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Maternal Immune Activation Hypotheses for Human Neurodevelopment: Some Outstanding Questions

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Abstract

The Maternal Immune Activation (MIA) hypothesis is a leading model for understanding prenatal influences on individual differences in, and clinical syndromes of, neurodevelopment. Experimental animal and human research has proliferated in recent years, and there is now a sizable research base. Several meta-analyses demonstrate general support for an association between prenatal immune activation and neurodevelopment in human research. However, questions remain about the nature of the immune activation, the network of underlying mechanisms involved, and the breadth of impact across behavioral phenotypes. Complementing recent reviews of results, the current review places particular emphasis on how advances in understanding mechanisms may be improved with greater attention to addressing the methodological variation and limitations of existing studies, and identifies areas for further clinical research.

Keywords

Maternal immune activation; prenatal; inflammation; neurodevelopment; developmental programming

The Maternal Immune Activation (MIA) hypothesis proposes that activation of the pregnant women's immune system may result in altered neurodevelopment of the fetus. The model has an established history in animal and human work; its increased prominence in recent years reflects greater appreciation for the role of the immune system in neurodevelopment

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and the scientific and public health urgency to identify and mollify prenatal conditions that may have lasting impact on the child's brain health. Many reviews and meta-analyses of the MIA literature have appeared in recent years(1–6). The review considers some of the outstanding questions that arise from the findings, concerning both mechanisms and methods. Our focus is on the application of MIA to human neurodevelopment, but recognize that MIA hypothesis is relevant beyond neurodevelopment(7) and that reliance on the animal work is essential for testing certain features of the model.

How is Maternal Immune Activation defined, and what is the nature of the exposure?

The MIA hypothesis offers a framework with wide application of sizable public health significance. That is because maternal *immune activation* may arise from a multitude of exposures, from distal markers such as seasonality or ambient pollution; clinical measures of immune-responsive features such as psychological stress or psychiatric symptoms; clinical measures of physical health such as obesity or autoimmune conditions; pathology reports of perinatal conditions such as chorioamnionitis; assessments of maternal infections and (febrile) illness; measures of immune markers in maternal circulation(3, 8–11).

Compounding this diversity of type is variation in collection methods. So, for example, reports of maternal prenatal illness, one of the most common targets, may derive from maternal self-reports or medical records. This difference methodology may lead to disparate rates of exposure and prediction of child outcomes. A recent report from the UK millennium cohort(12) is one of the very few studies to report both sources of maternal illness in relation to child outcomes. The authors found that maternal-reported infection (affecting 7.4%) was associated with Autism Spectrum Disorder (adjusted OR 1.77) but hospital-recorded infection (affecting 2.1%) was not (adjusted OR .97). Reliability of infection exposure may be improved by identifying a specific illness such as influenza(13–17) or urinary tract infection(18), but will miss important potential sources of immune activation. Alternatively, including serological evidence may augment reliability and validity of infection measures(14), but a summary of this literature was recently critically reviewed(19). These observations underscore the value in considering more than a single definition or source of illness/infection when testing MIA hypotheses. The UK millennium cohort study provides a valuable demonstration that large sample size – over 15,000 participants were included – does not inoculate against measurement differences and measurement unreliability that may underlie inconsistent results across studies.

The manner in which methods bound mechanism is equally evident when examining maternal immune markers. There are at least two methodological matters that bear directly on mechanism. One concerns how immune markers such as cytokines are assessed. Most studies of the MIA hypothesis examine circulating markers from blood draw. The contrast is with stimulated cytokines, where blood samples are exposed to select mitogens or antigens *in vitro* and responses are recorded. Results will vary between circulating and stimulated approaches, and there seems to be little connection between the two. Furthermore, rank-order response among individuals varies across different stimulation conditions. A second

matter concerns which immune markers are targeted. The list of markers for assessing immune activation is larger and more complex than current research practice indicates. That is, the focus is on a very limited list of cytokines that reflect, promote or are otherwise involved in an inflammatory response, such as interleukin (IL)-6 and IL-1b or the acute phase protein C-reactive protein (CRP). In contrast, cytokines performing additional forms of immune activation are rarely assessed, as are immune molecules with complementary functions (e.g., angiogenesis) such as growth factors that are important for neurodevelopment. There is the further challenge that the function of a cytokine will depend on the immediate environment. It is likely unrealistic for human studies to capture the ambient cell environments that would determine if, for example, IL-6 functioned in a pro- or anti-inflammatory state, but there is solid evidence for this ambiguity(20). A further compounding problem is that often an individual marker (often assessed on a single occasion) is used as a proxy for a complex and dynamic process that changes over gestation.

The slow but steady shift in the laboratory from high sensitivity ELISAs to multiplex platforms may help some of these concerns because they enable a broader coverage of immune markers in pregnancy; indeed, many commercially available platforms can accommodate several dozen markers. This resolves the problem of reliance on few markers, but creates a new one: how to optimize bioinformatics and immunological knowledge to model many immune markers with complementary and diverse functions. There is as yet no established or replicated method for analyzing multiplex platform results that synchronizes both immunology and data science. Accordingly, methodological and data analytic refinements, with replications, will be essential for leading this new wave of research on maternal immune activation.

There is wide-spread appreciation that prenatal maternal infections that may alter fetal brain development extend beyond the classic TORCH agents (*Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex virus) to include an array of agents associated with infection and inflammation as well as potentially inflammatory states associated with psychological symptoms or health behaviors. The MIA hypothesis poses major public health concerns; this section sought to highlight some challenges for advancing methodology and understanding mechanism.

What are the mechanisms implied by maternal immune activation?

A core hypothesis of the MIA model, particularly as applied to influenza, is that it is the maternal response to the virus – inflammation – rather than the virus itself that is the putative cause of altered brain development in the child. That hypothesis may not extend to all exposures because certain viruses, notably Zika(21), cross the placenta and may have more direct impact on fetal brain development. The key point is that generalizing mechanisms from one viral, bacterial, or parasitic infection to another may not be warranted(22).

Nonetheless, much of the focus in MIA research is inflammation, and attention has been directed to pro-inflammatory molecules such as IL-6 at each stage of the causal cascade, from maternal circulation to placenta activation to the fetal/child brain; that is also the

case for many clinical markers of immune activation, including psychological stress and obesity(23–29). Given basic research findings showing that inflammatory molecules may impair neuronal development, prenatal maternal IL-6 is predicted to be associated with poorer cognitive and neurodevelopmental outcomes, as reported in several studies, e.g.,(30); however, the opposite effects have been reported for infant cognition(31).

Complementing non-human primate research on prenatal inflammation and offspring neurogenesis and brain volume(32–35) are human studies associating maternal prenatal concentration of IL-6 and newborn and infant brain imaging in typically developing samples, e.g.(30, 31). Another major line of research examines pre- or perinatal infection or inflammatory molecules such as IL-1, IL-6, and TNF-alpha with neonatal white matter damage(36). One other pro-inflammatory cytokine to feature is IL-17, particularly in relation to autism/ASD(37). Prenatal exposure to IL-17 is also notable because of the evidence of alterations of IL-17 concentrations in individuals with ASD and other neurodevelopmental disorders(38–40). The human mechanism-related studies so far reported are not easy to summarize because, e.g., in the case of brain imaging studies, different measures of brain imaging reported and existing studies typically rely on small samples. An additional limitation of some studies is the focus on the pre-term baby, whose immune system is importantly different from a term baby(41). Furthermore, some of this work is also based on studies in low- and middle-income countries(42–46) in which nutritional deprivation and other confounding exposures may limit generalizability. Finally, studies relying on a single marker are limited because immune activation is unlikely to be adequately captured by a single marker, and may be a proxy for many kinds of changes in immunomodulation and metabolism(47, 48). These studies are, however, beginning to translate some of the key animal studies of mechanism.

Alternative mechanisms are attracting attention, as not all cytokines plausibly targeted in MIA research operate principally via inflammatory mechanisms. For example, transforming growth factor beta 1 (TGF-beta), which is involved in cell growth, proliferation and apoptosis, is linked to several clinical conditions such as schizophrenia(49, 50). Cytokines involved in angiogenesis (PlGF, VEGf) may also play an important role explaining the impact of maternal immune activation. Moreover, the number of studies documenting associations between maternal autoimmune disorders in pregnancy with neurodevelopmental disorders in the child(3) also argue for a mechanistic focus that is broader than inflammation.

Exposure to inflammation *in utero* is often presumed in studies of the MIA hypothesis, but immune activation may also or alternatively be associated with child neurodevelopment via multiple indirect pathways. Studies of prenatal maternal obesity offers several examples. Associations between maternal prenatal obesity with poor neurodevelopmental outcomes(51–54) may come about via inflammation(10, 55, 56) impact on the placenta(55, 57, 58) and increased perinatal risk(59), as well as via associated pathways, including glucocorticoid channels, dietary or metabolic pathways, or the microbiome(60–63). Including the causal cascade of exposure is an important direction for future work.

Several mechanistic questions are yet to be resolved in human studies of the MIA hypothesis. One is timing of the exposure. Whereas studies of the MIA in relation to schizophrenia suggest 1st or 2nd trimester exposure, no such evidence has yet been reported for other phenotypes, such as ADHD. Further research on timing of exposure may help clarify mechanism by exposing periods of ontogenetic vulnerability. A related matter needing attention is the blood-brain barrier, about little is known in relation to the MIA model, especially in humans(64–70). Changes in the blood-brain barrier permeability across gestation have obvious consequences for understanding the role of timing of exposures and fetal brain development. A further concern is severity. Experimental animal evidence implies that fetal/neonatal brain injury may result even where clinical markers of prenatal inflammation (from maternal or placental samples) is not clinically significant(71); that hastens further clinical research on the continuum of maternal immune activation. Also, research on sex differences may reveal hints about mechanism, and are especially needed given the differences in prevalence of many conditions associated with MIA. Sex differences moderating associations between maternal immune activation and brain or behavioral outcomes have been reported(72) and need replication. Furthermore, the substantial variability in response to MIA – with some but not others showing adverse effects – implies effect moderators, which could take many forms, and could hold clues for interventions. Individual differences in response to immune activation also raises the prospect of genetic influences; that hypothesis has received limited but nonetheless no reliable support so far(73).

One mechanism that we single out for particular attention is the role of the developing fetal/child immune system. The hypothesis here is that MIA may confer its effects on child neurodevelopment via its influence on the child's immune system. Several lines of evidence suggest that this is plausible. For example, non-human primate models show lingering effects of maternal immune activation on the offspring immune system, which may underlie brain and behavioral effects(27). More available are studies linking immune system function with brain and behavior in children(74). A study of infants in Bangladesh found that IL-1b and IL-6 at 6 months were inversely associated with motor development at 24 months and IL-4 was positively associated with cognitive development at 24 months(75). A separate study found that observational measure of fear at 17 months of age was positively associated with several cytokines; some (e.g., TNF-alpha) but not others (e.g., IL-10, INF-gamma) serve classic proinflammatory functions(76), suggesting that a model broader than inflammation may be needed. A case-control study found elevated concentrations of IL-8 and IL-1b in cord serum samples in children who later showed delayed cognitive ability, although the differences did not maintain after adjusting for confounders(77). Also, several reports in premature infants link immune markers collected at birth with individual differences in neurodevelopmental outcomes, such as ADHD(78). Associations between cytokines or chemokines in amniotic fluid and neurodevelopmental disorder has also been reported(79). These studies in diverse samples complement the substantial evidence base associating autism/ASD status with concurrently assessed immune markers(80, 81) and studies linking immune mechanisms with schizophrenia(82, 83) and suggest greater attention in MIA research on the offspring's developing immune system.

One compelling target in the fetal/child immune system for this MIA research is microglia, resident macrophages of the brain that are referred to as the brain's resident immune system. Microglia are inaccessible (at least not directly so) for human studies, but animal studies demonstrate an essential function of microglia on synaptic pruning related to brain circuitry(84) and neural plasticity underlying efficient neural circuits(85, 86). Microglia also shape early brain development by phagocytosis of cellular debris and neural precursor cells(86–88). The inability to access microglia directly in human studies naturally limits this line of study, but indirect measures, and possible suggestions for future research, have been proposed using positron emission tomography (PET) that assesses radiotracers that bind to microglia(89) and models of microglia-like cells(90).

Finally, prenatal influences such as maternal immune activation on the developing T cells in the fetal brain requires additional attention. To date, evidence linking T cell and brain development are limited to animal studies, which show that $CD4^+$ T cells (that produce, in particular, the cytokine IL-4) are a critical factor in normal brain development. In the absence of optimal numbers of these T cells, an imbalance between adaptive and innate responses ensues, and the subsequent pro-inflammatory skewing of the immune response (with higher levels of cytokines including IL-6, TNF-α, IL-1β and IL-17A) can result in behavioral deficits and poorer cognition(37, 91, 92). In support of these findings in rodent models is the human finding that decrements in adaptive T cell function and increased pro-inflammatory immune function is observed in children with Autism spectrum disorders (ASD)(93).

Challenges for establishing causal mechanisms

Animal models of the MIA hypothesis, which often rely on polyinosinic-polycytidylic acid (Poly (I:C)) and lipopolysaccharide (LPS) to mimic viral and bacterial infections, demonstrate the involvement of multiple neuronal mechanisms in the offspring brain such as neurogenesis, plasticity, and trafficking; effects on direct immune processes in the brain, e.g., involving microglia, are also well advanced. Although there are clearly methodological matters to be resolved(94), the evidence base for a causal effect is substantial and substantially attributable to the experimental control over the nature and timing of the exposure. In contrast, human studies of the MIA hypothesis rely on observational study designs which cannot de-confound pre-existing or co-occurring exposures that may impinge on or modify MIA effects; neither do they control timing, chronicity or severity of immune activation exposure that may be central for determining causal effects. These are notable limitations. Strategies for testing and deriving causal claims from observational and epidemiological approaches have been proposed(95) and in some cases applied, but demonstrating cause remains elusive.

Inferring causal mechanisms from developmental timing effects has been a central feature of the MIA hypothesis(96–98), but confirming gestational timing effects in observational studies of the MIA hypothesis is a challenge. Even establishing an *in utero* exposure may be complicated; for example, sources of maternal immune activation, such as pre-conception trauma(10) or pre-pregnancy obesity(99–101) may pre-date the pregnancy. Documenting *in utero* exposure to maternal immune activation will also require postnatal assessments, as

implied by evidence that exposure to maternal immune activation may not stop with birth but may carry on via breast milk(102–104).

What is the role of the placenta?

The placenta would have many important roles in an MIA model of fetal brain development given its role in transporting nutrients and gases; eliminating waste; transferring or blocking the transfer of viruses, immune markers, drugs, and environmental chemicals; altering the maternal immune system to prevent rejection; producing steroid and peptide/protein hormones. Its role as a source or modulator of prenatal inflammation has been widely discussed(105–107); histopathological markers of inflammation in the placenta have been well-characterized(108, 109) and associated with brain development in animal(110) and human studies(105, 111). Furthermore, clinical conditions considered as possible stand-ins for immune activation, such as obesity, are associated with compromised placental function(58, 112, 113).

Importantly, because the placenta is amenable to detailed interrogation, it is a natural target for mechanism-focused research in humans. However, aside from some notable examples, such as IL-6 signaling in trophoblasts(26), the role of the placenta is under-developed in particularly human research. Ignoring placental mechanisms will mis-specify the nature of prenatal influences, including maternal immune activation. Placenta perfusion studies raise doubts about transfer of certain cytokines across the placenta(114), but that would not rule out other mechanisms by which maternal circulating cytokines might alter placenta biology with implications for fetal brain development(115). Moving forward, incorporating placental mechanisms in MIA hypothesis testing, from modest efforts such as including medical record reports of chorioamnionitis to more intensive assessments that require timely collection and processing of placenta tissue, will advance our understanding of the causal cascade from maternal immune activation to child brain development.

How do immune activation models address pregnancy-specific immune adaptations?

It has been appreciated for some time that pregnancy is an immune-challenged state because of adaptations needed to accommodate the semi-allograft (i.e., the fetus) to promote a healthy pregnancy and, moreover, that these changes alter the pregnant mother's response to viruses and infectious agents(116). One dominant model of the pregnancy-related immune changes was that pregnancy shifts T cell responses from Th1 to Th2(117). That could explain a number of clinical observations as well as variation in pregnancy outcomes(118, 119); that hypothesis also aligns with pregnancy hormone-induced changes as, for example, progesterone inhibits short-term IFN-gamma synthesis and T cell differentiation into Th1 cells(120, 121) and estrogen enhances Th2 responses(122). However, this model is now generally regarded as too simple to explain all immune changes in pregnancy, e.g., fetal tolerance at the maternal-fetal interface, microchimerism, changes in T cell subsets and plasticity and response to fetal antigens(123–126).

These diverse pregnancy-induced changes set an important context for testing MIA hypotheses and suggest a number of applications. One is that immune activation is just one of the kinds of pregnancy-induced changed to the maternal immune system that may be relevant for understanding individual differences in fetal brain development. A second is that immune markers that signal inflammation in the non-pregnant individual may not carry the same meaning or have the same effect in a pregnancy individual. That may be especially relevant when using inflammatory states in pregnancy as a stand-in for immune activation or when seeking to understand the possible links between inflammatory markers and other health behaviors and biological markers, such as stress or affective symptoms. A third implication concerns timing of exposures and assessment frequency. It is not possible to capture a dynamically changing maternal immune system on a single occasion or very limited assessment schedule; characterizing a changing system requires multiple measures across gestation.

Which aspects of offspring neurodevelopment may be most responsive to prenatal immune activation?

A majority of studies of the MIA paradigm consider one of two clinical diagnoses/ syndromes, schizophrenia(14, 16, 127) and autism/ASD(128, 129). Other clinical diagnoses and syndromes are much less widely studied, and a small set of studies have associated measures of maternal immune activation with individual differences in cognitive abilities within the normal range(130–132). A recent meta-analysis(3) also included ADHD and Tourette syndrome, with a trend for an association with the former. Other meta-analyses have taken a broader approach to assessing the phenotype, but rely on few studies of this broader set of phenotypes(11).

A biological model of why MIA would lead to a selective targeting of neurodevelopmental (endo)phenotypes is not apparent in most studies or in patterns of results. That may get revised with integrated behavior- and brain-based studies. Alternatively, immune activation exposure may not be specific to neurodevelopmental mechanisms, brain regions, or clinical syndromes. That might result if the effects of immune activation on the developing brain are wide-spread and multifaceted. In this context, it is notable that animal studies provide a very long list of brain changes induced by maternal immune activation, including enlarged ventricles, volumetric and neuronal changes in many parts the brain (dentate gyrus, amygdala, prefrontal cortex), altered neuronal trafficking, reduced dendritic spine density, reduced synaptic density, altered synaptic pruning, altered cortical organization, and possibly increased microglia density and activation(35, 133, 134). Complementing these brain changes are many kinds of changes in neurotransmitter systems; GABAergic, dopaminergic, glutamatergic, serotonergic, and cholinergic systems have all been identified as being altered in animal MIA studies(133). An unavoidable translation of these findings is that human research needs to consider a diverse array of neurodevelopmental processes rather than a small number of clinical syndromes. Applying the NIMH Research Domain Criteria (RDoC) is one model for such work, and is evident in recent studies that associate measures of infant and child brain imaging data with prenatal maternal immune activity and activation(24, 135).

A follow-up question is when in development putative effects of maternal immune activation on the child would be detected. If, as implied by the experimental animal work, maternal immune activation in pregnancy substantially alters many brain regions and neurodevelopmental mechanisms, then effects would be detected early on. Studies of typically developing and clinical samples of infants and children(24, 135, 136) may therefore be especially valuable for assessing the MIA hypothesis and its clinical and public health significance.

What are the treatment implications from the MIA findings?

Efforts are underway to translate research findings on prenatal exposures for child health outcomes, including many prenatal exposures that may have their impact via maternal immune activation. Research findings show that these psychological and health behavior-, activity- and yoga-based interventions can be effective for reducing prenatal distress and improving prenatal health(137–139). Reliable evidence that these kinds of interventions modify maternal immune activation (consequently or independently of the clinical target) is not yet available, but provide a starting point for examining if/how altering prenatal maternal immune activation may not necessitate the use of anti-inflammatory pharmacology.

The sizable evidence base and clinical guidelines on the use of analgesics and antipyretics in pregnancy is another context for understanding the impact of the MIA model. Widespread use of these medications means that many observational studies exist on safety and efficacy(140, 141). The MIA hypothesis would suggest that deciphering safety data for the developing fetus needs to weigh the impact of illness exposure, with which medication exposure is inextricably linked. Indeed, some reports of the MIA hypothesis include medication not as the exposure but rather as a proxy for maternal immune activation. There are parallel difficulties in studies of anti-depression medication in pregnancy on child health outcomes.

A further clinical implication is to broaden the assessment and outcome context of immune manipulations to include neurodevelopmental assessments. Vaccinations for influenza in pregnancy is an example. The flu vaccine, which continues to attract attention for its safety in pregnancy(142), may be a valuable preventive interventions for schizophrenia and other adverse perinatal and obstetric outcomes that derive from influenza/maternal immune activation. Reducing rates of influenza and associated immune activation may benefit many forms of neurodevelopment outcomes in children.

Conclusion

The MIA hypothesis for human neurodevelopment has wide public health significance, a well-developed set of animal models, several plausible target mechanisms, and empirical evidence dating back decades. On the other hand, as recent meta-analyses show, there is sizable diversity of what is used as an index of maternal immune activation. A thesis of this paper is that the definition of immune activation is currently too restricted within each study and too diverse across studies to identify the mechanisms involved. Recently published guidelines for promoting rigor and reproducibility for MIA studies in animal

was recently proposed(94). Something of the kind may be needed for human studies of the MIA hypothesis in order to improve the clarity of the findings, advance understanding of mechanisms (and moderators), and offer practical future steps on measurement and assessment in clinical studies and, eventually, clinical practice.

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