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Maternal immune activation and autism spectrum disorder: From rodents to nonhuman and human primates

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Abstract

A subset of women who are exposed to infection during pregnancy have an increased risk of giving birth to a child who will later be diagnosed with a neurodevelopmental or neuropsychiatric disorder. Although epidemiology studies have primarily focused on the association between maternal infection and an increased risk of offspring schizophrenia (SZ), mounting evidence indicates that maternal infection may also increase the risk of autism spectrum disorder (ASD). A number of factors, including genetic susceptibility, the intensity and timing of the infection, and exposure to additional aversive postnatal events, may influence the extent to which maternal infection alters fetal brain development and which disease phenotype (ASD; SZ; other neurodevelopmental disorders) is expressed. Preclinical animal models provide a test bed to systematically evaluate the effects of maternal infection on fetal brain development, determine the relevance to human CNS disorders, and to evaluate novel preventative and therapeutic strategies. Maternal immune activation (MIA) models in mice, rats, and nonhuman primates suggest that the maternal immune response is the critical link between exposure to infection during pregnancy and subsequent changes in brain and behavioral development of offspring. However, differences in the type, severity, and timing of prenatal immune challenge paired with inconsistencies in behavioral phenotyping approaches have hindered the translation of preclinical results to human studies. Here we highlight the promises and limitations of the MIA model as a preclinical tool to study prenatal risk factors for ASD, and suggest specific changes to improve reproducibility and maximize translational potential.

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Prenatal Immune Challenge in Humans

Autism spectrum disorder (ASD) is a heterogeneous collection of neurodevelopmental disorders characterized by early onset deficits in social behavior and communication, paired with repetitive behaviors and restricted interests (1). Although underlying genetic and environmental cause(s) remain unknown for most ASD cases, recent evidence suggests that the prenatal immune environment may be a particularly promising area of ASD etiology research (2-4). This interest stems in part from our growing appreciation that immune signaling molecules play a key role in all stages of fetal brain development (5, 6). Experiences that alter the maternal-fetal immune environment, such as exposure to infection during pregnancy, may disrupt the finely orchestrated events of neural development and increase the risk of offspring central nervous system (CNS) disorders (7, 8). Although ASD is among the CNS disorders associated with prenatal exposure to infection, the field is not without controversy (9-13). Initial evidence was based primarily on case studies of ASD following prenatal exposure to infectious agents, such as rubella or cytolomegalovirus (14-19). More recently, epidemiological studies have reported increased risk of ASD associated with maternal infection during pregnancy, though results vary depending on gestational timing of the exposure, type of infectious agent and intensity of the maternal immune response. For example, an exploratory population-based sample of all children born in Denmark from 1980 through 2005 found no overall association between maternal infection diagnosis and ASD over the course of the entire pregnancy, but did report a nearly threefold increased risk for ASD following hospitalization for viral infection in the first trimester as well as an increased risk following hospitalization for bacterial infections in the second trimester (20). Self-report data obtained from a subset of the Denmark population study also failed to detect an association between common infections during pregnancy and an increased risk of ASD (21), though influenza exposure was specifically associated with a nearly twofold risk of ASD and febrile episodes greater than one week were associated with a nearly threefold increase. A study from Kaiser Permanente Northern California found that fever during pregnancy, particularly fever experienced without taking anti-fever medication, was associated with an increased risk of ASD, though overall experiences of maternal influenza exposure were not associated with an increased risk in this study (22). A subsequent study found that maternal infections diagnosed in a hospital setting, presumably associated with more severe infections, were associated with an increased risk of ASD, while infections diagnosed in outpatient settings were not associated ASD (23). Quantification of cytokines, chemokines and other inflammatory markers obtained from archived maternal sera (24, 25) and amniotic fluid (26, 27) lends further support to the link between maternal infection and increased ASD risk, though studies have yielded mixed results (28, 29). Although there is a clear need for additional epidemiological studies, the current data suggest that, at least for a subset of women, exposure to infection during pregnancy may increase the risk of ASD or other CNS disorders (30, 31).

Modeling Prenatal Immune Challenge in Animals

The diversity of infectious agents associated with an increased risk of CNS disorders suggests that the maternal immune response may be the common link between prenatal immune challenge and altered fetal brain development. This *maternal immune activation* (MIA) hypothesis has been tested in animal models by activating the immune system during pregnancy using a variety of immunogens and then observing changes in offspring brain and behavioral development that parallel features of human CNS disorders (for reviews, (32-35). Here we focus specifically on MIA models utilizing the immune activating agent, polyinosinic-polycytidylic acid (PolyIC), a double stranded RNA molecule that stimulates an immune response through activation of tolllike receptor TLR-3 (36). In the past decade, a number of laboratories have adopted the PolyIC model as means of activating the maternal immune response in a controlled and temporally restricted manner (37). However, many questions remain regarding the link between prenatal immune challenge and disease-specific outcomes associated with ASD, SZ or other CNS disorders (34). In some MIA models, the brain and behavior phenotypes of the offspring have been interpreted as being highly relevant to SZ, while others have focused on the relevance of the model to ASD. The emerging consensus among leaders in the field is that prenatal infection may be relevant to a number of CNS diseases and restricting interpretation to a specific human disorder may limit the utility and relevance of the MIA model (38, 39). Rather, prenatal immune challenge may serve as a “disease primer” into an altered trajectory of fetal brain development that, in combination with other genetic and environmental factors, may ultimately result in the emergence of ASD, SZ, or other CNS disorders (40). Here we evaluate the validity of the MIA model within the context of ASD, but readily acknowledge that the prenatal immune challenge model is likely relevant to a number of neurodevelopmental and neuropsychiatric diseases.

Assessing Validity of the MIA Model

Developing valid animal models to study complex human brain diseases, such as ASD, poses a major challenge to preclinical research efforts (41-43). Historically, the validity of animal models has been determined by: *(i) Construct validity* - etiological relevance of the model to human disease(s), *(ii) Face validity* -resemblance of outcome measures of the model to features of the human disease and *(iii) Predictive validity* -response of the model to therapeutic agents used to treat the human disease (44). A valid animal model of ASD is expected to stem from an etiologically relevant experimental paradigm and produce an animal that exhibits species-specific changes in behavior related to core features of ASD, such as early onset deficits in social behavior and communication, repetitive behaviors or restricted interests (45). Here we apply standard assessments of validity to evaluate the MIA model as a preclinical tool to study ASD, but first acknowledge changes underway as a result of the NIH led Research Domain Criteria (RDoC) initiative. RDoC provides a novel framework for psychiatric disorder research that utilizes a dimensional classification based on genes, neural circuits and behavioral constructs rather than traditional DSM criteria (46). Although there is tremendous potential for RDoC to improve translation of basic and clinical neurodevelopmental disorder research (47), we are still in the earliest stages of applying RDoC approaches (48, 49). Rather than evaluating the validity of the MIA model from an

RDoC perspective, we will instead highlight features of RDoC that we can integrate into our interpretation of preclinical models.

Cross-species comparisons, for example, allow preclinical researchers to compare the effects of prenatal immune challenge on evolutionarily conserved behavioral and biological outcome measures (50, 51). The PolyIC MIA model has attracted investigators with expertise in mouse, rat and nonhuman primate models, which in turn, has allowed the field to capitalize on the unique advantages of each species. Mice have been a favored species in biomedical research for years, in part due to their relative low cost and unparalleled genetic manipulations. Mouse models have laid the foundation for understanding the effects of MIA on fetal brain development and will undoubtedly continue to be an important species in MIA research, especially in models that incorporate genetic susceptibility. There are, however, limitations in relying on a single species to study complex human brain disorders, such as ASD. Rat models offer many of the advantages of mouse models in terms of cost, short gestational period, and the potential for genetic modifications, but also have more complex brains and display an enriched repertoire of social behavior (52). Given that impairments in social cognition are features of both ASD and SZ (53), the field of MIA research may benefit from species that allow for a more sophisticated evaluation of reciprocal social interactions. Rhesus monkeys live in large social hierarchies and communicate with a variety of social signals, including vocalizations, facial expressions and body postures (54). Brain regions underlying these complex behaviors show similar patterns of activity in humans and nonhuman primates (55), but are less well developed in rodents (56). Although the nonhuman primate model may provide a bridge from rodent models to human disease (57), the increased costs and ethical considerations constrain the use of nonhuman primates in research. Below we apply cross-species comparisons to evaluate the validity of the PolyIC MIA model as a preclinical tool to study ASD etiology, highlighting the unique contributions of mice, rat and nonhuman primate models.

(i) Construct Validity

The MIA model demonstrates high construct validity as prenatal exposure to infection has been implicated in the etiology of ASD (30). It is, however, important to recognize that the MIA model evaluates a single environmental risk factor while ASD likely results from a complex interplay of genetic and environmental factors. Single risk factor models are thus expected to produce a circumscribed series of brain and behavioral alterations, rather than the full symptomatology of complex human CNS disorders, such ASD. This limitation is important to bear in mind when interpreting the face validity of the MIA (or any other single hit) models of human disease and is entirely consistent with newly defined RDoC approaches to preclinical research.

(ii) Face Validity

MIA offspring demonstrate impairments in behavior that have been interpreted as relevant to both SZ and ASD (34). This overlap in the MIA animal model is perhaps not surprising, given that ASD and SZ may have common prenatal origins as well as overlapping symptomatology (39). However, preclinical MIA model researchers with an interest in SZ will often utilize behavioral phenotyping tools that target the core features of SZ, while

researchers interested in ASD may focus on core features of ASD. In the future, RDoc-inspired MIA models may provide a solution to this problem by focusing on a specific clinical behaviors and the underlying neurobiology rather than attempting to model a disease-specific constellation of symptoms. There is also a need to evaluate the developmental trajectory of the model to understand how MIA impacts the developing brain, which neural circuits are altered, and how behavioral pathology emerges over time. However, the majority of PolyIC challenge models report behavioral deficits that emerge after puberty, a time line more consistent with the diagnostic window of early adulthood for SZ, rather than early childhood for ASD. Early developmental periods have not been well characterized in MIA models, especially in the realm of social development. Thus it is not clear if MIA models have failed to yield consistent ASD-relevant impairments, or if the ASD-relevant behaviors and early developmental time points have not been thoroughly evaluated. Here we will focus specifically on interpreting the face validity of PolyIC MIA models that have yielded offspring with phenotypes relevant to the core features of ASD: (i) Social interactions and communication, (ii) Repetitive behaviors/restricted interests (Table 1). The reader is referred to a series of comprehensive MIA model reviews for a broader summary of associated ASD symptoms, such as anxiety, intellectual disability, sensory processing deficits, and seizures (32-35).

Given that impaired social functioning is the defining feature of ASD, we would expect a valid animal model to exhibit deficits in species-typical social interactions and communication. However, manifestation of social challenges varies greatly among individuals with ASD (58), and will require sophisticated behavioral phenotyping tools to evaluate in preclinical models (59). Unfortunately, characterization of social communication and interaction in most MIA models has been limited to simplistic, high-throughput approaches that may not capture the complexity of species-typical social development. For example, although several MIA models report changes in rodent pup isolation ultrasonic vocalizations (USVs) (60-63), the communicative function of these early distress calls is not clear. Later assessments of social behavior in MIA mouse offspring have relied heavily upon on simplistic, automated tools, such as the three-chamber social approach test to quantify sociability as indexed by a preference for a social versus a nonsocial stimulus (64). Several laboratories have now reported that mice exposed to PolyIC challenge during gestation fail to demonstrate species typical preferences for the social stimulus when evaluated in adolescence or adulthood (60, 62, 63, 65-72), though deficits may be strain specific (61). Only a small number of studies have evaluated the effects of MIA on complex, reciprocal social interactions. Given that MIA offspring show preliminary evidence of impaired social communication (62, 63) reciprocal interactions (73), these data suggest that additional studies utilizing a more comprehensive social development battery (45) are warranted.

The enhanced social repertoire and strain specific differences of the rat model (74) may provide a test bed to evaluate the effects of MIA on social development, though early social interactions have not been thoroughly characterized in the rat MIA model (75). Preliminary evidence also suggests that the nonhuman primate may provide a valuable tool to bridge the gap between rodent models and patient populations. For example, juvenile monkeys exposed to PolyIC at the end of the first or second trimester produce fewer “coo calls” (76), an affiliative vocalization that parallels features of human speech (77). The first-trimester MIA

exposed monkey offspring also deviated from species-typical social behavior by inappropriately approaching an unfamiliar animal, perhaps due to impairments in social processing later observed in a non-invasive eye tracking paradigm (78). The atypical social processing in the nonhuman primate MIA model parallels results from eye tracking studies in both ASD and SZ patient populations (79, 80), thus extending the results of rodent MIA models to more human-like behaviors amenable to RDoC interpretation.

In addition to deficits in social behavior, individuals with ASD also exhibit restricted, repetitive patterns of behavior, interests, or activities that can be modeled in animals (81). Mice prenatally exposed to PolyIC exhibit high levels of repetitive behaviors in marble burying and self-grooming tests (60-63, 68). Likewise, monkeys prenatally exposed to PolyIC at the end of the first or second trimester produce motor stereotypies and/or self-directed behaviors more frequently than controls (76). Higher order behavioral inflexibility can also be assayed in animal models with tasks, such as reversal learning paradigms, that require animals to modify their behaviors to adapt to changed conditions. PolyIC immune challenge models have yielded inconsistent results in this domain. Mice prenatally exposed to PolyIC at mid-gestation exhibited a slight trend towards enhanced reversal learning (82, 83), while mice with later exposure exhibited slower reversal learning (83). Mid to late gestational exposure to PolyIC in rats was found to induce deficits in reversal learning without affecting spatial acquisition (84), though other studies have reported inconsistent results (85, 86). Further investigation from a standardized cross-species battery of tests is needed to understand the impact of prenatal immune challenge on restricted interests and repetitive behaviors.

Animal models also provide an opportunity to improve translation between preclinical and clinical research efforts by identifying neural circuits associated with behavioral phenotypes through *in vivo* neuroimaging and postmortem histological studies (87). Although ASD lacks a unifying neuropathological signature, several hallmark features of the disorder have been documented in the MIA model (88, 89). For example, mice offspring born to dams injected with PolyIC demonstrate a spatially localized deficit in Purkinje cells (69, 90), which has been described in postmortem ASD tissue (91). Similarly, MIA exposed mice also demonstrate impaired expression parvalbumin and reelin (83, 92, 93), cellular markers expressed by distinct GABAergic interneuron populations that are also implicated in ASD neuropathology (94). Excessive microglial activation has been reported in a subset of postmortem ASD cases, though these findings may not be reflective of the majority of individuals with ASD (95-99). Microglia data generated from MIA models have also been inconsistent. Preliminary studies in rodents provided evidence of microglial activation following prenatal PolyIC challenge (73, 100, 101), though subsequent studies have failed to replicate these results (102-107). The MIA model does, however, produce long-lasting changes in brain cytokines (102, 108), consistent with reports of neuroinflammation in ASD. Preliminary evaluation of brain pathology in the nonhuman model indicates that prenatal immune challenge also impacts dendritic morphology in the dorsolateral prefrontal cortex (109). Although longitudinal neuroimaging data have yielded a wealth of information in rodent MIA models (35), these studies have not been carried out in the nonhuman primate model.

(iii) Predictive Validity

Predictive validity addresses the specificity of the animal model to treatments that are effective in the human disease (i.e., treatments that ameliorate the human symptoms should also reverse pathological features in the animal model). Antipsychotic drug administration delivered to immature MIA exposed rodent offspring attenuates the emergence of brain and behavioral abnormalities associated with SZ (110-112), though similar studies in humans have yielded mixed results (113). The MIA model may prove to be a valuable test-bed for novel therapeutic interventions targeting the core symptoms of ASD. For example, MIA mouse offspring treated with antipurinergic therapy (APT) (69, 70) or the gut bacterium *Bacteroides fragilis* (62) exhibit improved behavioral outcomes. Future studies are needed to explore emerging clinical (114) and preclinical (68, 73, 115) treatments targeting the immune system as a promising area of research for ASD drug discovery efforts.

Promises and Limitations of the MIA Model

Differences in the type, severity, and timing of prenatal immune challenge likely contribute to the outcomes of the MIA model in ways we are just beginning to understand (116, 117). Given that preclinical research is under increasing pressure to improve reproducibility (118, 119), the MIA model will undoubtedly benefit from renewed interest in refining experimental design standards (120). However, MIA models are also faced with a series of unique challenges that can be broken down into three major areas: *(i) Lack of paradigm consensus* – PolyIC induced MIA models utilize an array of approaches that vary in dose, route of administration, number of injections and gestational timing, resulting in dramatically different maternal cytokines profiles (83). Doses of PolyIC in rodent MIA models typically range from 1mg/kg to 20mg/kg, which can result in a range of maternal immune response properties and subsequent brain and behavioral outcomes in the offspring (82, 105, 121). Although higher doses of PolyIC are associated with more pronounced behavioral deficits (as well as litter loss) (82, 121, 122), recent evidence indicates that even low doses of PolyIC can induce long-lasting changes in brain development (123). . Methodological variability in the PolyIC model undoubtedly contributes to inconsistent results and has made it increasingly challenging to replicate outcomes, compare across studies and establish standard protocol guidelines. Perhaps more concerning, the lack of a consistent PolyIC challenge paradigm may have masked fundamental problems with the actual immune activating agents. *ii) Inconsistencies in immune-activating reagents* – Despite the fact that PolyIC is a synthetic analog used to activate the maternal immune response in a controlled and temporally restricted manner, variations in production standards can have significant effects on its ability to drive an immune response. PolyIC consists of a chain of double stranded inosine (I) and cytidine (C) which can vary in length/molecular weight and demonstrate different immune activating properties in *ex vivo* paradigms (124, 125). Recent *in vivo* evaluation of PolyIC in a rat model confirms that the same dosage of high-molecular-weight PolyIC can elicit a cytokine response nearly a magnitude in degree higher when compared with low-molecular-weight PolyIC (126). Given that the molecular weight of PolyIC is not reported by most vendors, and that the composition and preparation instructions can differ substantially from vendor to vendor, as well as between batches from the same vendors, different lots of PolyIC likely have dramatically different immunological properties (127). The need to establish consistent immune stimulation agents is of

paramount importance for the field. *(iii) Lack of maternal cytokine data* – These first two issues can be addressed, in part, by quantifying and reporting cytokine data from the pregnant dams as an index of which cytokines are driving the deleterious effects on brain development. Unfortunately, relatively few PolyIC challenge models measure or report dam cytokine data (128-132) (Table 2), and those that do often focus exclusively on a single cytokine, such as IL-6. Although IL-6 plays a critical role in the MIA model (72), it is unlikely that any single cytokine on its own is responsible for the deficits observed in MIA (105). For example, a recent study highlights the role of IL-17, which is upregulated by IL-6, and may be a major contributor to pathology in the MIA model (60). This could be an important piece of the MIA puzzle and may help to explain some of the variance between studies, as IL-17 producing cells varies greatly between mouse colonies (133). Reinstating the use of dose response trials implemented by early PolyIC based MIA models (82, 121), reporting litter size/loss, and carrying out comprehensive evaluations of the maternal immune response will improve reproducibility efforts and provide insight into the mechanism by which prenatal immune challenge impacts fetal development.

In spite of these challenges, the MIA model provides an opportunity to systematically evaluate the effects of prenatal immune challenge in a controlled environment, exploring questions that cannot be examined in human studies. Recent MIA models have begun to identify the molecular mechanisms linking MIA, placental dysfunction and abnormal fetal development (123) and to compare the consequences of immune challenge at specific gestational time points (134). Adult mice exposed to PolyIC challenge at mid gestation (GD 9) demonstrate deficits in the latent inhibition effects of associative learning, suppressed spatial exploration and impairments in sensorimotor gating, while PolyIC challenge later in gestation (GD 17) has a more restricted effect on behavior (83, 93, 130). Although MIA rat models comparing gestational timing have yielded mixed results (86, 116), the first nonhuman primate PolyIC model also indicates that early gestational exposure yields offspring with more pronounced behavioral impairments (76). It is, however, important to note that extrapolating gestational timing across species is not always straightforward, as the gestational period of rhesus monkeys (165 days) and humans (280 days) is much longer than that of mice/rats (18-23 days) (135). For example, first trimester prenatal immune challenge in primates coincides with massive neuron generation and extensive periods of cell migration and axon growth, which in the rodent occurs mostly in the third trimester and early postnatally (136, 137). Determining which neurodevelopmental processes are most vulnerable to prenatal immune challenge and how gestational timing may impact specific neural circuits and behaviors is one of the most important areas for future research in this field.

One of the most promising recent developments in the MIA model is the potential to combine prenatal immune challenge with other etiologically relevant risk factors. MIA combined with mutations in SZ (66, 138) or ASD (139, 140) relevant genes exacerbates aspects of the MIA mouse offspring behavioral phenotype. Likewise, exposure to aversive postnatal events, including maternal care by a surrogate mother exposed to an immune challenge during gestation (141-143) or exposure to juvenile stress (144), also exacerbate outcome measures of the mouse MIA model. Although the additive effects of postnatal stress has not been thoroughly explored in other species (145), the intriguing results from the

mouse studies suggest that the cumulative impacts of prenatal immune challenge and aversive postnatal stressors may provide insight into populations vulnerable to neurodevelopmental and neuropsychiatric disease. The challenge for the next generation of MIA models, is to integrate multiple etiologically relevant “hits” while improving the overall reproducibility of the model.

Future Directions

Given the heterogeneity of symptoms and complex etiology of ASD, it is not surprising that preclinical researchers have struggled to establish valid animal models (146). Although we would not expect a single-hit model to recapitulate the entire spectrum of brain and behavioral changes characteristic of ASD, here we provide evidence that prenatal immune challenge results in impairments to core features of ASD. We have also provided specific suggestions to improve the model, highlighting the need for (i) consistent MIA paradigms, (ii) standardization of immune activating agents, (iii) quantification and reporting of maternal cytokine data, (iv) expanding behavioral phenotyping tools to include a broad range of assessments throughout development and (iv) integrating longitudinal neuroimaging and postmortem pathology. With these changes, the MIA model may help us to understand which pregnancies are most vulnerable to prenatal immune challenge, which gestational time points are most sensitive, how to safely manage the maternal immune response during pregnancy to prevent deleterious effects on fetal brain development.

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Table 1

ASD Relevant Behaviors on MIA Models

Author Year *(Reference)*	Species Strain Sex	PolyIC Protocol	Three Chamber Social Approach	Reciprocal Social Interaction	Other Social (USV, eye tracking etc.)	Repetitive Behaviors	Restricted interests/Cognitive inflexibility
Aavani et al. 2015 (65)	Mice C57BL/6 Both	20mg/kg, i.p. on GD13-15	Decreased sociability (PND40) No change (PND120)	ND	ND	ND	ND
Abazyan et al. 2010 (66)	Mice mhDISC1 Males	5.0mg/kg, i.v. on GD9	Decreased sociability	ND	ND	ND	ND
Bitanihirwe et al. 2010 (67)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD17	Decreased sociability	ND	ND	ND	ND
Choi et al. 2016 (60)	Mice Roc(t)FL C57BL/6 Males (Both for USV)	20mg/kg, i.p. on GD12.5	Decreased sociability	ND	Increased calls (pups)	Increased marble-burying	ND
Hsiao et al. 2012 (68)	Mice C57BL6/J Both	20mg/kg, i.p. on GD12.5	Decreased sociability	ND	ND	Increased marble-burying	ND
Hsiao et al. 2013 (62)	Mice C57BL/6N Both	20mg/kg, i.p. on GD12.5	Decreased sociability and social preference	ND	Decreased calls (adults)	Increased marble-burying	ND
Malkova et al. 2012 (63)	Mice C57BL6/J Both	5.0mg/kg, i.p. on GD10.5, 12.5 and 14.5	Decreased sociability	ND	Decreased calls (pups and adults)	Increased marble-burying Increased self-grooming	ND
Meyer et al. 2005 (82)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD9	ND	ND	ND	ND	Enhanced tendency on reversal learning
Meyer et al. 2006 (83)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD9 or 17	ND	ND	ND	ND	No change (GD9) Slowed reversal learning (GD17)
Naviaux et al. 2013 (69)	Mice C57BL6/J Both	3mg/kg on GD 12.5 and 1.5mg/kg on GD 17.5, i.p	Decreased sociability (Deficit more pronounced in males)	ND	ND	ND	ND
Naviaux et al. 2014 (70)	Mice C57BL6/J Males	3mg/kg on GD 12.5 and 1.5mg/kg on GD 17.5, i.p.	Decreased sociability	ND	ND	ND	ND
Pineda et al. 2013 (71)	Mice C57BL6/J Both	2.5mg/kg, i.p. on GD12-16	Decreased sociability	ND	ND	ND	ND
Schwartzer et al. 2013 (61)	Mice C57BL6/J BTBR Both	20mg/kg, i.p. on GD12.5	Decreased sociability	ND	Increased calls (pups)	Increased marble-burying	ND
Smith et al. 2007 (72)	Mice C57BL6/J Both	20mg/kg, i.p. on GD12.5	Decreased sociability	ND	ND	ND	ND
Zhu et al. 2014 (73)	Mice C57BL/6 Both	20mg/kg, i.p. on GD9	ND	Decreased interaction	ND	ND	ND
Han et al. 2011 (84)	Rats Sprague-Dawley Males	0.5mg/kg, i.p. on GD15-18	ND	ND	ND	ND	Slowed reversal learning
Wolff et al. 2011 (85)	Rats Sprague-Dawley Males	4.0mg/kg, i.v. on GD15	ND	ND	ND	ND	Enhanced reversal learning
Yee et al. 2012 (75)	Rats Sprague-Dawley Males	4.0mg/kg, i.v. on GD15	ND	ND	Increased calls (22-kHz) No change (50-kHz/Audible)	ND	ND
Zuckerman et al. 2005 (86)	Rats Sprague-Dawley Males	4.0mg/kg, i.v. on GD15	ND	ND	ND	ND	Enhanced reversal learning
Bauman et al. 2014 (76) Machado et al. 2015 (78)	Rhesus macaque Both	Early/Mid 0.25mg/kg, i.v., GD43, 44, 46 or GD100, 101, 103	Inappropriate interactions with novel animals	ND	Decreased affiliative calls; Failure to attend to salient social cues	Increased motor stereotypies and self-directed behaviors	ND

USV: Ultrasonic vocalization

ND: Not determined

mhDISC1: mutant human disrupted-in-schizophrenia 1 DN-DISC1: dominant-negative disrupted-in-schizophrenia

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Table 2

MIA Models Reporting Dam Cytokine Data

Author Year ***(Reference)***	**Species Strain Sex**	**PolyIC Protocol and Cytokine Analyses**	**Dam Cytokine Response Following PolyIC pg/ml**					
			IL-1β	**IL-6**	**IL-10**	**TNF-α**	**IFN-γ**	**IL-17**
Choi et al. 2016 (60)	Mice Roc(t)FL Both	20mg/kg, i.p. on GD12.5 Serum cytokine levels evaluated 3hr post injection (2 days after injection for IL-17a)	Increased	Saline Almost none	Not changed	Increased	ND	Saline Almost none
				GD12.5 300 (3h) 0 (24h)				GD12. 5 700 (2 days)
Connor et al. 2012 (129)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD12.5 or 17.5 Serum cytokine levels evaluated 3hr post injection	Saline 20	Saline Almost none	ND	Saline Less than 20	Saline Less than 100	ND
			GD12.5 30 (2h)	GD12.5 12000 (2h)		GD12.5 55 (2h)	GD12.5 600 (2h)	
			GD17.5 5 (2h)	GD17.5 4000 (2h)		GD17.5 30 (2h)	GD17.5 Less than 100 (2h)	
Meyer et al. 2006 (130)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD6, 9, 13, 17 Serum cytokine levels evaluated 3hr and 6hr post injection	ND	ND	Saline 0.5	Saline Less than 5	ND	ND
					GD9 16 (3h) 10 (6h)	GD9 124 (3h) 6 (6h)		
					GD17 8 (3h) 17 (6h)	GD17 42 (3h) 5 (6h)		
Meyer et al. 2006 (83)	Mice C57BL6/J Both	5.0mg/kg, i.v. on GD9 or GD17 Serum cytokine levels evaluated 3hr and 6hr post injection	Saline Not detectable	Saline Less than 10	Saline Less than 5	Saline Less than 1 (3h) Less than 5 (6h)	ND	ND
			GD9/17 3.5-4.5 (3h) Not detectabl e (6h)	GD9/17 8000-10000 (3h) 150-400 (6h)	GD9/17 10-30 (3h), 10-20 (6h)	GD9/17 100-200 (3h) Around 5 (6h)		
Meyer et al. 2008 (131)	Mice FVG Both	5.0mg/kg, i.v. on GD6, 9, 13, 17 (Sigma-Aldrich) Serum cytokine levels evaluated 1.5hr and 5hr post injection	Saline Less than 5	Saline Less than 5	Saline Less than 5	Saline Less than 5 GD9	ND	ND
			GD9 Not increased (1.5 and 5h)	GD9 800 (1.5h) 100 (5h) macIL-10tg mice showed significantly lower concentratio n than WT	GD9 75 (1.5h) 10 (5h) macIL-10tg mice showed significantly higher concentratio n than WT even in saline condition	400 (1.5h) 15 (5h) macIL-10tg mice showed significantly lower concentratio n than WT		

Author Year *(Reference)*	Species Strain Sex	PolyIC Protocol and Cytokine Analyses	Dam Cytokine Response Following PolyIC pg/ml					
			IL-1β	**IL-6**	**IL-10**	**TNF-α**	**IFN-γ**	**IL-17**
Vuillermot et al. 2012 (132)	Mice Nurr1+/-Males	2.0mg/kg, i.v. on GD17 Serum cytokine levels evaluated 2hr post injection	-	Saline Less than 1	Saline Less than 2	Saline Less than 2	ND	ND
				GD17 4 (2h) Nurr1$^{+/-}$ mice showed higher base line and poly IC treatment decreased it	GD17 4 (2h) Nurr1$^{+/-}$ mice showed significantly lower concentratio n than WT	GD17: 3.5 (2h) Nurr1$^{+/-}$ mice showed significantly lower concentratio n than WT		
Smith et al. 2007 (72)	Mice C57BL6/J Both	20mg/kg, i.p. on GD12.5 Serum cytokine levels evaluated 3hr post injection	Saline Almost none	Saline Almost none	ND	ND	ND	ND
			GD12.5 50000 (3h)	GD12.5 130 (3h)				
Ballendine et al. 2015 (128)	Rats Long-Evans Males	4.0mg/kg, i.v. on GD15 High MW Serum cytokine levels evaluated 3hr post injection	GD15 3-fold higher (3h)	GD15 2-fold higher (3h) but not significant	ND	GD15 6-fold higher (3h)	Same level as vehicle treatment	ND
Missault et al. 2014 (105)	Rats Wistar-Hannove r Males	2.0, 4.0 and 8.0mg/kg, s.c on GD9 or GD15 Serum mRNA expressio n level were evaluated 6hr post injection	GD9 Same level as vehicle treatment (6h)	GD9 Same level as vehicle treatment (6h)	GD9 Same level as vehicle treatment (6h)	GD9 4-fold higher expression in 8mg/kg (6h)	ND	ND
			GD15 2-fold higher in 4mg/kg (6h)	GD15 >5-fold higher in 4mg/kg (6h) but not significant	GD15 Same level as vehicle treatment (6h)	GD15 Same level as vehicle treatment (6h) The dams that lost weight following MIA (4mg/kg) showed a significant increase in TNF-a 6hr post injection.		

ND: Not determined USV: Ultrasonic vocalization

SI: Social interaction LI: Latent inhibition DA-R: Dopamine receptor

NMDA-R: N-methyl-D-aspartate receptor