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Review

Primate Models as a Translational Tool for Understanding Prenatal Origins of Neurodevelopmental Disorders Associated With Maternal Infection

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ABSTRACT

Pregnant women represent a uniquely vulnerable population during an infectious disease outbreak, such as the COVID-19 pandemic. Although we are at the early stages of understanding the specific impact of SARS-CoV-2 exposure during pregnancy, mounting epidemiological evidence strongly supports a link between exposure to a variety of maternal infections and an increased risk for offspring neurodevelopmental disorders. Inflammatory biomarkers identified from archived or prospectively collected maternal biospecimens suggest that the maternal immune response is the critical link between infection during pregnancy and altered offspring neurodevelopment. This maternal immune activation (MIA) hypothesis has been tested in animal models by artificially activating the immune system during pregnancy and evaluating the neurodevelopmental consequences in MIA-exposed offspring. Although the vast majority of MIA model research is carried out in rodents, the nonhuman primate model has emerged in recent years as an important translational tool. In this review, we briefly summarize human epidemiological studies that have prompted the development of translationally relevant MIA models. We then highlight notable similarities between humans and nonhuman primates, including placental structure, pregnancy physiology, gestational timelines, and offspring neurodevelopmental stages, that provide an opportunity to explore the MIA hypothesis in species more closely related to humans. Finally, we provide a comprehensive review of neurodevelopmental alterations reported in current nonhuman primate models of maternal infection and discuss future directions for this promising area of research.

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MATERNAL INFECTION AND OFFSPRING NEURODEVELOPMENT

As this review has been written in the midst of the ongoing COVID-19 pandemic, it is sobering to note that exposure to maternal infection during pregnancy is associated with increased risk of offspring neurodevelopmental disorders (NDDs) (1). Decades of converging evidence from epidemiological and preclinical research suggest that the maternal immune response is the critical link between exposure to a variety of viral and bacterial infections during pregnancy and alterations in fetal brain development (2). Although most women report experiencing at least one infection during pregnancy (3), it is also important to note that the vast majority of exposed offspring will not experience significant neurodevelopmental changes. However, for a subset of women, maternal infection and the subsequent immune response may serve as a disease primer into an altered trajectory of fetal brain development that, in combination with other genetic and environmental factors, increases the likelihood of offspring NDDs (4).

Not only is the immune system critical in mediating successful pregnancy (5), but immune signaling molecules, such as cytokines, also play a critical role in fetal brain development (6). Thus, the complex cascade of changes associated with maternal infection and the subsequent maternal immune response (7) is uniquely positioned to influence the developing fetal brain. Even in the absence of an acute inflammatory event triggered by infection, variations in maternal cytokine levels during pregnancy have been associated with offspring neurobehavioral outcomes, including early alterations in brain growth, functional connectivity, behavioral development (8–12), and long-lasting dysregulation of stress response circuitry (13). Collectively, these studies suggest that changes in the maternal-fetal immune environment during pregnancy can have long-lasting consequences, ranging from subtle differences in offspring brain and behavioral development to severe NDDs.

There is a critical need to understand factors that determine risk and resilience to changes in the maternal-placental-fetal immune environment and to develop evidence-based guidelines to manage infection during pregnancy (14). While previous gestational therapeutic strategies have focused on preventing vertical transmission of congenital disease–associated TORCH pathogens

(*Toxoplasma gondii*, other, rubella virus, cytomegalovirus, and herpes simplex virus) (15), new approaches are needed to address potential insults associated with the maternal immune response that is a common feature of many viral and bacterial infections. In this review, we first discuss epidemiological data linking maternal infection and offspring NDDs, with a focus on seroepidemiological approaches that provide mechanistic hypotheses that can be tested in preclinical models. We next describe the role of translationally relevant maternal immune activation (MIA) models and highlight relevant features of the nonhuman primate (NHP) that closely resemble human pregnancy and offspring neurodevelopment. We then provide a comprehensive summary of NHP MIA models and conclude by summarizing current knowledge gaps and future directions.

HUMAN MATERNAL IMMUNE RESPONSE

The majority of studies investigating prenatal origins of NDDs have focused on schizophrenia (SZ) and autism spectrum disorder (ASD) (16), though the association between maternal infection may extend to other NDDs (1). Initial evidence linking maternal infection with SZ stemmed from the observation that birth during the winter and spring months was associated with an increased risk of SZ, possibly owing to seasonal viral exposures [reviewed in (17)]. Subsequent studies using large birth cohorts reported increased risk of SZ in offspring born to women who experienced infections during pregnancy (18–26). Likewise, initial associations between maternal infection and ASD were primarily based on case studies following in utero exposure to maternal infections (27–32). Large-scale epidemiological studies further strengthened this association, though factors such as type of infectious agent and the timing of the gestational exposure have emerged as important considerations (33–41). Recent studies also indicate that the magnitude of the maternal immune response also plays a critical role (38), as associations with offspring ASD have been linked to maternal fever episodes (34,39), particularly episodes not treated with antifever medication (35) or when diagnosed in hospitals (36). These studies suggest that the acute maternal immune response associated with more severe infections may serve as the common biological pathway linking various maternal infections and aberrant fetal brain development (Figure 1).

The association between maternal infection and offspring neurodevelopment is further supported by a growing body of seroepidemiological studies that use archived or prospectively collected maternal biospecimens from mothers of individuals in whom an NDD was later diagnosed. Maternal inflammatory biomarkers generated in response to infection may cross the placenta and/or indirectly stimulate additional downstream changes in the maternal-placental-fetal immune environment that disrupt finely orchestrated events of fetal brain development (42–46). Biomarkers of maternal infection, including influenza antibodies (47), cytokines (48–50), and levels of maternal complement components (51), have been associated with offspring psychosis. Likewise, quantification of cytokines, chemokines, and other inflammatory markers obtained from archived maternal sera (52,53) and amniotic fluid (54,55) lends further support to the link between maternal infection and increased ASD risk, though not all studies have found positive associations (56). Recent efforts have focused on exploring disease-specific maternal inflammatory pathways associated with other NDDs, including attention-deficit/hyperactivity disorder, depression, bipolar disorder, and other neuropsychiatric conditions (57–62). Collectively, the growing epidemiological literature provides compelling evidence linking the maternal immune response to offspring NDDs, though underlying mechanisms are difficult to ascertain owing to constraints associated with human research, including differences in study design, timing of biospecimen collection, methods for determining maternal infection exposure, and long delays before clinical diagnosis of affected offspring. Preclinical models have emerged as complementary translational tools to explore the impact of acute exposure to maternal inflammatory biomarkers identified in these seroepidemiological studies.

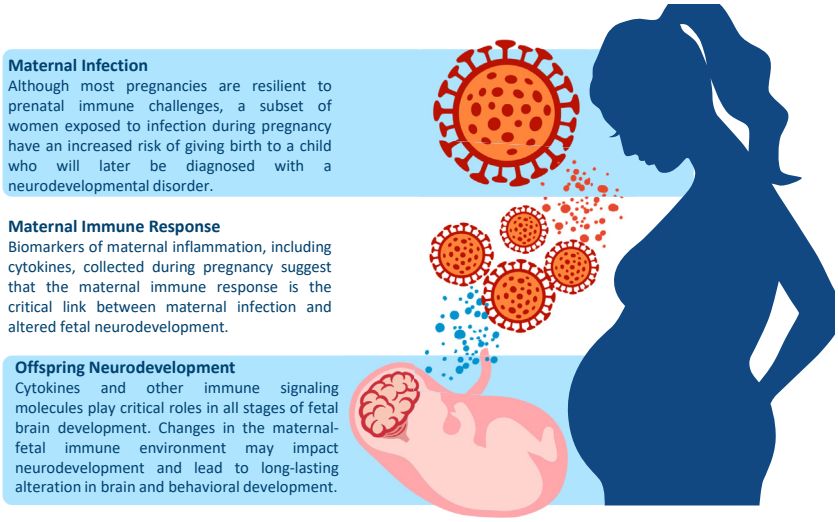

Figure 1. Schematic representation of associations between maternal infection, biomarkers of maternal inflammation, and changes in human fetal brain development.

TRANSLATIONALLY RELEVANT MIA MODELS

Pioneering studies in mice suggested that artificially stimulating the maternal immune response during pregnancy yielded offspring with deficits similar to those born to influenza-exposed dams (63,64) and prompted widespread interest in the MIA model. Despite significant challenges associated with methodological variability, offspring born to MIA-treated dams exhibit many reproducible changes in brain and behavioral development relevant to human NDDs (65). The vast majority of MIA models have used rodent model systems to provide foundational knowledge on the neurodevelopmental consequences of MIA exposure [for review, see (66–68)], though there is increasing interest in developing MIA models in other species, including ferrets and pigs (69,70). Here, we focus specifically on the translational potential of the NHP model to bridge the gap between rodent MIA models and patient populations with respect to physiological similarity in gestation and development as well as an expanded repertoire of social and cognitive outcomes to measure in offspring. NHP models account for a very small percentage of research in the United States (71), with the majority of NHP studies performed in macaques (72). We focus this review primarily on the rhesus macaque (*Macaca mulatta*), but also incorporate the common marmoset (*Callithrix jacchus*), which is playing an increasing role in gestational research (73). NHPs are the closest model to human pregnancy, sharing similarities in placental and pregnancy physiology, maternal-fetal interface, gestational timeline, and fetal brain development. Moreover, the neuroanatomical complexity and sophisticated behavioral repertoire of NHP offspring allow us to test hypotheses about prenatal immune challenge, from molecular mechanisms through complex behavior, with assays that correspond more closely to behavior or neurobiology observed in humans (Figure 2). NHP features most germane to the MIA model are briefly described below, with a more comprehensive review of the translational utility of the NHP model provided by Tarantal *et al.* (74).

Placental Structure and Pregnancy Physiology

Determining which pregnancies are at risk and which are resilient to the impact of maternal infection is a major challenge for the MIA model field. Given that rodent MIA models exhibit within-litter variability (75) and sex differences (76) associated with placental physiology, the ability to extend the model into NHPs that give birth to one offspring, such as the rhesus macaque, or bear small twin or triplet litters sometimes with a chimeric placenta, such as the common marmoset, provide important translational opportunities (77,78). Moreover, the pronounced differences in placental structure and physiology between rodents and primates influences the maternal-placental-fetal immune environment and is thus an important consideration (78,79). Although humans, rats, mice, and many NHPs possess a hemochorial placenta in which the trophoblast layer is in direct contact with the maternal blood and not separated by endothelium and/or epithelium (80), striking differences can be found when comparing the anatomy, cell types, and molecular biology of rodent versus primate placentas (81,82).

Gestational Timelines and Prenatal Brain Development

Identifying gestational time points that are most vulnerable to prenatal immune challenge presents another translational challenge for the MIA model field. Although extrapolating gestational timing of humans (280 days) to other species such as mice/rats (18–23 days) is not always straightforward, and offspring are born at different stages of later brain development, rhesus monkey gestation (165 days) and marmoset gestation (144 days) are more similar to that of humans (83). Rhesus monkey gestation can be divided into first (gestational days 0–55), second (gestational days 56–110), and third (gestational days 111–165) trimesters that closely parallel stages of human fetal brain development. Peak periods of neurogenesis for subcortical structures, including the amygdala (84) and thalamus (85), as well as the early stages of neurogenesis for the striatum (86) and hippocampus (87),

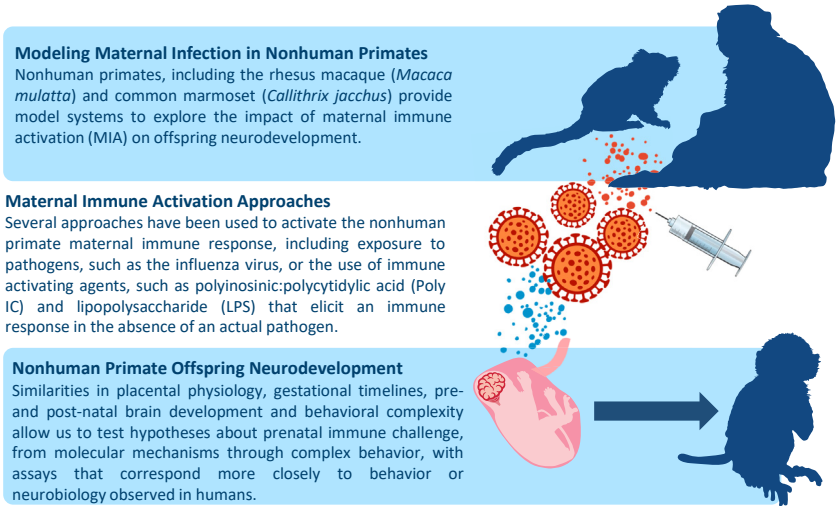

Figure 2. Schematic representation of nonhuman primate models of maternal infection.

occur in the macaque first trimester, while the early stages of corticogenesis begin at the end of the first trimester and continue through the second trimester (88). Emerging evidence from macaques indicates that microglia play a critical role in regulating cell production during this time and raises the possibility that MIA-induced changes in the maternal-fetal immune environment could alter the timing and trajectory of these critical neurodevelopmental processes (89). Although less is known about fetal development of the marmoset, the near-lissencephalic (i.e., lacking cortical folds) marmoset brain presents new opportunities to bridge the gap between rodent models and studies in primates with gyrencephalic brains (i.e., brains with a folded cerebral cortex), including humans and rhesus monkeys (90–92).

Neuroanatomical Organization

Regions of the human brain commonly implicated in NDDs are well developed in the NHP (93). The prefrontal cortex (PFC), for example, has expanded during primate evolution and is considered one of the key regions for regulating social cognition in primates (94,95). Cytoarchitectonic regions identifiable in human and NHP brains that are not present in rodents bring into question the existence of the homologous PFC region in rodents (96,97). Likewise, the amygdala exhibits similar patterns of connectivity and nuclei distribution in humans and NHPs (98,99) that differ substantially from rodents (100). The rhesus monkey exhibits a protracted period of brain and behavioral development uniquely suited to explore the emergence of MIA-induced changes (101–103). Pubertal onset for male and female macaques generally begins at 2.5 and 3.5 years, respectively (104,105), and coincides with a sensitive period of dramatic neural reorganization and plasticity (106). Moreover, there are areas of the brain that are important for advanced social cognition, such as face-selective patches identified in macaque inferotemporal cortex, that appear to be unique to higher-order primates (107). Although the brain of the common marmoset is considerably smaller compared with larger primates, marmosets also share many of the basic neuroanatomical organizational features described above (108). Recent advances to promote neuroimaging studies of marmosets facilitated through the Marmoset Brain Mapping Project (marmosetbrainmapping.org) have produced comprehensive brain atlases focused on cortex (109), white matter (110), and the recently released population-based in vivo standard templates and tools (111).

Behavioral Repertoire

Behavioral deficits in rodent MIA models initially focused on adult-onset changes in behavior (112,113), though increasing attention has been paid to the developmental progression of MIA-induced behavioral changes (114–116). With a protracted period of social and cognitive development compared with rodents, monkeys provide an opportunity to explore the postnatal neurodevelopmental trajectory of risk associated with prenatal immune challenge (117,118). Macaques live in large social groups of related animals and, similar to humans, use vision as their primary sensory modality (119) and rely on facial expressions and body postures for communication (120). Recent advances in more naturalistic eye-tracking methods have increased our understanding of how monkeys process social information (121) and provide a translational opportunity to human eye-tracking studies that have documented changes in individuals with NDDs, including both ASD and SZ (122,123). Moreover, rhesus monkeys develop increasingly sophisticated problem-solving skills as they mature, which can be assessed with translationally relevant cognitive paradigms (124,125). While rhesus monkeys have traditionally been the standard NHP model species for humans, marmoset social organization and behavior allow for new opportunities for studies of social behavior not easily carried out in rhesus monkeys. Marmosets are more distantly related to humans (40 million years ago) than rhesus monkeys (25 million years ago), but, similar to many humans and in contrast to rhesus monkeys, they live in small family groups with pair bonding and engage in cooperative rearing of young, including paternal and intergenerational sibling care (126,127). This social organization may contribute to the tendency for marmosets to perform prosocial behaviors, such as food sharing and imitation [for review, see (128)]. Furthermore, separation of an individual from the family group in an experimental context can reliably serve as a psychosocial stressor to assess reactivity (129). While their capabilities have not been as widely explored as rhesus macaques, marmosets can perform discrimination tasks early in development (130) and have been used in more complex cognitive paradigms, including using eye fixations under restraint, using touchscreens (131,132), and visual detection and discrimination tasks requiring complex motor behavior (133,134).

NHP MODELS OF MATERNAL INFECTION

The greater physical, psychological, and social needs of laboratory-housed NHPs are also associated with greater ethical considerations and increased cost for their care. While studies using NHPs are less common and the number of animals studied is more limited than in rodent or human studies, we provide examples below of ways in which translational NHP models have provided new insight into the impact of acute prenatal immune challenge on offspring neurodevelopment (Table 1). In this section, we summarize the methodological approaches used to induce MIA and evaluate neurobiological outcomes in NHP offspring. It is important to note that even sophisticated NHP models do not recapitulate NDDs observed in humans. In recent years, the MIA model has evolved from the initial characterization as a model of ASD or SZ toward a more hypothesis-based model for examining the effects of maternal inflammation on neural systems relevant to multiple neurodevelopmental conditions (135). Our description of neurobehavioral outcomes and comparisons between animal models and clinical disorders reflects this subtle, but important, shift in interpretation. We include maternal influenza exposure models as well as models that artificially stimulate the maternal immune response using poly(I:C) (polyinosinic:polycytidylic acid), a synthetic double-stranded RNA molecule that mimics the genetic information for many viruses and is recognized by toll-like receptor 3 or lipopolysaccharide (LPS), the cell wall component of gram-negative bacteria recognized by toll-like receptor 4 (136,137). In contrast to rodent models that can be completed in a matter of months, we are at the earliest stages of exploring the impact of MIA in the

Table 1. Summary of Nonhuman Primate Models of Maternal Infection and Maternal Immune Activation (MIA)

Studies	Species	Infection, Design, and Timing	Assessments	MIA Offspring Behavioral Development	MIA Offspring Brain Development	MIA Offspring Other Biological Outcomes
Short *et al.* (138)	Rhesus Macaque (*Macaca mulatta*)	Pregnant rhesus monkeys were exposed to human-derived H3N2 influenza strain intranasally in the third trimester (producing *N* = 12 offspring, 7 males and 5 females) compared with a combination of saline-treated and untreated control animals (producing *N* = 7 offspring, 3 males and 4 females)	Behavioral Assessments • Behavioral maturation, attentional processes, and neuromotor reflexes at 2 weeks • Infants observed (1–4 months) with mothers in home cages for three 5-min periods/week Neuroimaging • MRI (~1 year) Other Outcomes • Adrenal activity assessment (1.5 years)	Neonatal Reflexes and Development • No group differences on most measures • Males performed more poorly than control animals on orientation subscale Mother-Infant Interactions • Spent less time in contact with their mothers, were more likely to move off their mother and explore the cage at an earlier age, and demonstrated signs of arousal including an increased likelihood of vocalizing	Global Measures • Reduced ICV Gray Matter • Less gray matter in prefrontal, frontal (right only), cingulate, insula (right only), parietal, and temporal-auditory regions (before ICV correction); after ICV correction for smaller total brain size, significant differences remained in cingulate and parietal areas White Matter • Significant differences restricted primarily to parietal lobes and left temporal-auditory region before ICV correction; white matter volume in left parietal region remained significantly smaller after ICV correction, though cingulate white matter was proportionally greater in influenza group MIA Correlations • Significant negative correlations were found for cingulate volume and magnitude of mothers' antibody response • Size of lateral ventricles was positively correlated with mothers' antibody response	Adrenal Activity • No group differences in basal and stress-induced cortisol

Table 1. Continued

Studies	Species	Infection, Design, and Timing	Assessments	MIA Offspring Behavioral Development	MIA Offspring Brain Development	MIA Offspring Other Biological Outcomes
Willette *et al.* (139)	Rhesus Macaque	Pregnant rhesus monkeys (N = 9) were given LPS injections (IV) on gestational days 125 and 126 (third trimester) at either 2 ng/kg (n = 1) or 4 ng/kg (n = 8), producing N = 9 LPS-exposed offspring. Control group consisted of saline-treated (n = 2) and untreated (n = 7) animals, producing N = 9 control offspring. There were 4 males and 5 females in each group, although data for both sexes were combined	Behavioral Assessments • Behavioral maturation, attentional processes, and neuromotor reflexes (2 weeks) • Social interactions between infant and its mother (1–4 months) and with peers (6–7 months) • Stress reactivity using a modified human intruder test (8–9months) • Response to acoustical startle via PPI paradigm (10–12 months) Neuroimaging • MRI (~1 year) Other Outcomes • Blood collected (2, 4, and 7 months) • IL-6 tolerance assessment (1.5 years)	Neonatal Reflexes and Development • Higher emotionality ratings Mother-Infant and Peer Interactions • No group differences with mothers or peer-rearing groups Human Intruder Reactivity • Less reactive despite showing more baseline exploration Response to Startle • As juveniles, demonstrated a dysregulated response characterized by augmented (rather than suppressed) startle to PPI	Global Measures • Marginally larger ICV, results for gray matter and white matter unchanged after ICV correction Gray Matter • No group differences in global gray matter • Selective gray matter increases in parietal and frontal areas and in hippocampus and putamen • Marginally thicker gray matter in right parietal and frontal lobes, but thinner gray matter in medial temporal lobe White Matter • Significant increase in mean global white matter volume • All white matter regions were significantly larger	Cortisol Levels • Heightened cortisol levels 2 days after moving to a new cage • Following overnight dexamethasone treatment, morning cortisol levels were initially more suppressed, but by afternoon, cortisol levels were elevated compared with control animals IL-6 levels • Initially had more cellular reactivity when blood was stimulated in vitro with PHA during preweaning phase but showed the opposite pattern 1 month after weaning
Weir *et al.* (40)	Rhesus Macaque	Pregnant dams (N = 4) received poly(ICLC) injections (IV) on gestational days 43, 44, 46, 47, 49, and 50; 3 doses were evaluated: 0.25 mg/kg (1 female offspring), 0.5 mg/kg (1 male and 1 female offspring), and 1 mg/kg (1 male offspring). Control dams (N = 5) received saline injections, producing N = 5 male offspring	Behavioral Assessments • General health and development • Home cage observations to screen for maladaptive behaviors Neuroimaging • None Other Outcomes • DLPFC brain pathology evaluated via Golgi	Home Cage Observations • Exhibited more whole-body stereotypies at 6 months	N/A	Dendritic Morphology • No group differences in morphological measures of basal dendritic arborization • Apical dendrites smaller in diameter and significantly larger number of oblique dendrites

Table 1. Continued

Studies	Species	Infection, Design, and Timing	Assessments	MIA Offspring Behavioral Development	MIA Offspring Brain Development	MIA Offspring Other Biological Outcomes
Bauman *et al.* (141); Machado *et al.* (142); Rose *et al.* (143); Bauman *et al.* (144); Page *et al.* (145); Hanson *et al.* (K.L. Hanson, Ph.D., *et al.*, unpublished data, November 2020)	Rhesus Macaque	Poly(ICLC) injections (0.25 mg/kg IV) comparing first trimester (N = 7, 5 males and 2 females). Control animals received saline injections (N = 8, 3 males and 5 females) or were untreated (n = 3, 1 male and 2 females); first vs. second trimester	Behavioral Assessments Bauman *et al.* (141) (see Table S2) • Behavioral maturation, attentional processes, and neuromotor reflexes (1 week) • Biobehavioral assessment of health, behavior, temperament, and adrenal regulation (3 months) • Social interactions between each infant and its mother and with peer-rearing group (1–12 months) • Stress reactivity assessed using modified human intruder test (1, 3, and 6 months) • Solo observations in a novel cage (10 and 22 months) • Response to a novel peer (24 months) Machado *et al.* (142) • Eye tracking (first-trimester males) Neuroimaging Bauman *et al.* (144) • PET (first- and second-trimester males) Other Outcomes Rose *et al.* (143) • Immune system development Page *et al.* (145) • Brain tissue, gene expression Hanson *et al.* (K.L. Hanson, Ph.D., *et al.*, unpublished data, November 2020) • Brain tissue, dendritic morphology	0- to 6-Month Assessments • No consistent group differences in physical growth, motor or reflex development, adrenal activity, interactions with mothers, or development of threat detection in first 6 months of life Solo Observations • At 10 and 22 months, second-trimester MIA offspring produced significantly more repetitive behaviors; first-trimester MIA animals also produced more repetitive behaviors than control animals, but this difference did not reach statistical significance until the latter time point. At 22 months, second-trimester MIA offspring produced significantly fewer affiliative vocalizations than control animals Novel Social Partner • At 24 months, first-trimester MIA offspring exhibited inappropriate social interactions with unfamiliar animals; first-trimester MIA offspring also produced significantly fewer affiliative vocalizations than control animals Social Attention • At 2.5 years, first-trimester male MIA offspring differed from control animals on several measures of social attention, particularly when viewing macaque faces depicting the fear grimace facial expression • MIA offspring had a longer latency before fixating on the eyes, had fewer fixations directed at the eyes, and spent less total time fixating on the eyes of the fear grimace images	PET • First- and second-trimester MIA groups were not significantly different in age, weight, or FMT index of influx and were considered as one MIA group (N = 9), regardless of trimester of exposure • MIA-exposed late adolescent offspring had significantly higher FMT index of influx compared with control animals	Immune Function • Elevated production of innate immune cell associated cytokines early in life, shifting to a more TH2 type response as animals aged Gene Expression • Changes in a large number of genes across the brain that revealed dysregulated synaptic connectivity and enhanced myelination Dendritic Morphology • Increase in dendritic branching in pyramidal cells in infra- and supragranular layers in DLPFC • Significant decrease in apical dendrite diameter in infragranular layers in DLPFC • No significant differences observed in morphology of hippocampus neurons

Table 1. Continued

Studies	Species	Infection, Design, and Timing	Assessments	MIA Offspring Behavioral Development	MIA Offspring Brain Development	MIA Offspring Other Biological Outcomes
Vlasova *et al.* (147)	Rhesus Macaque	Pregnant dams received poly(ICLC) injections (0.25 mg/kg IV) on gestational days 43, 44, and 46 to produce a large (N = 14) cohort of MIA-exposed males; control dams (N = 14) received saline injections (n = 10) or were untreated (n = 4)	Behavioral Assessments • Behavioral maturation, attentional processes, and neuromotor reflexes (1 week) • Social interactions between infant and its mother (0–6 months) and with peers (6–18 months) • Reversal learning (18 months) and the following tests (33–45 months): continuous performance task, progressive ratio breakpoint, probabilistic reversal learning, intradimensional/extradimensional shift Neuroimaging • MRI (~6, 12, 24, 36, and 45 months) Other Outcomes • Weight, crown-rump length, head circumference (~6, 12, 24, 36, and 45 months)	General Development • No group differences in neuromotor reflexes, behavioral maturation, attention, or social interactions with mother or peer in home cage Cognitive Development • Similar overall cognitive performance to control groups with some subtle differences • Increased omission errors in reversal learning, more misses during 2 stages of intradimensional/extradimensional shift (both reversal stages), and had a significantly increased number of false alarms on continuous performance task	Structural MRI • Significant gray matter volume reductions in prefrontal and frontal cortices at 6 months that persisted through the final time point at 45 months along with smaller frontal white matter volumes at 36 and 45 months	Physical Growth • No group differences in overall health or physical development via weight, crown-rump length, and head circumference
Santana-Coelho *et al.* (148)	Common Marmoset (*Callithrix jacchus*)	Pregnant dams (N = 8) received 3 poly(ICLC) injections (SC) on gestational days 63, 65, and 67 (5 mg/kg) producing N = 7 (4 female) offspring. Control dams (N = 7) received saline injections (n = 3) or were untreated (n = 4), collectively producing N = 10 (6 female) viable offspring	Behavioral Assessments • Marmoset Assessment Tests (Matscore) for motor skills, sensory skills, and weight (1–3 days) • Isolation-induced vocalization test (2, 4, and 8 weeks) • Social preference and stranger interaction tests (3.5 and 9 months) Neuroimaging • None Other Outcomes • Weight (before all testing)	Neonatal Development • No group difference in infant health, vitality, and neurodevelopment Vocalization Reactivity • No group differences in total number of vocalizations • Females emitted fewer vocalizations than control females at 8 weeks • Males produced less vocal diversity until 8 weeks Social Preference • No group differences in females at 3.5 months • Males at 3.5 months spent more time in the nonsocial chamber than in the social chamber • No group difference at 9 months Stranger Interaction Reactivity • At 3.5 months, males spent significantly more time in the stranger's chamber • At 9 months, males and females spent less time with the stranger than control animals	N/A	Physical Growth • Female offspring heavier than control animals at 37 weeks

DLPFC, dorsolateral prefrontal cortex; ICV, intracranial volume; IL, interleukin; IV, intravenous; LPS, lipopolysaccharide; MRI, magnetic resonance imaging; N/A, not available; PET, positron emission tomography; PHA, phytohemagglutinin; PPI, prepulse inhibition; SC, subcutaneous; TH2, T helper cell type 2.

NHP model. However, we expect neurodevelopmental outcomes in the NHP MIA model to be influenced by gestational timing, magnitude of the maternal immune response, and additional genetic and environmental insults as described in the rodent MIA model.

Rhesus Monkey Maternal Influenza Models

Coe's group developed the first NHP model to investigate the impact of prenatal influenza exposure on offspring development (138). Pregnant monkeys were intranasally exposed to human-derived H3N2 strain of influenza during the early third trimester. Maternal infection was verified, and influenza-exposed and control offspring were evaluated from birth through 1.5 years. Early behavioral and stress assessments were similar between the two groups, though influenza-exposed offspring demonstrated a more rapid autonomy from the mother by 4 months old. Influenza-exposed offspring also exhibited a reduction in both intracranial volume (ICV) and gray matter in the prefrontal, frontal, cingulate, insula, parietal, and temporal-auditory regions, paired with white matter reductions in the parietal lobes and the left temporal-auditory region. Although the extent of regional gray matter reduction was reduced after ICV correction, volumetric decreases were still evident in the frontal and parietal lobes and the cingulate gyrus of influenza-exposed animals, as were white matter volume reductions in the parietal lobe. This pioneering study both provided evidence linking maternal influenza exposure with alterations in NHP offspring brain and behavioral development, and provided a translational framework to explore the long-term consequences of prenatal immune challenge on NHP neurodevelopment.

Rhesus Monkey Maternal LPS Models

In parallel, Coe's group also developed the first rhesus monkey MIA model using LPS to elicit a maternal immune response in the early third trimester (139). Rhesus macaques born to dams exposed to LPS exhibited subtle alterations in behavior throughout development, including heightened responsiveness during neonatal development assessments at 2 weeks of age, followed by less reactivity during an anxiety assessment at 8 to 9 months. The LPS-exposed offspring also exhibited periodic findings of physiological differences, including increased cellular reactivity to in vitro blood stimulated early in development and differential response to negative glucocorticoid feedback after an overnight dexamethasone treatment. In contrast to the reduction in ICV described above for influenza-exposed offspring, the LPS-exposed offspring demonstrated marginally larger ICV compared with control offspring at 1 year. Although global gray matter did not differ statistically between groups, selective gray matter increases in LPS monkeys were seen in parietal and frontal areas, in addition to the hippocampus and putamen. LPS monkeys had a significant increase in mean global white matter volume, with nearly all regions significantly larger in LPS-exposed monkeys compared with control offspring. The study provided the first evidence that artificially stimulating the maternal immune response in NHPs results in changes in offspring brain and behavioral development.

Rhesus Monkey Maternal Poly(I:C) Models

In collaboration with the late Dr. Paul Patterson, our laboratory developed the first poly(I:C)-based NHP MIA model. Over the past decade, we have generated 3 cohorts of rhesus monkey offspring born to MIA-treated dams: 1) first-trimester dosing cohort, 2) pilot comparison of first- versus second-trimester exposure, and 3) first-trimester male offspring cohort that has recently completed comprehensive brain and behavioral phenotyping from birth through 4 years of age.

First-Trimester Dosing Cohort. The first cohort was generated to evaluate 3 doses of a modified form of poly(I:C) stabilized with poly(ICLC) (poly-L-lysine) (140). Pregnant dams received 6 injections in the late first trimester of 0.25 mg/kg, 0.5 mg/kg, or 1 mg/kg poly(ICLC) (n = 1 dam, n = 2 dams, n = 1 dam, respectively) or saline (n = 4). Interleukin 6 data confirmed a robust immune response and thus guided our final MIA-induction protocol of 3 injections used for future cohorts. General health and development were monitored along with periodic screening of offspring for maladaptive behaviors, including the increased frequency of whole-body stereotypies exhibited by the MIA-treated offspring at 6 months of age. The brain tissue obtained from the offspring of the dosing cohort at 3.5 years was then used to carry out an initial assessment of brain pathology in the NHP MIA model by quantifying dendritic morphology in layer III pyramidal neurons in the dorsolateral PFC (DLPFC). Our results showed that MIA-treated offspring have a narrower apical dendritic diameter and more oblique dendrites compared with control offspring and highlighted the frontal cortex as a potentially vulnerable region in NHPs exposed to prenatal immune challenge.

First- Versus Second-Trimester Exposure Cohort. We then conducted a pilot comparison of NHP offspring born to dams that received 3 poly(ICLC) injections in the late first (n = 6) or second (n = 7) trimesters that included an evaluation of offspring behavior (141,142), immune (143), and brain [K.L. Hanson, Ph.D., *et al.*, unpublished data, November 2020; (144,145)] development. Although there were no consistent differences early in development, the offspring exposed to MIA in either trimester displayed increased repetitive behaviors and changes in social development as they matured, with more differences specifically between first- and second-trimester offspring compared with control offspring summarized in Figure S3 in Bauman *et al.* (141). When evaluated with unfamiliar conspecifics, first-trimester MIA offspring also deviated from species-typical social behavior by inappropriately interacting with an unfamiliar animal and later exhibited atypical patterns of social attention when evaluated in a novel eye-tracking paradigm (142). The male MIA-treated offspring from this cohort also underwent in vivo positron emission tomography scanning at approximately 3.5 years of age using the tracer FMT to measure presynaptic dopamine levels in the striatum (144). Analysis of FMT signal in the striatum showed that MIA-exposed monkeys had a significantly higher FMT index of influx as compared with control animals—a hallmark feature of human psychosis (146). The MIA-treated animals also exhibited alterations in immune function relevant to NDDs, characterized by elevated

production of innate inflammatory cytokines both at baseline and following stimulation at 1 year and 4 years of age, including elevated interleukin 1β paired with increased production of T helper cell type 2 cytokines, interleukin 4, and interleukin 13 (143). Finally, RNA sequencing of PFC, anterior cingulate, hippocampus, and primary visual cortex implicated alterations in transposable element biology, synaptic connectivity, and myelination with relative hippocampal vulnerability in the adolescent brain of MIA-exposed NHPs (145). We have also recently replicated the findings of aberrant dendritic morphology in the DLPFC (140), with both first- and second-trimester MIA-exposed monkeys exhibiting an increase in dendritic branching in pyramidal cells in both infra- and supragranular layers in DLPFC, paired with a significant decrease in apical dendrite diameter in the infragranular layers of the DLPFC. Collectively, these transcriptional and neuropathological changes may provide unique insight into prodromal changes in the brain during a vulnerable period of late adolescent/early adulthood and suggest that the NHP MIA model may provide a translational tool to examine underlying molecular and cellular biology of brain development impacted by prenatal immune challenge.

First-Trimester Longitudinal Behavior and Neuroimaging Cohort. To systematically explore the developmental trajectory of risk associated with prenatal immune challenge, we have recently generated a third cohort of first-trimester MIA-exposed (n = 14) and control (n = 14) male monkeys that have undergone longitudinal neuroimaging paired with comprehensive behavioral characterization. These studies are ongoing, including a comprehensive assessment of social and immune system development paired with multimodal neuroimaging. Our preliminary findings indicate that MIA-exposed animals exhibited volumetric reductions in brain growth throughout development paired with subtle changes in cognitive development (147). Specifically, longitudinal magnetic resonance imaging revealed significant gray matter volume reductions in the frontal and prefrontal cortices of infant MIA-treated offspring that persisted throughout development, along with smaller frontal white matter volumes in MIA-treated offspring that emerged during adolescence. These findings provide the first longitudinal evidence of early postnatal changes in brain development in MIA-exposed NHPs and establish a model system to explore the emergence of brain and behavioral changes from birth through late adolescence. Additional datasets are currently in preparation for publication, including a comprehensive assessment of social and immune system development paired with multimodal neuroimaging.

Marmoset Maternal Poly(I:C) Models

The recently established marmoset MIA model (148) provides an opportunity to explore the impact of prenatal immune challenge in a species that is playing an increasing role in neurodevelopmental research. For a NHP, marmosets are comparatively small; have a higher reproductive efficiency with respect to gestation, delivery intervals, and litter size; and overall have a shorter life history and development, becoming sexually mature at around 1.5 years of age (149). Similar to the rhesus monkey MIA model, poly(ICLC) was used to elicit a maternal immune response during the late first trimester (administered on days 63, 65, and 67), and offspring were studied through adolescence (9 months old). There was a significant increase in inflammatory cytokines, such as tumor necrosis factor α, in poly(I:C)-treated dams, although notable sickness behaviors were not generally observed. As with the rhesus monkey MIA model, there were no immediate effects of MIA on infant health and development. Yet, subtle and sex-specific behavioral differences emerged as MIA-exposed females demonstrated reduced vocalizations when separated from their social group at 8 weeks of age and MIA-exposed males spent more time in a nonsocial chamber in a modified 3-chamber sociability assay at 3.5 months. Furthermore, both male and female MIA-exposed offspring spent less time with a stranger conspecific at 9 months of age than control offspring. Cross-species comparisons between the marmoset and rhesus monkey MIA models may provide additional opportunities to explore neurobiological underpinnings in NHPs prenatally exposed to immune challenge.

FUTURE DIRECTIONS

Sex as a biological variable has been understudied in the MIA model literature, despite mounting evidence in rodent models indicating that male and female offspring exhibit sex-specific trajectories in neurobehavioral development (150). The underrepresentation of female offspring in the current NHP MIA models represents critical gaps in our knowledge, which will be the focus of our next cohort of MIA-exposed offspring. Further, while much progress has been made in our understanding of the link between maternal infection and offspring NDD risk, it has become increasingly clear that we currently do not know which pregnancies are vulnerable and which are resilient to prenatal immune challenge. The preclinical MIA model provides a platform to systematically evaluate susceptibility, resilience, and underlying phenotypic heterogeneity in response to prenatal immune challenge. This, in turn, provides a framework for translating results from preclinical models to evidence-based guidelines to improve women's health and pregnancy outcomes. Although the prenatal environment might be considered a period of vulnerability for NDD-related insults, we consider it to be a time when preventive strategies and therapeutic interventions may be most effective. Given that millions of pregnant women experience infection each year, even a small decrease in risk could have a significant public health effect on NDD outcomes.

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