of neurons expressing Nurr1, a transcription factor critical for the development of the dopaminergic system, were increased in the ventral tegmental area (VTA) (Li *et al.*, 2014; Vuillermot *et al.*, 2012; Vuillermot *et al.*, 2010). However, MIA late in gestation caused a decrease in the number of tyrosine hydroxylase-positive neurons in the VTA (Vuillermot *et al.*, 2012). Levels of dopamine and its metabolites have been found to be elevated in some brain regions, but decreased or not changed in other regions in MIA offspring (Abazyan *et al.*, 2010; Giovanoli *et al.*, 2013; Kirsten *et al.*, 2010; Ozawa *et al.*, 2006; Winter *et al.*, 2009). Peripubertal stress increased the level of dopamine in the hippocampus of MIA offspring (Giovanoli *et al.*, 2013). In addition, stimulated dopamine release was greater in the striatum of MIA offspring (Zuckerman *et al.*, 2003). There was also altered expression of dopamine receptors D1R and D2R throughout development (Baharnoori *et al.*, 2013; Buschert *et al.*, 2016; Meehan *et al.*, 2017; Meyer *et al.*, 2008b; Meyer *et al.*, 2008c; Ozawa *et al.*, 2006; Vuillermot *et al.*, 2010). MIA also caused a decrease in D2R expression in mice heterozygous for Nurr1 (Vuillermot *et al.*, 2012). Expression and activation of glycogen synthase kinase 3 beta (GSK3β) and protein kinase B (AKT), two kinases that are involved in dopaminergic signaling, were altered in MIA offspring as well (Bitanihirwe *et al.*, 2010b; Willi *et al.*, 2013). Inhibiting GSK3β normalized some behaviors in MIA offspring (Willi *et al.*, 2013) and cognitive performance was correlated with the number of cells that express AKT1 in the mPFC (Bitanihirwe *et al.*, 2010b). There was also a decrease in the expression of dopamine transporter (DAT) in MIA offspring (Baharnoori *et al.*, 2013; Vuillermot *et al.*, 2010). Accordingly, the absence of latent inhibition and hypersensitivity to amphetamine in MIA offspring are thought to be a result of elevated dopamine transmission in the

mesolimbic pathway (Zuckerman *et al.*, 2003). Taken together, these results suggest that dopaminergic signaling is sensitive to a prenatal immune insult, but the exact alterations are age and brain region specific.

4. Immune alterations

Anomalies in MIA offspring, specifically in terms of behavior, anatomy, physiology, and neurotransmitter systems are becoming increasingly well characterized, but much is still unclear, especially the link between maternal inflammation and the phenotypes in the offspring described above. The next two sections will describe the major immune changes in the mother and the offspring (Figure 4) and the epigenetic mechanisms that may mediate the effects of MIA.

4.1 Cytokines

Cytokines are small signaling molecules of the innate immune system that also have defined roles in neurodevelopment (Garay and McAllister, 2010). Altered cytokine levels may both contribute to and be a result of epigenetic alterations in MIA offspring. Examples of epigenetic regulation by cytokines include regulation of DNA methyltransferase 1 expression and subcellular localization by interleukin-6 (IL-6) (Hodge *et al.*, 2007; Hodge *et al.*, 2001) and inhibition of histone deacetylase activity by IL-17a (Zijlstra *et al.*, 2012). Conversely, expression of cytokines such as IL-1β and tumor necrosis factor α (TNF-α) are regulated by epigenetic mechanisms including DNA methylation and microRNA expression (Cheray and Joseph, 2018).

In all MIA models, there is an initial increase in circulating cytokine levels in the mother, as would be expected following an immune insult. Two specific maternal cytokines appear to be critical for mediating the behavioral abnormalities in MIA offspring: (IL-6) and IL-17a. IL-6, a pro-inflammatory cytokine, reaches peak levels 3 hours after exposure to Poly (I:C) (Meyer *et al.*, 2006b). It activates the JAK/STAT3 pathway in fetal cells of the placenta, leading to altered production of placental factors that are important in fetal development (Hsiao and Patterson, 2011). Maternal administration of recombinant IL-6, in the absence of any other infection, was sufficient to induce a deficit in PPI and lack of latent inhibition in the offspring, behaviors which are relevant for ASD and schizophrenia (Smith *et al.*, 2007). Further supporting the role of IL-6, Smith and colleagues also found that offspring of dams who received anti-IL-6 antibodies in addition to Poly (I:C) did not have aberrant gene expression or behaviors in tests for latent inhibition, PPI, anxiety, and social interaction. Offspring of immune-challenged IL-6 knockout mice also did not develop behavioral abnormalities. Elevated IL-6 appears to be detrimental because of the activation of the IL-6 pathway in the placenta. Deletion of IL-6 receptor IL-6Rα in placental trophoblasts prevents MIA-induced neuron loss and behavioral impairments in the offspring (Wu *et al.*, 2017).

Downstream of IL-6, maternal IL-17a is also essential for MIA-induced phenotypes in the offspring. IL-17a was elevated in the placenta and maternal serum following immune activation, leading to an increase in IL-17a receptor subunit A (IL-17Ra) in the fetal brain (Choi *et al.*, 2016). Blocking IL-17a with IL-17a antibodies prevented cortical malformations and the upregulation of IL-17Ra in the fetal brain as well as the emergence of

abnormal behaviors in adult MIA offspring (Choi *et al.*, 2016). The role of IL-17a in MIA led to the discovery that the maternal gut microbiome is a critical factor in the development of brain and behavioral abnormalities in MIA offspring. IL-17a is elevated in the maternal serum if segmented filamentous bacteria are present in the maternal microbiota. These bacteria are major contributors to the differentiation of TH17 cells, which produce IL-17a. Behavioral abnormalities and cortical patches were not observed in offspring of immune challenged mothers that lacked segmented filamentous bacteria (Kim *et al.*, 2017).

Other maternal cytokines that are increased in the periphery following infection during pregnancy include tumor necrosis factor-α (TNF-α), IL-10, IL-1β, IL-4, and IFN-β (Ashdown *et al.*, 2006; Ballendine *et al.*, 2015; Choi *et al.*, 2016; Giovanoli *et al.*, 2013; Giovanoli *et al.*, 2015; Money *et al.*, 2017; Wu *et al.*, 2015) (Table 3). While altered levels of these maternal cytokines may impact neurodevelopment and contribute to aberrant phenotypes in MIA offspring, they are not sufficient to induce changes. Maternal administration of TNF-α alone was not sufficient to induce PPI deficits like those seen in MIA offspring (Smith *et al.*, 2007). In addition, induction of MIA in TNF-knockout mothers did not prevent the emergence of MIA-induced behavioral impairments in the offspring (Konefal and Stellwagen, 2017). The increase in maternal IL-10, which is considered to be anti-inflammatory, may actually attenuate the effects of IL-6 and IL-17a considering that overexpression of IL-10 in macrophages prevented the emergence of MIA-induced behavior, while IL-10 overexpression in the absence of an inflammatory stimulus was associated with deficits in spatial exploration and associative learning (Meyer *et al.*, 2008a). In addition, IL-10 administration prevented MIA-induced fetal loss and white matter damage (Pang *et al.*, 2005; Robertson *et al.*, 2006).

Many cytokines are also dysregulated in the serum of MIA offspring throughout development (Table 4). In a comparison of LPS versus Poly (I:C)-induced MIA, only Poly (I:C)-induced MIA offspring exhibited significant increases in IL-2, IL-5, and IL-6 (Arsenault *et al.*, 2014), however a direct measure of the magnitude of the maternal immune response, such as maternal serum levels of IL-6, was not reported, so it is uncertain whether LPS and Poly (I:C) induced comparable maternal immune responses in this study. A long term study in rhesus monkeys showed a shift in circulating cytokines from alterations in cytokine levels primarily of the innate immune system at 1 year of age to a more T_H2 cytokine phenotype in 4 year old MIA offspring (Rose *et al.*, 2017). Adult mice exposed to prenatal Poly (I:C) were also shown to have an altered peripheral cytokine profile (Hsiao *et al.*, 2012).

Cytokine expression in the developing brain varies across regions (Table 5). The initial dysregulation occurs as early as three hours after Poly (I:C) injection and is characterized by elevated levels of IL-6 in the fetal brain and an increase in STAT3 activation (downstream of IL-6 receptor activation), predominantly in the prepontine hindbrain and pontine hindbrain (Wu *et al.*, 2017). Evidence for immune activation in the fetal brain was also observed in the LPS model of MIA. Twenty-four hours after administration of the third dose of LPS, several interferon-related genes were overexpressed (Hsueh *et al.*, 2018). Immune dysregulation in the brain of MIA offspring is persistent, as evidenced by the upregulation of several inflammatory markers prenatally and in adulthood in the amygdala of MIA offspring

(O'Loughlin *et al.*, 2017). A pattern of cytokine dysregulation in MIA offspring emerged in the frontal and cingulate cortices where there was an increase in pro-inflammatory cytokines at birth, reduced levels when critical neurodevelopmental processes such as synaptogenesis and neuronal plasticity are at their peaks, and a return to increased levels of pro-inflammatory cytokines in adult MIA offspring (Garay *et al.*, 2013). There is not a clear pattern of cytokine alterations in the hippocampus, but the majority of alterations appeared to occur more in the developing MIA offspring than in adults when there was a single immune insult (Garay *et al.*, 2013; Giovanoli *et al.*, 2016a; Giovanoli *et al.*, 2015). Increased IL-6 persisted in the hippocampus for 6 months when IL-6 was administered three times during embryonic development (Samuelsson *et al.*, 2006). Synergism between MIA and peripubertal stress was manifested in the hippocampus as an increase in levels of IL-1β and TNF-α compared to control offspring or offspring exposed only to MIA (Giovanoli *et al.*, 2013). Among the cytokine alterations in the cerebellum of MIA offspring, increased expression of TNF-α and its receptor TNFRI at P14 stand out because of their involvement in regulating synapses (Pendyala *et al.*, 2017). These changes in the brain are not caused by infiltration of circulating cytokines, as it was demonstrated that the blood brain barrier is not compromised and there is no immune cell infiltration in the brain of MIA offspring (Garay *et al.*, 2013). However, we cannot dismiss the possibility that peripheral immune changes induce some of the behavioral phenotypes commonly observed in MIA offspring by activation of afferent nerve fibers, a mechanism known to transmit immune signals from the periphery to the brain, resulting in impairments in cognition as well as social and exploratory behavior (Dantzer, 2001; Larson and Dunn, 2001).

The recent observations that IL-1 receptor type I knock out embryos implanted in wild type mothers exhibited attenuated MIA-induced cytokine changes and normal KCC2 expression (Corradini *et al.*, 2018), suggest that the effects of MIA depend not only on maternal cytokine elevations, but also on cytokine dysregulation in the fetal brain.

4.2 Microglia

Microglia, the resident immune cells in the brain, were once considered to only play a role during brain injury and disease, but are now known to have critical roles in neurodevelopment and homeostasis in the brain. Microglia begin to colonize the brain around E9 in rodents and at the beginning of the second trimester in humans (Chan *et al.*, 2007) where they are involved in both the support and elimination of neurons and the activity-dependent pruning of synapses (Bilimoria and Stevens, 2015). Given this evidence, it is clear that it is crucial for microglia to function properly during neurodevelopment and throughout life. Despite evidence for alterations in cytokine production in the brain, many studies reported no change in the density or activation state of microglia in MIA offspring (Buschert *et al.*, 2016; Corradini *et al.*, 2018; Garay *et al.*, 2013; Giovanoli *et al.*, 2013; Giovanoli *et al.*, 2015; Giovanoli *et al.*, 2016b; Li *et al.*, 2018; Missault *et al.*, 2014; Paylor *et al.*, 2016; Pratt *et al.*, 2013; Smolders *et al.*, 2015). However, an almost equal number of studies found that MIA increased microglia density in various brain regions (Hadar *et al.*, 2017; Juckel *et al.*, 2011; Li *et al.*, 2014; Mattei *et al.*, 2014; Mattei *et al.*, 2017; Van den Eynde *et al.*, 2014; Wu *et al.*, 2018; Zhu *et al.*, 2014). On postnatal day 2, MIA offspring exhibit increased density of microglia in the supraventricular corpus callosum, a region

where microglia accumulate before migrating to other brain regions (Zhang *et al.*, 2018). In contrast, regions to which microglia migrate from the supraventricular corpus callosum including the corpus callosum, striatum, somatosensory cortex, and hippocampus of MIA offspring have lower density of microglia compared to controls. This suggests that MIA induces a delay in tangential microglial migration. In addition, a greater proportion of microglia in the hippocampus had the more immature amoeboid morphology, suggesting a delay in microglia maturation as well as migration (Zhang *et al.*, 2018).

When there is an increase in the number of microglia, there is also often an increase in the number of amoeboid microglia, indicative of activated microglia (Juckel *et al.*, 2011; Missault *et al.*, 2014; O'Loughlin *et al.*, 2017; Van den Eynde *et al.*, 2014; Zhu *et al.*, 2014). Amoeboid microglia have been observed as early as P7 (O'Loughlin *et al.*, 2017) and as late as P180 (Van den Eynde *et al.*, 2014) in various brain regions. Activated microglia can also be identified by cell surface proteins such as MHCII and CD68. Microglia were found to have increased MHCII expression in the medial prefrontal cortex of MIA offspring (Hadar *et al.*, 2017) and a greater number of microglia expressed CD68 in the embryonic brain (Wu *et al.*, 2018). Others found that MIA alone did not increase microglia activation (Antonson *et al.*, 2017; Giovanoli *et al.*, 2015; Giovanoli *et al.*, 2016b; Smolders *et al.*, 2015), but MIA followed by exposure to peripubertal stress transiently increased expression of CD68 and CD11b (markers for activated microglia) in the hippocampus and medial prefrontal cortex (Giovanoli *et al.*, 2016a; Giovanoli *et al.*, 2013). Binding of radioactive ligands to translocator protein, which is often used to measure glia activation in schizophrenia studies, also showed increased binding in the hippocampus of MIA offspring with a confirmed deficit in PPI (Mattei *et al.*, 2017). This would suggest an increase in the number of activated glia, but a phagocytic activity assay, which measured the number of microglia that phagocytosed fluorescent beads, showed that cultured hippocampal microglia from MIA offspring have reduced phagocytic activity. However, it is important to note that translocator protein is not solely expressed by microglia (Cosenza-Nashat *et al.*, 2009) and that microglia behave differently in vitro than in vivo (Jeong *et al.*, 2013).

The variations reported above might be less surprising considering that there are also variable findings in schizophrenia studies; some have reported increases in microglia density and activation while other studies have reported no change (Laskaris *et al.*, 2016). However, there is evidence that aspects of experimental design could explain these differences. Poly (I:C) administered to rats on E10 had no effect on IBA1 immunoreactivity while Poly (I:C) on E19 increased IBA1 immunoreactivity (Duchatel, 2018). The age of the animals at the time of testing also matters, as there was an increase in the number of microglia in the hippocampus of P2, but not P80 MIA offspring (Li *et al.*, 2014). The brain region studied may also determine whether or not microglia density is affected by MIA, as within the same study, microglia density was increased in the nucleus accumbens, but the other regions investigated showed no change in microglia density (Mattei *et al.*, 2014). In addition, a Poly (I:C) injection on E19 increased IBA1 immunoreactivity in the corpus callosum, but not the cingulate cortex (Duchatel, 2018). However, the main effect of MIA on microglia may be that of priming (Knuesel *et al.*, 2014), resulting in abnormal responses of microglia to subsequent insults. For example, MIA alone did not visibly affect microglia, but microglia were activated by the combination of MIA and peripubertal stress (Giovanoli *et al.*, 2013).

Another study, in which MIA offspring received an injection of LPS in adulthood, demonstrated that microglia from the hippocampus of MIA offspring express higher levels of IL-1β following the second LPS insult compared to control offspring that received an LPS injection. However, microglia isolated from the whole brain of MIA offspring exhibited reduced cytokine production following LPS injection (Schaafsma *et al.*, 2017).

The effect of these microglial alterations on neuron-microglia interactions is not clear, but there is support for a reduction in neuron-mediated suppression of microglia activity as well as altered glutamatergic transmission. MIA alone or when followed by peripubertal stress caused alterations in CD200R and CD172a expression. These molecules interact with neuronal CD200 and CD47, respectively, which also have altered expression in MIA, suggesting that there is aberrant neuron-microglia inhibitory signaling (Giovanoli *et al.*, 2013). It is also suggested that MIA-induced microglia activation and neuroinflammation during prenatal development causes increased AMPAR-mediated evoked EPSCs in adult MIA offspring (Roumier *et al.*, 2008). This is based on the observation that mice with a loss of function of the DAP12 gene, a gene that is transiently expressed by microglia during prenatal development, exhibited microglia activation and mild neuroinflammation at P0, followed by increased AMPAR-mediated neurotransmission in adults (Roumier *et al.*, 2008).

4.3 Astrocytes

Astrocytes, under normal conditions, perform many signaling and support functions in the brain. Under inflammatory conditions, they enter a state of astrogliosis which is characterized by functional, structural, and genetic changes. Astrogliosis has been observed to varying degrees in models of MIA with several groups observing an increase in the expression of common astrocyte markers such as glial fibrillary acidic protein (GFAP) and S100β in the brain and cerebral spinal fluid of MIA offspring when MIA is induced with LPS (Cai *et al.*, 2000; de Souza *et al.*, 2015; Hao *et al.*, 2010; O'Loughlin *et al.*, 2017; Rousset *et al.*, 2006). A prenatal IL-6 injection led to increased astrocyte density and branching in MIA offspring (Samuelsson *et al.*, 2006). But administration of Poly(I:C) during gestation did not appear to induce astrogliosis in MIA offspring (Giovanoli *et al.*, 2015; Giovanoli *et al.*, 2016b; Paylor *et al.*, 2016) or in MIA offspring subjected to peripubertal stress (Giovanoli *et al.*, 2013). The presence or absence of astrogliosis could be justified by considering the intensity of MIA. Astrogliosis was observed when pregnant dams were repeatedly exposed to LPS, but a single Poly (I:C) injection did not induce astrogliosis. Histological analysis of astrocytes in MIA is a good starting point, but functional studies to address the roles of astrocytes in the MIA model are still needed.

5. Epigenetic reprogramming of brain development induced by MIA

To date, the epigenetic alterations investigated in MIA offspring include histone modifications, DNA methylation, and microRNA expression. Here we will discuss these MIA-induced epigenetic modifications and their relationship to MIA-induced brain and behavior phenotypes described above.

Consistent with the concept of windows of susceptibility, alterations in histone acetylation depend on the time of MIA or the age of the animal. For example, global acetylation of

histones H3 and H4 was reduced in the cortex of juvenile, but not adult, MIA offspring (Tang *et al.*, 2013). In the hippocampus, MIA in mid-gestation had no effect on histone acetylation (Tang *et al.*, 2013), but MIA early in the second half of gestation induced an increase in global acetylation of histone H3 and a decrease in global acetylation of histone H4 (Reisinger *et al.*, 2016). The increased acetylation of histone H3 is likely due to the observed decrease in levels of histone deacetylase 1 (Reisinger *et al.*, 2016). In contrast to global changes in acetylation, modifications at specific gene promoters are directly related to altered gene expression. Histones H3 and H4 were both hyperacetylated at the serotonin transporter (SERT) promoter in MIA offspring, resulting in increased SERT expression (Reisinger *et al.*, 2016). In the cortex of juvenile and adult MIA offspring, hypoacetylation of histone H3 at lysine residues 9 and 14 was observed in the promoter regions of several genes that are implicated in the pathology of schizophrenia, many of which are involved in neurodevelopment or glutamatergic neurotransmission (Tang *et al.*, 2013). Hypoacetylation in these promoter regions was associated with decreased gene expression. In the hippocampus, acetylation of histone H3 was increased in the promoter regions for a number of schizophrenia-related genes that are overexpressed in the hippocampus of juvenile MIA offspring (Tang *et al.*, 2013).

DNA hypomethylation and hypermethylation have both been observed in MIA offspring (Basil *et al.*, 2014; Basil *et al.*, 2018; Labouesse *et al.*, 2015; Richetto *et al.*, 2017b). In the first study to identify altered DNA methylation in MIA offspring, methylation of long interspersed element 1 (LINE1) was observed to be decreased in in the hypothalamus of adolescent female but not male MIA offspring (Basil *et al.*, 2014). LINE1 activity may be further dysregulated in the hypothalamus of female MIA offspring given that the authors also found hypomethylation in the promoter region of methyl-CpG-binding protein 2 (Mecp2), which regulates LINE1 activity (Muotri *et al.*, 2010). Hypomethylation of LINE1 has not been investigated in other brain regions of MIA offspring, but given that methylation of LINE1 represses its transcription (Muotri and Gage, 2006), hypomethylation could be responsible for the overexpression of LINE1 in the prefrontal cortex of MIA offspring (Bundo *et al.*, 2014). Altered expression of LINE1 has implications for neurodevelopment, given that LINE1 is a retrotransposon and can modulate gene expression of neuron-associated genes (Muotri and Gage, 2006).

Analysis of methylation changes across the entire genome at single nucleotide resolution revealed that MIA induces hypomethylation as well as hypermethyaltion in the adult prefrontal cortex (Richetto *et al.*, 2017b). Hypomethylation was more prominent, regardless of whether MIA was induced during middle or late gestation. However, only a fraction of the differentially methylated sites in the two groups overlapped. Gene ontology term enrichment analysis of the genes located in regions of differential methylation identified neuronal differentiation as having a high enrichment score in both MIA groups. However, enrichment of subterms within this category differed between the two groups; a greater number of genes involved in GABAergic differentiation were differentially methylated in offspring exposed to MIA late in gestation. Despite the abundance of changes in methylation in adult MIA offspring, when select genes were tested for methylation and expression the day after birth, no changes were found (Richetto *et al.*, 2017b), suggesting a potentially delayed effect of MIA on the mechanisms regulating DNA methylation.

Consistent with the known function of DNA methylation, MIA-induced changes in methylation of specific genes were accompanied by altered levels of mRNA (Richetto *et al.*, 2017b). Of significance, increased methylation and/or hydroxymethylation of cytosines in the promoter regions of *GAD1* and *GAD2* enhanced MeCP2 binding and consequently decreased GAD67 and GAD65 mRNA expression in the mPFC of MIA offspring (Labouesse *et al.*, 2015). Hypermethylation in two segments of the promoter region of the myelin-associated oligodendrocytic basic protein was associated with reduced gene and protein expression in adult MIA offspring (Richetto *et al.*, 2017a).

A study of microRNA expression in the entorhinal cortex found that MIA offspring have 21 differentially expressed microRNAs (Hollins *et al.*, 2014). Some of the same microRNA were affected when MIA offspring were exposed to HU210, a synthetic cannabinoid, in adolescence, but this second hit also altered the expression of different microRNAs. An interesting finding in this study is that this combination of pre- and post-natal insults affected the left and right hemispheres differently, in terms of microRNA expression. Many of the differentially expressed microRNAs are located in the long arm of chromosome 6, a region under the control of Mef2 transcription factors. This study found a decrease in *Mef2c* and *Mef2d* mRNA in the entorhinal cortex of rats following MIA and synthetic cannabinoid exposure, but an increase in Mef2a and Mef2d expression in cultured cortical neurons has also been reported (Elmer *et al.*, 2013). In addition, expression of several microRNAs with relevance to neuro-immune interactions or models of depression were found to be upregulated in the hippocampus of MIA offspring (Berger *et al.*, 2018).

An interesting question addressed by many of these studies is whether epigenetic alterations are associated with behavioral abnormalities. Some epigenetic changes may precede the emergence of abnormal behaviors given that many epigenetic changes occurred in juvenile MIA offspring while hyperactivity and decreased exploratory behavior were observed only in adult MIA offspring (Tang *et al.*, 2013). Altered histone acetylation can also be concurrent with behavioral abnormalities such as reduced sucrose preference (Reisinger *et al.*, 2016). On the other hand, methylation of histone H3 was not significantly altered in the cortex of adult MIA offspring, but these animals had cognitive deficits (Connor *et al.*, 2012). There is a correlation between increased methylation of the *GAD1* promoter and working memory deficits and impairments in social interaction, but methylation of the *GAD2* promoter was not found to be significantly correlated with working memory performance or levels of social interaction. Spatial recognition memory was also negatively correlated with methylation of CpG343 in the promoter region of myelin-associated oligodendrocytic basic protein in the mPFC of adult MIA offspring (Richetto *et al.*, 2017a). Taken together, these findings suggest that epigenetic alterations at specific sites may impact behavior (Labouesse *et al.*, 2015).

Some of these epigenetic effects are proposed to be heritable, given that two studies of inbred mice found persistent behavioral abnormalities and altered gene expression in MIA offspring (F1) as well as in the second (F2) and third (F3) generations of offspring of MIA offspring (Ronovsky *et al.*, 2017; Weber-Stadlbauer *et al.*, 2017). The F2 generation in an outbred mouse line also displayed behavioral abnormalities, though not in the same direction as the F1 offspring (Berger *et al.*, 2018). Distinct behavioral and genetic characteristics were

passed through the maternal and paternal lines, but the effects tended to be greater when both parents were MIA offspring.

Whether these epigenetic alterations induced by MIA directly induce the brain and behavioral changes described below remains to be determined. Thus far, only correlation, not causation, has been shown in the context of MIA-induced epigenetic and behavioral alterations. Gene expression profiling studies have identified hundreds of differentially expressed genes in the brain of developing MIA offspring (Fatemi *et al.*, 2005; Garbett *et al.*, 2012; Lombardo *et al.*, 2018; Richetto *et al.*, 2017a; Smith *et al.*, 2007), a subset of which have been associated with specific epigenetic changes. Expression of additional dysregulated genes can likely be linked to MIA-induced epigenetic alterations, thus providing a link between epigenetic dysregulation and brain and behavior changes. Future work should address additional epigenetic mechanisms that are known to contribute to the phenotypes that have been observed in MIA offspring.

6. Pharmacological interventions

A number of therapeutic strategies have been tested on MIA offspring. Antipsychotics that are currently on the market have been shown to be effective for treating MIA-induced phenotypes. Paliperidone was shown to regulate Toll-like receptor 3 signaling and improve performance in the T maze (MacDowell *et al.*, 2017). Clozapine improved long-range synchrony, latent inhibition, working memory, and novel object recognition in MIA offspring, but impaired working memory in control offspring (Dickerson *et al.*, 2012; Meyer *et al.*, 2010a; Ozawa *et al.*, 2006; Zuckerman *et al.*, 2003). Chronic administration of lurasidone in adulthood restored levels of GAD67 and parvalbumin protein in the dorsal hippocampus (Luoni *et al.*, 2017). The effects of risperidone as preventive treatment were tested by administering risperidone during adolescence, before most symptoms emerge. Risperidone treatment prevented latent inhibition deficiency, hypersensitivity to amphetamine, and the loss of PV-positive cells (Piontkewitz *et al.*, 2012; Richtand *et al.*, 2011). Haloperidol, clozapine, or fluoxetine can also effectively prevent MIA-induced behaviors (Meyer *et al.*, 2010b; Richtand *et al.*, 2012).

Anti-inflammatory drugs have also been effective in treating phenotypes of MIA offspring. Different minocycline treatment regimens have produced similar results. Minocycline reduced microglia activation and density and rescued behaviors such as PPI and social interaction/preference (Mattei *et al.*, 2014; Mattei *et al.*, 2017; Zhu *et al.*, 2014). It also restored neurogenesis and normalizes the expression of many microglial genes differentially expressed following MIA (Mattei *et al.*, 2014; Mattei *et al.*, 2017). In a two-hit model using subthreshold MIA and peripubertal stress in which minocycline was administered in the drinking water one day before and throughout the stress paradigm, microglia activation and behaviors that emerged in stressed MIA offspring were blocked with minocycline treatment (Giovanoli *et al.*, 2016a). However, anxiety-like behavior displayed by MIA offspring not exposed to stress was not ameliorated with minocycline treatment. Ibudilast, a type IV-phosphodiesterase that suppresses the production of pro-inflammatory cytokines, prevented spine loss and reduced marble burying in MIA offspring when administered to MIA offspring through the milk of lactating dams (Coiro *et al.*, 2015). In addition, suppression of

the kynurenine pathway during puberty with celecoxib, a cyclo-oxygenase-2 inhibitor, prevented hypersensitivity to MK-801 in adult MIA offspring (Zavitsanou *et al.*, 2014). Diets rich in n-3 polyunsaturated fatty acids, which are known to have anti-inflammatory properties (Trepanier *et al.*, 2016) have beneficial effects on MIA-induced phenotypes when given to the mother during gestation and lactation or given to the offspring (Basil *et al.*, 2018; Labrousse *et al.*, 2018). Diets low in n-3 polyunsaturated fatty acids fed to the mother exacerbated LPS-induced cytokine elevations in the maternal plasma and fetal brain (Labrousse *et al.*, 2018). These offspring exhibited spatial memory deficits while MIA offspring of mothers given a balanced diet in terms of polyunsaturated fatty acids did not have spatial memory deficits (Labrousse *et al.*, 2018). Another group, which used Poly(I:C) to induce MIA, found that a diet rich in n-3 polyunsaturated fatty acids given to the offspring prevented MIA-induced PPI deficits and methylation changes in the hypothalamus (Basil *et al.*, 2018; Li *et al.*, 2015).

In addition to general anti-inflammatory drugs, some tested drugs target specific systems that are dysregulated in MIA offspring. To target the abnormalities in the GABAergic system, a benzodiazepine with partial selectivity for the α2, α3, and α5 subunits of the $GABA_A$ receptor was used. This treatment did not restore working memory or social interaction, but it did prevent MIA-induced hypersensitivity to amphetamine (Richetto *et al.*, 2015). Treatment with the purinergic receptor inhibitor suramin normalized motor coordination and social preference, as well as the number of Purkinje cells in lobule VII of the cerebellum in MIA offspring (Naviaux *et al.*, 2013). Antagonists for dopamine receptors D1R and D2R normalize PPI deficits in MIA offspring (Vuillermot *et al.*, 2010). Co-administration of Poly (I:C) and parachlorophenylalanine, an inhibitor of tryptophan hydroxylase, prevented the MIA-induced reduction in serotonergic axon density (Goeden *et al.*, 2016). Administration of 7,8-dihydroxyflavone, an agonist for the BDNF receptor tropomyosin receptor kinase B, during adolescence rescued MIA-induced impairments in PPI, novel object recognition, PV-immunoreactivity, and BDNF expression and signaling (Han *et al.*, 2016), and normalized C1q expression (Han *et al.*, 2017a). 7,8-dihydroxyflavone given to the mother during pregnancy and lactation also prevented cognitive deficits (Han *et al.*, 2017b).

Supplements given to the mother during gestation can prevent the emergence of abnormalities in MIA offspring. When the mother's diet was enriched with choline, mRNA levels of the nicotinic acetylcholine receptor alpha 7 subunit were normalized (Wu *et al.*, 2015). Choline supplementation also restored normal marble burying, but did not prevent the PPI deficit in MIA offspring. Subcutaneous administration of the active form of vitamin D at the same time as Poly(I:C) normalized social approach and marble burying behavior in juvenile MIA offspring and amphetamine hypersensitivity in adult MIA offspring (Luan *et al.*, 2018; Vuillermot *et al.*, 2017). Co-administration of vitamin D also restored dorsoventral positioning of mature dopaminergic neurons in the fetal brain (Luan *et al.*, 2018). The effect of vitamin D was not due to its anti-inflammatory properties as vitamin D did not block the elevation of cytokines in the maternal plasma and fetal brain (Vuillermot *et al.*, 2017). Rather, vitamin D supplementation promotes expression of the transcription factor Nurr1 in mature dopaminergic neurons (Luan *et al.*, 2018), suggesting an effect of vitamin D on epigenetic mechanisms. Using a similar approach with zinc resulted in a reduction in the

number of GFAP positive cells, apoptotic cells, and TNF-α positive cells in the fetal brain (Chua *et al.*, 2012) while dietary zinc supplementation throughout pregnancy improved novel object recognition in the offspring (Coyle *et al.*, 2009). N-acetylcysteine in the drinking water of LPS-injected dams prevented synaptic plasticity deficits and improved working memory in MIA offspring (Lante *et al.*, 2008). Water containing molecular hydrogen has been shown to be neuroprotective when given to either the mothers or the offspring (Imai *et al.*, 2016; Imai *et al.*, 2018; Nakano *et al.*, 2015).

Dietary intervention during juvenile or adolescent stages can also prevent the MIA-induced phenotypes in the offspring. A diet containing glucoraphanin, a precursor to the antioxidant sulforaphane, rescues the deficit in PV immunoreactivity and impairments in novel object recognition in adult MIA offspring (Matsuura *et al.*, 2018). In addition, a ketogenic diet given for 3–4 weeks increases sociability and decreases grooming behavior in male MIA offspring (Ruskin *et al.*, 2017). D-serine in the drinking water during adolescence prevented cognitive impairments in adult MIA offspring (Fujita *et al.*, 2016).

An interesting finding is that when pregnant dams received influenza vaccination 12 days prior to immune activation with LPS, the offspring did not exhibit many MIA-induced phenotypes including altered social behavior, anxiety- and depression-like behaviors, abnormal cortical lamination, and microglial activation (Wu *et al.*, 2018). RNA sequencing results suggest that prenatal vaccination promotes expression of several genes involved in neuronal differentiation, which may underlie the abrogation of MIA-induced phenotypes in offspring of mothers that had been vaccinated (Wu *et al.*, 2018).

A common theme linking many of these interventions is their potential to modulate the epigenome. Indeed, dietary supplementation with n-3 polyunsaturated fatty acids has already been shown to normalize PPI and DNA methylation in MIA offspring (Basil *et al.*, 2018; Li *et al.*, 2015). A number of other agents with therapeutic effects in MIA offspring have been shown elsewhere to regulate epigenetic mechanisms. For example, haloperidol, clozapine, and sulforaphane modulate DNA methylation (Dong *et al.*, 2016; Kaufman-Szymczyk *et al.*, 2015; Swathy and Banerjee, 2017). Haloperidol has also been shown to repress specific microRNAs that can also regulate DNA methylation (Swathy and Banerjee, 2017). Posttranslational modifications of histones can be regulated by risperidone, suramin, and sulforaphane (Kaufman-Szymczyk *et al.*, 2015; Li *et al.*, 2004; Villalba and Alcain, 2012). Whether these agents regulate the epigenome in MIA offspring remains an important direction for future study.

In summary, the efficacy of current antipsychotics in normalizing behaviors in MIA offspring suggests that the MIA model has predictive validity and can be used to test drugs for treating neurodevelopmental disorders for which maternal infection is a risk factor. In addition, anti-inflammatory drugs are promising candidates for new drugs. Thirdly, supplementation of a mother's diet may help limit the adverse effects of maternal infection on neurodevelopment. Using agents to target epigenetic mechanisms is an important therapeutic strategy that remains to be addressed in the MIA model.

7. Conclusions

The developing brain is highly susceptible to environmental insults. Epidemiological data suggest that maternal infection during pregnancy increases the risk of neuropsychiatric disorders such as schizophrenia and autism in the offspring. The preclinical studies described here provide strong support for the association between prenatal immune insult and altered brain development that results in behavioral abnormalities. The mechanisms that link transient prenatal inflammation with delayed impairment of neuronal functions have begun to be investigated at the cellular and molecular levels spanning alterations in the immune molecules and cells, altered neuronal neurochemistry and function as well as epigenetic alterations. All of the major epigenetic mechanisms – histone modifications, DNA methylation, and microRNA expression – have been now shown to be associated with MIA. Moreover, we reviewed how these alterations have contributed to variations in phenotypes such as behavior through hypermethylation of DNA and altered histone methylation and acetylation; expression of components of glutamatergic, GABAergic, and serotonergic neurotransmission through hypoacetylation of histones, DNA hypermethylation, or hyperacetylation of histones, respectively; and expression of genes involved in neurodevelopment through reduced DNA methylation. Providing further support that epigenetic alterations are a key mechanism underlying MIA-induced phenotypes is the transgenerational aspect of MIA, whereby MIA induces behavioral alterations in the F1, F2, and F3 generations, suggesting an inheritable mechanism (such as epigenetics) is involved. In addition, the number of therapeutic interventions that may work through epigenetic modulation that have proven beneficial in MIA offspring strongly suggest that normalization of epigenetic mechanisms has the potential to alleviate a range of MIA-induced phenotypes. The current epigenetic studies offer a partial explanation of the mechanism involved in the production of the phenotypes observed in MIA offspring, but several questions remain. How does MIA induce a wide range of epigenetic alterations? Do these changes directly cause the diverse brain and behavioral phenotypes observed in MIA offspring? Can (and should) we effectively target specific epigenetic mechanisms for therapeutic purposes? In addition to these epigenetic-centered questions, in the future, impairments in specific brain circuits underlying specific behavioral impairments will be important to define. In addition, beyond the classical developmental disorders it is becoming increasingly evident that early insults could also be linked to neurodegenerative disorders such as Alzheimer’s disease, making this a question relevant to a larger population. Although studies investigating the interaction between genetic susceptibility and neurodevelopmental disorders have begun to emerge, similar studies with genetic risk factors for neurodegenerative disorders are still missing and will be a fruitful area of investigation. Finally, the animal models of MIA will continue to provide an important platform for preclinical testing of therapeutic reagents.

Abbreviations

ASD	autism spectrum disorder
GFAP	glial fibrillary acidic protein
GSK3β	synthase kinase 3 beta

IL	interleukin
LPS	lipopolysaccharide
MIA	maternal immune activation
mEPSC	miniature excitatory postsynaptic current
mIPSC	miniature inhibitory postsynaptic current
mPFC	medial prefrontal cortex
Poly (I:C)	polycytidylic acid
PPI	prepulse inhibition
PV	parvalbumin
SZ	schizophrenia
TNF-α	tumor necrosis factor-α
USV	ultrasonic vocalizations
VTA	ventral tegmental area

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Highlights:

- Exposure to maternal immune activation (MIA) during specific windows of prenatal development can alter the normal trajectory of brain development.
- MIA is associated with increased risk factor for various neurodevelopmental and neurodegenerative disorders.
- MIA acts synergistically with genetic and environmental factors for neurodevelopmental disorders.
- MIA results in altered immunological milieu for the developing brain.
- MIA results in diverse alterations in neuron number, structure and function in different brain regions.
- Global and specific epigenetic mechanisms have a potential to explain the diverse changes associated with MIA.

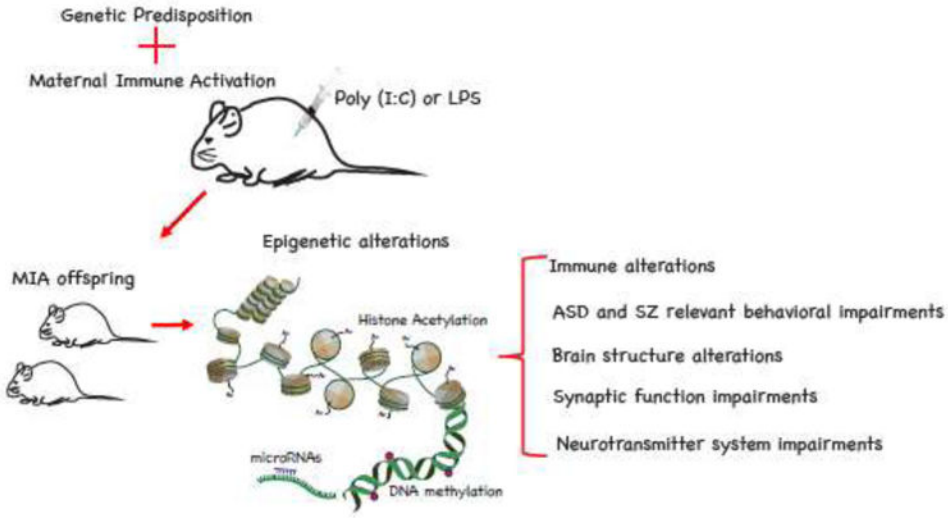

Figure 1: The maternal immune activation model.

Strong immunological stimulation of the gestating dam with immune-stimulating reagents such as Poly (I:C) or LPS (or a mild stimulus that interacts with maternal genetic susceptibility) result in epigenetic alterations including histone acetylation, DNA methylation, and microRNA expression that contribute to a spectrum of molecular alterations, neuronal dysfunctions, and behavioral phenotypes in the MIA offspring.

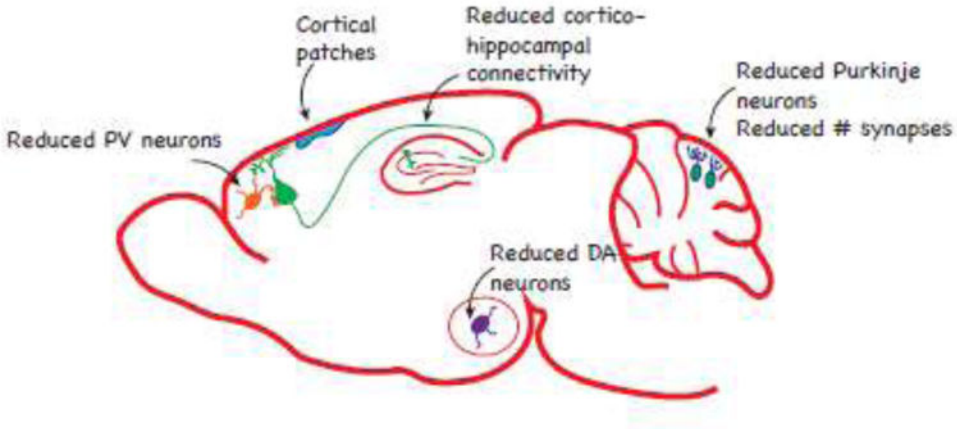

Figure 2: Brain anatomic changes in MIA offspring.

Brain alterations such as reduced brain volume (Fatemi *et al.*, 2008; Patrich *et al.*, 2016b; Piontkewitz *et al.*, 2011; Short *et al.*, 2010) is mediated by loss of neurons in several brain regions (Fatemi *et al.*, 1999; Meyer *et al.*, 2008c; Naviaux *et al.*, 2013; Shi *et al.*, 2009; Wischhof *et al.*, 2015b; Zhang and van Praag, 2015). MIA also results in formation of disorganized cortical patches (Choi *et al.*, 2016; Shin Yim *et al.*, 2017).

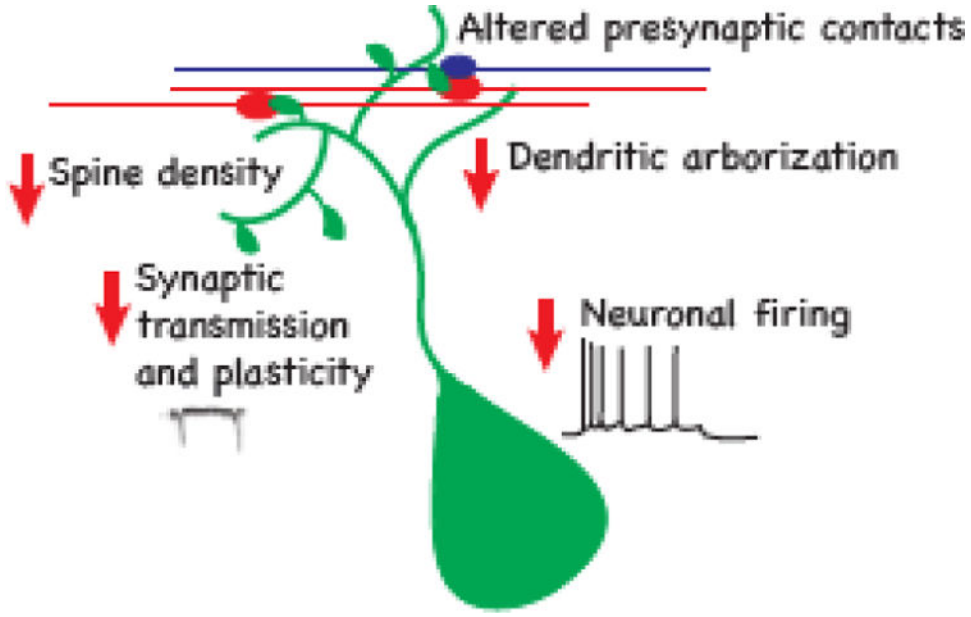

Figure 3: Structural and functional neuronal impairments in MIA offspring.

Reduced dendritic branching (Baharnoori *et al.*, 2009; Fernandez de Cossio *et al.*, 2017; Li *et al.*, 2014; Zhang and van Praag, 2015) and dendritic spine density have been observed in MIA (Coiro *et al.*, 2015). Altered innervation of dendritic spines was observed in the cortex and the cerebellum (Coiro *et al.*, 2015; Pendyala *et al.*, 2017). Impaired synaptic transmission, mainly in the form of reduced synaptic transmission (Canetta *et al.*, 2016; Coiro *et al.*, 2015; Ito *et al.*, 2010; Oh-Nishi *et al.*, 2010; Patrich *et al.*, 2016a; Shin Yim *et al.*, 2017; Zhang and van Praag, 2015) has been observed in the cortex and hippocampus. In addition to the synaptic impairments, neurons in the hippocampus have altered membrane properties that result in reduced excitability (Patrich *et al.*, 2016b).

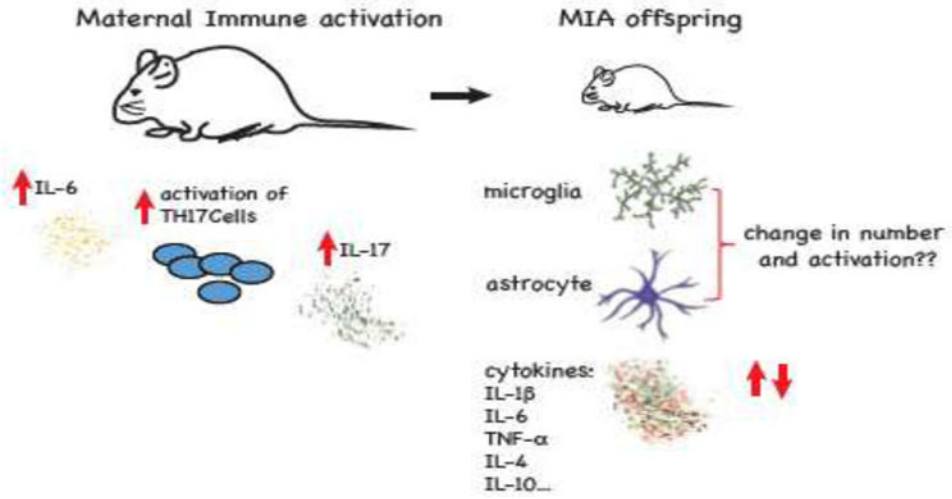

Figure 4: Maternal and MIA offspring immune changes.

Immunological response includes increase in pro-inflammatory cytokines IL-6 and IL-17 and activation of T_H17 cells. In addition to peripheral immune alterations, long lasting changes in the expression of multiple cytokines were observed in the brain of the MIA offspring.

Table 1:

Altered behaviors in MIA offspring

	P0–7	P8–21	P22–35	P36–60	>P60
Communication deficits	6	14, 21, 47, 63, 70	ND	ND	8, 47
Altered social behavior	ND	ND	Affiliation 80 Recognition 61, 80 Interaction 34, 58	Affiliation 80 Recognition 80 Interaction 82	Affiliation 2, 3, 8, 10, 14, 20, 21, 34, 37, 42, 47, 48, 58, 59, 61, 65, 70, 71 Recognition 21, 42, 58, 61, 65 Interaction 8, 33, 63
Stereotypic/repetitive behavior	ND	ND	ND	58, 63	8, 14, 15, 21, 36, 47, 70, 79
Impaired object recognition	ND	ND	24, 32	42	17, 24, 32, 40, 42, 48, 59, 62, 78
Impaired learning and memory	ND	ND	27, 38, 39	7	16, 27, 37, 45, 50, 56, 60, 61, 65, 68,74, 83
Altered latent inhibition	ND	ND	ND	42, 53	25, 26, 42, 50, 51, 53, 54, 71, 74, 83
Altered drug sensitivity	ND	ND	Amphetamine 55	ND	Amphetamine 12, 22, 26, 28, 50, 54–56, 83 Methamphetamine 62 MK-801 26, 28, 54–56
PPI deficits	ND	ND	ND	42, 69, 78	11, 23, 25, 26, 28, 29, 31, 32, 42, 44, 48–50, 54, 56, 59 62, 66, 67, 71, 73, 74, 77–79, 81
Depressive-like behavior	ND	ND	80	80	2, 5, 9, 10, 18, 57, 58, 64
Altered behavior in open field	ND	ND	78	42, 72, 78	35, 40–43, 72, 74, 75
Anxiety-like behavior	ND	ND	34, 78, 80	34, 78	2, 13, 18, 33, 50, 52, 54, 62, 68, 70, 71, 75
Impaired motor coordination	ND	ND	30	1, 30	1, 81
Altered food hoarding	ND	ND	ND	ND	27, 75

Other

P0–7: Reflex impairments [4]

Delayed acquisition of the forelimb grasp reflex [6]

P8–21: ↓ grip strength; ↓approaches toward maternal nest; impaired associative learning [6]

P36–60: ↑ risk assessment in elevated plus maze [42]

>P60: Faster acquisition of the delayed alternation task; impaired set shifting [13]

Impaired temporal perception [19]

↑ ethanol intake and preference [43]

Perseverative behavior [52]

↓ basal home cage activity [68]

Altered burrowing and food consumption; impaired balance [75]

↑ latency to initiate sexual behavior [76]

ND: not determined

References:

1- Aavani et al., 2015

2- Abazyan et al., 2010 (G)

3- Antonson et al., 2017

4- Arsenault et al., 2014

5- Babri et al., 2014

6- Baharnoori et al., 2010 (L)

7- Batinić et al., 2016

8- Bauman et al., 2014

9- Berger et al., 2018

10- Bitanihirwe et al., 2010a

11- Borrell et al., 2002 (L)

12- Buschert et al., 2016

13- Canetta et al., 2016

14- Choi et al., 2016

15- Coiro et al., 2015

16- Connor et al., 2012

17- Coyle et al., 2009 (L)

18- da Silveira et al., 2017

19- Deane et al., 2017

20- Ehninger et al., 2012 (G)

21- Fernández de Cossío et al., 2017 (L)

22- Fortier et al., 2004 (L)

23- Fortier et al., 2007 (L)

24- Fujita et al., 2016

25- Garay et al., 2013

26- Giovanoli et al., 2013 (S)

27- Giovanoli et al., 2015

28- Giovanoli et al., 2016a (S)

29- Giovanoli et al., 2016b (S)

30- Girard et al., 2009 (L)

31- Hadar et al., 2017

32- Han et al., 2016

33- Hava et al., 2006 (L)

34- Hsueh et al., 2018

35- Kirsten et al., 2010

36- Kirsten et al., 2017

37- Labouessee et al., 2015

38- Lanté et al., 2007 (L)

39- Lanté et al., 2008 (L)

40- Li et al., 2014

41- Ling et al., 2009 (L)

42- Lipina et al., 2013 (G)

43- Liu et al., 2004 (L)

44- Luan et al., 2018

45- MacDowell et al., 2017

46- Machado et al., 2015

47- Malkova et al., 2012

48- Mattei et al., 2017

49- Meehan et al., 2017

50- Meyer et al., 2005

51- Meyer et al., 2006a

52- Meyer et al., 2006b

53- Meyer et al., 2006c

54- Meyer et al., 2008a (G)

55- Meyer et al., 2008b

56- Meyer et al., 2008c

57- Missault et al., 2014

58- Morais et al., 2018

59- Mueller et al., 2018

60- Murray et al., 2017

61- O'Leary et al., 2014 (G)

62- Ozawa et al., 2006

63- Pendyala et al., 2017

64- Reisinger et al., 2016

65- Richetto et al., 2017a

66- Romero et al., 2007 (L)

67- Romero et al., 2010 (L)

68- Schaafsma et al., 2017 (L)

69- Shi et al., 2003

70- Shin Yim et al., 2017

71- Smith et al., 2007

72- Van den Eynde et al., 2014

73- Vuillermot et al., 2011 (G)

74- Vuillermot et al., 2012 (G)

75- Wang et al., 2010 (L)

76- Wijkstra et al., 1991 (L)

77- Wischhof et al., 2015a (L)

78- Wischhof et al., 2015b (L)

79- Wu et al., 2015

80- Wu et al., 2018 (L)

81- Zhang and van Praag, 2015

82- Zhu et al., 2014

83- Zuckerman et al., 2003

References noted with (L) *used LPS; all others used Poly (I:C) except* Arsenault et al., 2014 *which compared both immunogens.* (G) *indicates gene-environment interaction studies.* (S) *indicates MIA offspring were exposed to peripubertal stress.*

Table 2:

Alterations in neurotransmitter systems

Age	Alteration	Immunogen	Reference
<P0	↑ choline acetyltransferase (basal forebrain)	Poly (I:C)	Pratt et al., 2013
	↑ mGluR5 (whole brain)	Poly (I:C) or LPS	Arsenault et al., 2014
	↑ GABA; ↓ Glutamate (whole brain)	LPS	Batinić et al., 2017
P0–7	↓ 5HT1A and 5HT1B mRNA (frontal cortex)	LPS	Baharnoori et al., 2010
P8–21	↑ mGluR5 (right hemisphere)	Poly (I:C)	Arsenault et al., 2014
P22–35	↑ $GABA_A$ receptor α2 and α4 subunits mRNA (mPFC)	Poly (I:C)	Richetto et al., 2014
	↓ *Gria1, Gria2,* and *Slc17a7* mRNA (cortex); ↑ *Gria1, Gria2,* and *Slc17a7* mRNA (hippocampus)	Poly (I:C)	Tang et al., 2013
	↓ *Grin1, Grin2a, Grin2b* mRNA (hippocampus); ↓ GABA (frontal cortex)	Poly (I:C)	Fujita et al., 2016
	↓ DAT immunoreactivity (caudate putamen, nucleus accumbens)	Poly (I:C)	Vuillermot et al., 2010
	↓ D2R (PFC); ↓ DAT (nucleus accumbens core and shell)	LPS	Baharnoori et al., 2010
>P60	↓ $GABA_A$ receptor α2, α4, and α5 subunits mRNA, ↑ $GABA_A$ receptor α4 subunit mRNA (mPFC)	Poly (I:C)	Richetto et al., 2014
	↓ GAD67, parvalbumin (dorsal hippocampus)	Poly (I:C)	Luoni et al., 2017
	↓ *Gria1* mRNA (cortex and hippocampus);	Poly (I:C)	Tang et al., 2013
	↓ *Gria2* mRNA (striatum)		
	↓ EAAT3 expression	LPS	Kentner et al., 2016
	↑ NMDAR channels (cingulate cortex, striatum); ↑ NR2A (hippocampus, cortex, striatum); ↑ NR2A:NR2B ratio (hippocampus); ↑ *Grin1* mRNA (nucleus accumbens shell);↑ *Grin2a* mRNA (cortex, DG, CA1)	Poly (I:C)	Rahman et al., 2017
	↑ $GABA_A$ receptor α1 and α2 subunits mRNA (ventral hippocampus); ↑ α3 subunit mRNA (cortex)	Poly (I:C)	Richetto et al., 2015
	↑ dopamine (nucleus accumbens)	Poly (I:C)	Giovanoli et al., 2013
	↑ dopamine receptor 1 mRNA (hippocampus)	Poly (I:C)	Buschert et al., 2016
	↓ D1R and D2R immunoreactivity (mPFC); ↓ GluR1 immunoreactivity (nucleus accumbens shell)	Poly (I:C)	Meyer et al., 2008b
	↑ alpha 7 nicotinic acetylcholine receptor mRNA (hippocampus)	Poly (I:C)	Wu et al., 2015
	↑ Acetylcholine (striatum); ↑ glutamate (ventral hippocampus)	LPS	Batinić et al., 2017
	↑ D1R immunoreactivity (caudate putamen, nucleus accumbens shell); ↑ D2R immunoreactivity (nucleus accumbens shell)	Poly (I:C)	Vuillermot et al., 2010
	↑ dopamine (PFC, lateral globus pallidus); ↓ serotonin (nucleus accumbens, lateral globus pallidus, hippocampus)	Poly (I:C)	Winter et al., 2009
	↑ $5\text{-}HT_{2A}$ (males, PFC)	LPS	Wischhof et al., 2015a
	↑ Serotonin transporter (hippocampus)	Poly (I:C)	Reisinger et al., 2016
	↓ D1R immunoreactivity (mPFC); ↓ NR1 immunoreactivity (dorsal hippocampus); ↑ $GABA_A$ receptor α2 subunit immunoreactivity (ventral hippocampus)	Poly (I:C)	Meyer et al., 2008c
	↑ D1R mRNA (nucleus accumbens)	Poly (I:C)	Meehan et al., 2017
	↓ D2R expression (PFC)	LPS	Baharnoori et al., 2013

Age	Alteration	Immunogen	Reference
	↓ dopamine (striatum)	LPS	Kirsten et al., 2010

Abbreviations: 5HT: 5-hydroxytryptamine; D1R/D2R: dopamine receptor 1/2; DAT: dopamine transporter; EAAT: excitatory amino acid transporter

Table 3:

Alterations in maternal cytokines

Time after MIA	Alteration	Immunogen	Reference
1 hour	↑ IL-1β, IL-2, IL-4, IL-6, IL-10, IL- 15, IL-17A, IL-27p28, TNF-α, CXCL1, CXCL2, MCP-1[1]	1 or 5 mg/kg Poly (I:C), i.v.	Mueller et al., 2018
1.5 hours	↑ IL-10, IL-6, TNF-α (wild type); ↑ IL-10; ↓ IL-6, TNF-α (transgenic mice overexpressing IL-10 in macrophages, compared to wild type) [2]	2 mg/kg Poly (I:C), i.v.	Meyer et al., 2008a
2 hours	↑ IL-6, TNF-α [3]	0.05 mg/kg LPS, i.p.	Ashdown et al., 2006
	↑ IL-17a [3]	75 μg/kg LPS, i.p.	Wu et al., 2018
	↑ IL-6, IL-10, TNF-α (wild type); ↓ IL-6, IL-10, TNF-α (in *Nurr1* heterozygous mice compared to wild type) [2]	2 mg/kg Poly (I:C), i.v.	Vuillermot et al., 2012
3 hours	↑ IL-1β, IL-6, IL-10, TNF-α [2]	5 mg/kg Poly (I:C), i.v.	Meyer et al., 2006b
	↑ IL-6, TNF-α [3]	5 mg/kg Poly (I:C), i.v.	Connor et al., 2012
	↑ IL-1β, TNF-α [4]	4 mg/kg Poly (I:C), i.v.	Ballendine et al., 2015
	↑ IL-1β, IL-4, IL-6, TNF-α [1]	5 mg/kg Poly (I:C), i.v.	Giovanoli et al., 2015
	↑ IFN-β, IL-1β, IL-6, TNF-α [3]	20 mg/kg Poly (I:C), i.p.	Choi et al., 2016
	↑ Eotaxin, IL-6, IL-10, IL-12p40, IL-17, MCP-1, RANTES, TNF-α [4]	20 mg/kg Poly (I:C), i.p.	Money et al., 2017
	↑ TNF-α [3]	0.25, 0.1, and 0.05 mg/kg LPS, i.p. (consecutive days)	Schaafsma et al., 2017
	↑ IL-1β, IL-6 [3]	0.05 mg/kg LPS, i.p.	Ashdown et al., 2006
4 hours	↑ IL-6, IL-10, TNF-α [2]	1 mg/kg Poly (I:C), i.v.	Giovanoli et al., 2013
	↑ IL-10, IL-6, TNF-α (wild type); ↑ IL-10; ↓ IL-6, TNF-α (transgenic mice overexpressing IL-10 in macrophages, compared to wild type) [2]	2 mg/kg Poly (I:C), i.v.	Meyer et al., 2008a
5 hours	↑ IL-10/TNF-α ratio [2]	5 mg/kg Poly (I:C), i.v.	Meyer et al., 2006a
6 hours	↑ IL-6, IL-10 [2]	5 mg/kg Poly (I:C), i.v.	Meyer et al., 2006b
	↑ IL-1β [5], TNF-α [3,5]	4 mg/kg Poly (I:C), s.c.	Missault et al., 2014
	↑ IL-1β, IL-2, IL-6, IL-10, IL-15, IL- 17A, IL-27p28, TNF-α, CXCL1, CXCL2, MCP-1; ↑/↓ IL-4 (depending on caging conditions) [1]	1 or 5 mg/kg Poly (I:C), i.v.	Mueller et al., 2018
	↑ IFN-β, IL-1β, IL-17a, TNF-α [3]	20 mg/kg Poly (I:C), i.p.	Choi et al., 2016
>24 hours	↑ IL-6 (24 hours; no difference at 48 hours) [6]	2 mg/kg Poly (I:C), i.p.	Goeden et al., 2016

Superscripts indicate methods used to measure cytokines:

[1] V-Plex electrochemiluminescence assay

[2] Multiplexed particle-based flow cytometry assay

(3) Enzyme-linked immunosorbent assay

(4) Bead- based multiplex assay

(5) qPCR

(6) Cytometric bead array

For the studies in this table, the immunogen was administered via either intraperitoneal (i.p.), intravenous (i.v.) or subcutaneous (s.c.) injection.

Table 4:

Alterations in peripheral cytokines in MIA offspring

Age	Alteration	Immunogen	Reference
P0–7	↑ G-CSF, IFNγ, IL-1β, IL-3, IL-6, IL-12(p40), TNF-α; ↓ GM-CSF, IL-1α, IL- 2, IL-3, IL-12(p70) [1]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
P8–21	↑ TNF-α [1]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
	↑ IL-2, IL-5, IL-6 [2]	5 mg/kg Poly (I:C), i.v. (3 consecutive days)	Arsenault et al., 2014
P22–35	↑ IL-1β, IL-6, IL-9; Decreased IL-3 [1]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
	↓ IL-6, TNF-α [3]	5 mg/kg Poly (I:C), i.v.	Pacheco-López et al., 2011
	↑ IL-1β, IL-6 [4]	25, 25, and 50 μg/kg LPS on 3 consecutive days	Hsueh et al., 2018
P36–60	↑ IL-1β, IL-6, IL-10 [4]	25, 25, and 50 μg/kg LPS on 3 consecutive days	Hsueh et al., 2018
>P60	↓ IFN-γ, IL-2 [3]	5 mg/kg Poly (I:C), i.v.	Pacheco-López et al., 2011
	↑ CCL2, G-CSF, IFNγ, IL-2, IL-6, IL- 13, TNF-α [1]	3 doses of 0.25 mg/kg Poly I:C-LC, i.v.	Rose et al., 2017
	↑ IL-6, IL-17 released by splenic CD4+ T cells upon stimulation [2]	20 mg/kg Poly (I:C), i.p.	Hsiao et al., 2012

Abbreviations: CCL: chemokine (C-C motif) ligand; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon

Superscripts indicate methods used to measure cytokines:

[1] Bead-based multiplex assay

[2] Enzyme- linked immunosorbent assay

[3] Multiplexed particle-based flow cytometry assay

[4] Cytometric bead array

For the studies in this table, the immunogen was administered via either intraperitoneal (i.p.) or intravenous (i.v.) injection.

Table 5:

Alterations in brain cytokines during development of MIA offspring

Age	Alteration	Immunogen	References
<P0	↑ IL-1β and TNF-α mRNA (whole brain) [1]	500 μg/kg LPS, i.p. on 2 consecutive days	Cai et al., 2000
	↓ Fas ligand, fractalkine, IL-3, IL-4, IL-5, lympotactin, M-CSF, MIG, MIP-1α, TARC, TECK, TNF-α,VCAM-1 (whole brain) [2]	20 mg/kg Poly (I:C), i.p.	Ehninger, 2014
	↑ TNF-α (whole brain) [3]	5 mg/kg Poly (I:C), i.v. or 120 μg/kg LPS, i.p. (3 consecutive days)	Arsenault et al., 2014
	↑ *Il-6* mRNA (whole brain) [4]	20 mg/kg Poly (I:C), i.p.	Wu et al., 2015
	↑ *Il6* mRNA (whole brain) [4]; ↑ IL-4, IL-6, IP-10 (whole brain, IL-6$^{+/-}$ offspring, WT mother) [5]	20 mg/kg Poly (I:C), i.p.	Wu et al., 2017
	↑ IL-1β, IL-6, TNF-α, IL-10 mRNA (whole brain) [4]	50 μg/kg LPS, i.p.	O'Loughlin et al., 2017
P0–7	↑ IL-1β (P1); ↓ TNF-α (P7) mRNA (whole brain) [4]	300 μg/kg LPS, i.p. (2 consecutive days)	Rousset et al., 2006
	↑ GM-CSF, G-CSF, IL-1β, IL-10, IL- 12(p70); ↓ IL-2, IL-4, IL-5, IL-10, IL-12(p40) (frontal cortex); ↑ IFNγ, IL-12(p70), IL-17; ↓ IL-2, IL-5, IL-6, IL-10 (cingulate cortex); ↑ IL-6, IL-9; ↓ IL-1β, IL-2, IL-3, IL-4, IL-5, IL-10 (hippocampus) [5]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
	↑ FasL, IL-2, IL-3, IL-6; ↓ Eotaxin-2 (cerebellum) [2]	20 mg/kg Poly (I:C), i.p.	Pendyala et al., 2017
	↑ IL-1β mRNA (amygdala) [4]	50 μg/kg LPS, i.p.	O'Loughlin et al., 2017
	↓ GM-CSF, IFNγ, IL-1α, IL-1β, IL-2, IL-5, IL-9, IL-10, IL-13 (frontal cortex); ↓ GM- CSF, IFNγ, IL-1β, IL-10, IL-17 (cingulate cortex); ↑ IL-1α, IL-6; ↓ IL-2, IL-5, IL-9 (hippocampus) [5]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
P8–21	↑ MIP-1γ; ↓ ICAM-1, IL-10 [2]; ↑ TNF-α [2,3] (cerebellum)	20 mg/kg Poly (I:C), i.p.	Pendyala et al., 2017
	↓ G-CSF, GM-CSF, IL-1β, IL-3, IL-5, IL- 6, IL-10, IL-12(p40), IL-12(P70) (frontal cortex); ↓ G-CSF, IL-1β, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12(p40), IL-12(p70), IL-17 (cingulate cortex); ↓ IL-6 (hippocampus) [5]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
P22–35	↑ MIP-1γ; ↓ IFNγ, IL-17 (cerebellum) [2]	20 mg/kg Poly (I:C), i.p.	Pendyala et al., 2017
	↑ IL-1α, IL-6, IL-9, IL-10 (frontal cortex); ↑ IFNγ, IL-10 (cingulate cortex) [5]	20 mg/kg Poly (I:C), i.p.	Garay et al., 2013
>P60	Increased IL-1β (hippocampus) [6]	5 mg/kg Poly (I:C), i.v.	Giovanoli et al., 2016b

Abbreviations: FasL: fas ligand; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte- macrophage colony-stimulating factor; IFN: interferon; M-CSF: macrophage colony-stimulating factor; MIG: monokine induced by interferon-gamma; MIP: macrophage inflammatory protein; TARC: thymus and activation-regulated chemokine; TECK: thymus expressed chemokine; VCAM: vascular cell adhesion molecule

Superscripts indicate methods used to measure cytokines:

[1] RT-PCR

[2] Cytokine antibody array

[3] Western blot

(4) qRT-PCR

(5) Bead-based multiplex assay

(6) Meso-Scale Discovery V-Plex electrochemiluminescence assay

For the studies in this table, the immunogen was administered via either intraperitoneal (i.p.) or intravenous (i.v.) injection.