Title

Impact of Maternal Immune Activation on Nonhuman Primate Prefrontal Cortex Development: Insights for Schizophrenia

Journal

Biological Psychiatry, 92(6)

ISSN

0006-3223

Authors

Hanson, Kari L
Grant, Simone E
Funk, Lucy H
et al.

Publication Date

2022-09-01

DOI

10.1016/j.biopsych.2022.04.004

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2023 January 31.

Published in final edited form as:

Biol Psychiatry. 2022 September 15; 92(6): 460–469. doi:10.1016/j.biopsych.2022.04.004.

Impact of Maternal Immune Activation on Nonhuman Primate Prefrontal Cortex Development: Insights for Schizophrenia

Kari L. Hanson,

Simone E. Grant,

Lucy H. Funk,

Cynthia M. Schumann,

Melissa D. Bauman

Department of Psychiatry and Behavioral Sciences (KLH, SEG, LHF, CMS, MDB), MIND Institute (KLH, CMS, MDB), and California National Primate Research Center (MDB), University of California, Davis, Davis, California

Abstract

Late adolescence is a period of dynamic change in the brain as humans learn to navigate increasingly complex environments. In particular, prefrontal cortical (PFC) regions undergo extensive remodeling as the brain is fine-tuned to orchestrate cognitive control over attention, reasoning, and emotions. Late adolescence also presents a uniquely vulnerable period as neurodevelopmental illnesses, such as schizophrenia, become evident and worsen into young adulthood. Challenges in early development, including prenatal exposure to infection, may set the stage for a cascade of maladaptive events that ultimately result in aberrant PFC connectivity and function before symptoms emerge. A growing body of research suggests that activation of the mother's immune system during pregnancy may act as a disease primer, in combination with other environmental and genetic factors, contributing to an increased risk of neurodevelopmental disorders, including schizophrenia. Animal models provide an invaluable opportunity to examine the course of brain and behavioral changes in offspring exposed to maternal immune activation (MIA). Although the vast majority of MIA research has been carried out in rodents, here we highlight the translational utility of the nonhuman primate (NHP) as a model species more closely related to humans in PFC structure and function. In this review, we consider the protracted period of brain and behavioral maturation in the NHP, describe emerging findings from MIA NHP offspring in the context of rodent preclinical models, and lastly explore the translational relevance of the NHP MIA model to expand understanding of the etiology and developmental course of PFC pathology in schizophrenia.

Address correspondence to Cynthia M. Schumann, Ph.D., at cschumann@ucdavis.edu, or Melissa D. Bauman, Ph.D., at mdbauman@ucdavis.edu.

CMS and MDB contributed equally to this work as joint senior authors.

The authors report no biomedical financial interests or potential conflicts of interest.

EPIDEMIOLOGICAL EVIDENCE

Exposure to infection during pregnancy is associated with an increased risk of neurodevelopmental disorders in offspring, including schizophrenia (1). Mounting evidence indicates that disruption in fetal neurodevelopment may be due to the mother's immune response to the pathogen rather than the pathogen itself (2). This maternal immune activation (MIA) hypothesis is supported by a growing body of seroepidemiological studies that link specific maternal inflammatory biomarkers with offspring neurodevelopmental outcomes, ranging from subtle alterations to profound neurodevelopmental disorders (3). Preclinical animal models of MIA-exposed offspring offer powerful translational tools to evaluate the neurobiological consequences of artificially activating the maternal immune system during gestation in a controlled environment (1,4,5). While rodent model systems have greatly advanced our understanding of the link between MIA and atypical offspring neurodevelopment (6), nonhuman primates (NHPs) and humans share greater similarities in placental structure and pregnancy physiology, maternal-fetal interface, gestational timeline, fetal brain development, and overall brain structure–particularly in the prefrontal cortex (PFC) (7). The NHP model has emerged as a powerful tool to evaluate a diverse range of gestational conditions, such as obesity, poor diet, and maternal stress, that are associated with maternal inflammation and adverse neurodevelopmental outcomes (8). Indeed, emerging data from human (9–11,148) and NHP (12) studies suggest that natural variation in maternal cytokines, in the absence of an infection, can influence offspring neurodevelopment.

UNIQUE FEATURES OF NHPs

While no animal model can recapitulate human-specific, behaviorally defined brain disorders (13), here we focus on the unique translational potential of the most commonly employed NHP in biomedical research, the rhesus macaque (*Macaca mulatta*). Similar to humans, rhesus monkeys live in large social hierarchies and rely on sophisticated multimodal communicative repertoires (14). Brain regions underlying social and cognitive processing show similar patterns of activity in humans and NHPs (15). Figure 1 details the organization and complexity of the PFC in the rodent, monkey, and human brain. Although cross-species definitions of PFC vary (16–18), expansion of PFC regions has been a hallmark of primate evolution, with the elaboration of associative territories involved in executive function, emotional processing, and communication. Rhesus monkey and human brains follow very similar patterns in early gestation, when the symmetrical division of cortical progenitor cells yields units comprised of asymmetrically dividing progenitor cells, ultimately resulting in the production of cortical columns (19–21). Radial glia guide the migration of cortical neurons, yielding region-specific patterns of cytoarchitectural organization. This nearly 2-month-long period of neurogenesis and migration in the primate brain reflects its greater size and complexity (22), as neurons develop in place, producing dendritic arbors and developing spines across the primate life span (23,24). Importantly, the onset of rapid synaptogenesis occurs prenatally in humans and monkeys, but postnatally in rodents, representing a unique vulnerability in primate cortical development in utero that cannot be reproduced in rodent models. The process of myelination in the brain also follows species-specific trajectories (25), beginning postnatally in rats and mice and

prenatally in monkeys and humans–though not uniformly across all regions. The PFC may be especially vulnerable to prenatal insults such as MIA owing to its complexity as well as its unique protracted course of development and maturation. Myelination in the PFC continues long past sexual maturity, culminating around rodent postnatal day 90 to 100, age 13 years in the monkey (26), and into the third decade of life in humans (27,28). A complex interplay between glial cells, including oligodendrocytes and microglia, and neuronal cells contributes to the development of long-range connectivity in the brain and supports the structural development of myelin in white matter (29). Alterations to myelin development and structure are a particularly important feature of schizophrenia (30) and thus represent a critical pathway that may be affected by MIA in unique ways in the primate brain.

ESTABLISHING THE NHP MIA MODEL

In this review, we focus on the poly(I:C) (polyinosinic:polycytidylic acid)–based rhesus monkey MIA model established in our laboratory that characterizes offspring neurodevelopment through the critical period of late adolescence/early adulthood (birth to 4 years of age) that captures dynamic PFC-related changes in brain and behavioral development. We first evaluated behavioral development in NHP offspring born to dams injected with the viral mimic, poly(I:C), in the late first or second trimester (31,32) and later expanded our characterization of this cohort to include immune system evaluation (33), in vivo positron emission tomography imaging (34), and postmortem cellular and molecular studies [K.L. Hanson, Ph.D., *et al.,* unpublished data, May 2022; (35)]. Although we are at the earliest stages of exploring neuropathology in the NHP MIA model, the gestational timing of the prenatal immune challenge may provide some insight into which stages of fetal brain development may be affected. Peak periods of neurogenesis for subcortical structures, including the amygdala (36), thalamus (37), striatum (38), and hippocampus (39), occur during the late first trimester. In macaques, corticogenesis also begins at the end of the first trimester and continues through the second trimester (40). Exposure to prenatal immune challenge may disrupt these finely orchestrated events and could initiate a cascade of aberrant brain and behavioral development. Alterations in offspring social development were observed in offspring exposed to MIA in the first (but not second) trimester, which led us to focus exclusively on MIA induction in the late first trimester in our subsequent larger cohorts (41).

Social Development in MIA NHP Offspring

Our initial NHP MIA model generated two cohorts of offspring born to dams that received three injections of a modified form of poly(I:C) in either the late first or the second trimester, and these cohorts were compared with offspring born to saline-injected or untreated dams (31). Both groups of MIA-exposed offspring initially exhibited species-typical patterns of development and were indistinguishable from control offspring in the majority of early developmental assessments. MIA-treated offspring developed a species-typical repertoire of vocalizations, body postures, and facial expressions used to facilitate rhesus monkey social interactions and did not differ from control offspring in the amount of time they spent engaged in social interactions, including reciprocal play behavior with age-matched peers. However, when the MIA animals were temporarily removed from these

familiar environments and observed alone, they produced more motor stereotypic behaviors compared with control animals. Under these conditions, the second-trimester MIA–exposed offspring also demonstrated a reduction in affiliative coo call vocalizations that are thought to serve the function of reestablishing contact with conspecifics (42–44). Interestingly, the group with first-trimester MIA exposure demonstrated a reduction in coo calls when removed from their home cage and introduced to an unfamiliar peer in a modified version of the rodent social approach test described below, suggesting that the presence of an unfamiliar animal may differentially impact social buffering for the MIA groups (45,46).

In contrast to rodents, rhesus monkeys exhibit a species-typical hesitation before immediately approaching and interacting with an unfamiliar animal–failure of which can have negative consequences, including physical harm (47,48). However, the first-trimester MIA–exposed offspring more frequently approached the unfamiliar animals and spent nearly twice as much time in the immediate proximity of the novel animal compared with the other two groups. We next initiated a series of noninvasive eye-tracking studies to evaluate gaze patterns of the NHPs with first-trimester MIA exposure when viewing social images depicting rhesus monkey facial expressions (32). MIA-treated offspring showed a reduction in average fixation time after the first presentation that was not observed in control offspring. The MIA-treated animals also took longer than the control animals to direct their attention to the eyes and looked less at the eyes than control animals when viewing fearful/submissive faces. Collectively, these initial studies indicate that MIA-treated NHPs fail to regulate species-typical social behavior across both controlled and semi-naturalistic contexts in response to potentially threatening stimuli. As described below, we consider these impairments in species-typical social behavior demonstrated by the MIA-treated NHP offspring to be translationally relevant to changes in social cognition in individuals with schizophrenia (49). Additional studies are under way to map the emergence of changes in species-typical development in our most recent cohort of MIA-exposed NHPs, which, as described below, includes longitudinal eye-tracking data. As our understanding of rearing practices and housing conditions that reduce stress among laboratory-reared NHPs has advanced in the 15 years since the original cohort was created (50–52), these more recent studies may also provide insight into interactions between enhanced enrichment, social buffering, and stress reduction (45,53) and the emergence of MIA-induced behavioral changes.

Cognitive Development in MIA NHP Offspring

Recent work in a cohort of first-trimester MIA–exposed male offspring has explored the emergence of brain and behavioral changes from birth to 4 years of age (41), highlighting the effects of MIA on the cognitive phenotype. In addition to forthcoming comprehensive assessment of social development, the NHP MIA offspring were tested using a variety of cognitive tasks relevant to PFC function, beginning with a reversal learning paradigm at 18 months of age, followed by additional cognitive assessments from 3 to 4 years that included the continuous performance test, probabilistic reversal learning task, progressive ratio breakpoint task, and intradimensional/extradimensional task. These tasks assess attention, reward learning, motivation, and set shifting, similar to paradigms used in schizophrenia research. Overall, MIA offspring performed similarly to control offspring, while exhibiting

subtle, but consistent differences in measures of omission errors (reversal learning), misses in the intradimensional/extradimensional task, and an increased number of false alarms on the continuous performance test. These differences appear to reflect a difficulty adaptively forming and using a task set or an overemphasis of negative feedback on performance. In the vast majority of measures, MIA offspring perform similarly to control offspring, in contrast to the relatively robust changes found in brain imaging. Age at testing likely contributes to variability in findings, as NHP late adolescence may be comparable to the age of the prodromal phase seen in individuals with schizophrenia.

PFC Vulnerability in NHP MIA Model

In our early analyses, the PFC had already emerged as uniquely vulnerable to in utero MIA exposure in NHPs. The same animals that exhibited subtle impairments in cognitive performance described above also underwent longitudinal neuroimaging at 6 months and yearly from ages 1 to 4 (41). MIA-treated offspring demonstrated a significant reduction in frontal and prefrontal gray matter that was first detected at 6 months of age and persisted through the final scan at nearly 4 years of age. Additionally, there was a significant reduction in underlying white matter that emerged between 3 and 4 years of age. Taken together, it appears that volumetric reductions are specific to the frontal lobes in MIA NHP offspring and persist across the early life span. As described below, volumetric reductions have emerged as a consistent outcome in rodent MIA models (54) and have been reported following prenatal influenza exposure in NHPs (55). Although future cellular and molecular studies on postmortem brain tissue from this cohort are needed to provide insight into the neurobiological mechanisms underlying this reduction, preliminary in vivo neuroimaging results (56) suggest a significant increase in extracellular free water, a potential biomarker for neuroinflammation seen in first-episode psychosis (57–59) that has also been noted in rats exposed in utero to MIA (60).

We have initiated studies to evaluate brain tissue from our early pilot cohorts, finding differences in dendritic morphology of pyramidal cells in dorsolateral prefrontal cortex (DLPFC) of MIA-exposed NHP offspring (61). Specifically, analyses of Golgi-stained neurons revealed reduced diameter of apical dendrites as well as increased branching of apical dendrites from tissue obtained in late adolescence. These results were replicated in a subsequent cohort (K.L. Hanson, Ph.D., *et al.*, unpublished data, May 2022) that additionally found outcomes were not affected by first- or second-trimester exposure. Though it is not known when these morphological changes emerged, atrophy of apical dendrites in PFC neurons (including reduced diameter) has been associated with chronic stress (62,63). Given that peripubertal stress has been shown to exacerbate some of the MIA-induced changes in rodent offspring neurodevelopment (64,65), our ongoing studies include more comprehensive assessments of biological indices of stress, including cortisol and inflammatory biomarkers. Interestingly, increased apical dendritic branching has also been shown in rats exposed to high levels of ethanol in adolescence (66). The structure of dendritic trees determines the electrophysiological properties of neurons (67–71), and morphological variability of branch points may significantly alter synaptic activity by decreasing differential impedance, affecting cellular excitability (72). Thus, MIA exposure resulting in changes to the morphology of apical dendrites may have significant

consequences for membrane excitability and neuronal function and the balance of inputs to cortical neurons.

We have also observed differences in gene expression in MIA NHP offspring from initial pilot cohorts that further hint at aberrant neurodevelopment affecting the PFC (35). RNA sequencing was performed in the DLPFC and the anterior cingulate cortex along with the hippocampus and primary visual cortex, and results were compared between NHP offspring with first- and second-trimester MIA exposure and control animals. Similar to morphological findings, differences in gene expression showed a high degree of concordance between first- and second-trimester MIA–exposed NHP offspring, with the notable exception of greater downregulation of the serotonin receptor-associated gene *HTR3A* in first-trimester MIA–exposed NHP offspring. Importantly, gene expression differences were observed with region-specific effects: the DLPFC showed a significantly higher number of differently expressed genes than the anterior cingulate cortex, where effects were minimal. This finding underscores the importance of examining the highly derived DLPFC region, which may be especially vulnerable to the effects of MIA that cannot be observed in rodent PFC.

COMPARISON WITH RODENT MIA MODELS

Although the focus of this review is on NHP MIA models, it is important to acknowledge that the vast majority of MIA models have used rodents to provide foundational knowledge on the neurodevelopmental consequences of MIA exposure. Alongside increased costs and methodological constraints associated with their extended life history and development, the greater physical, psychological, and social needs of primates require unique ethical considerations for their use in research in captivity. Rodent models additionally offer expanded utility in modeling genetic differences, environmental stressors, and drug treatment effects as well as allowing for the use of complex mechanistic protocols, including optogenetic or chemogenetic manipulations. It is also possible to generate larger cohort sizes among litters, which can reduce the variability in a model that is quite variable (6), while also increasing statistical power. Although NHPs are an excellent modeling system for MIA to compare to the human condition, foundational studies in the rodent are valuable for establishing mechanisms of MIA in a reasonably short time frame. Below we briefly summarize the extensive literature of behavioral and PFC-related pathologies across rodent MIA models, despite significant evolutionary differences between mice and rats that impact performance in these behavioral domains (73,74).

Overview of Social and Cognitive Deficits in the Rodent MIA Models

More comprehensive reviews of behavioral alterations in rodent MIA models (75,76) have demonstrated the influence of sex, strain, species, vendor, MIA-induction methods, and postnatal testing paradigms and ages. Despite methodological variability, changes in species-typical social development have emerged as a common feature of many rodent MIA models (6). MIA-exposed rodent offspring consistently show impairments in social approach, especially when MIA induction occurs in early to mid-gestation (75). Although early MIA models focused on adult-onset changes in behavior, several recent studies have demonstrated

social behavior deficits in prepubertal animals (77,78), suggesting that impairments in social behavior might be an early indicator of MIA-induced behavioral pathology. Indeed, several studies have reported alterations in pup ultrasonic vocalizations (79–81), which are often interpreted as an early communicative signal of mother-pup interaction. Alterations in social behavior have also emerged as a key behavioral outcome that can be used to stratify MIA-exposed mice into susceptible and resilient groups (82), though additional factors including offspring sex, inflammatory status, and postnatal environment may also play a role in the emergence of MIA-induced social deficits (82–86). MIA-induced changes in cognitive abilities have also been reported in numerous rodent studies. Working memory is commonly assessed using the spontaneous alternation task or T-maze alternation task, and most MIA studies report a deficit in the rodent's ability to remember the arms it has previously entered (87–93). Tests that require associative learning or memory beyond working memory capacity include the novel object recognition task, Morris water maze, latent inhibition, and fear conditioning. MIA rodents in general also tend to have deficits in these associative learning tasks (77,94–101,147), although some studies have reported no differences in learning between control and treatment groups (102). Evidence suggests that performance on associative or working memory–based learning with a reward component is more variable. On touch screen visual discrimination, simple odor discrimination, set shifting, and trial-unique nonmatching-to-location tasks, many studies report a decrease in performance in MIA offspring (92,103–108), though several studies show performance equal to or greater than control animals (103–112). Although early MIA models focused on adult-onset changes in behavior, cognitive deficits have also been reported in MIA-exposed juveniles (77,87).

Overview of PFC Pathology in Rodent MIA Models

The rodent MIA field is quickly evolving and will likely provide additional insight into potential mechanistic differences underlying social and cognitive deficits, which will clarify what changes, if any, are occurring in the PFC and other relevant brain regions. MIA-exposed rodent offspring demonstrate numerous alterations in cellular and molecular properties, neurochemistry, structure, and function in different brain regions (113). Given the role of the PFC in mediating social and cognitive processes across species (114,115), it is not surprising that many rodent MIA models have noted PFC pathology. Global volumetric reductions are consistently noted in rodent MIA models (54), with reduced frontal volume reported in both mid-gestation MIA–treated rats (116,117) and late first trimester MIA–treated NHPs (41). Emerging cellular and molecular findings in rodent models have hinted at important future directions for guiding investigations into the long-term effects of MIA in the NHP PFC. Disruptions to immune processes in the rodent PFC are of particular translational interest, though the effects of MIA on activated microglia, a common target of investigations in schizophrenia, remain controversial (118). A popular hypothesis in the etiology and presentation of neurodevelopmental disorders highlights the disruption in the balance between inhibitory and excitatory neuronal signaling, which has been implicated in schizophrenia (119,120). Interestingly, rodent MIA models have demonstrated significant changes in excitatory and inhibitory neurotransmission, specifically implicating the interaction of dendritic spines with vGlut2 and GAD65 positive presynaptic puncta (121). Further evidence of disruptions to the GABAergic (gamma-aminobutyric

acidergic) system includes reduced expression of GAD65/67 messenger RNA and hypermethylation of GAD (glutamic acid decarboxylase) promoter regions in the PFC (88). Additionally, evidence from rodent models suggests selective vulnerabilities in inhibitory cell types: MIA-exposed rats showed a significant decrease in the number of parvalbumin-positive inhibitory interneurons surrounded by perineuronal nets in the medial PFC (122). Systemic loss of perineuronal nets is known to be a feature of schizophrenia, and investigating the impacts of changes in parvalbumin-positive interneuron architecture may be of particular interest for understanding altered cellular communication. Critically, alterations to the GABAergic system show a protracted developmental trajectory in NHPs, such that inhibitory synapses of interneurons onto pyramidal neurons in the DLPFC strengthen in adolescence (123), particularly in parvalbumin-positive subtypes (124). Further, disruptions to multiple neurotransmitter systems, including dopamine and serotonin, have been identified in rodent MIA models. Given the centrality of dopamine to many hypotheses of schizophrenia pathophysiology and that more extensive dopaminergic innervation is a hallmark of primate PFC, examining these systems in an NHP model may be of exceptional importance. Of course, these systems require examination in the context of the broader network of motivational and reward-related circuitry, implicating frontostriatal and frontoamygdalar circuitry, the latter of which shows distinctive patterns of change in inhibitory neurotransmission (125) between subjects exposed to either prenatal or postnatal immune activation.

TRANSLATIONAL RELEVANCE TO SCHIZOPHRENIA

We suggest that the protracted period of development, sophisticated behavioral repertoire, and complex PFC neuroanatomy positions the NHP MIA model to bridge the gap between rodent MIA models and clinical studies (Figure 2). The primate PFC undergoes rapid and dynamic refinement during the adolescent period (126), and MIA may set the stage for altered neurodevelopment with long-term consequences that ultimately manifest during the critical time when symptoms of psychiatric illness occur (127,128). Following a period of typical early development, the MIA-exposed NHPs in our research begin to exhibit changes in brain and behavioral development spanning a period roughly equivalent to early childhood through late adolescence that are translationally relevant to the neurodevelopmental trajectory of schizophrenia (129). Our early studies (31,32) revealed alterations in species-typical social development in MIA-exposed NHPs that are relevant to core domains of social cognition impacted by schizophrenia (130). The restricted scan path strategy and reduced attention to salient facial features exhibited by MIA-exposed NHPs in late adolescence shares features with individuals with schizophrenia (131). The development of noninvasive eye-tracking methods (132) has allowed us to incorporate longitudinal eye tracking into our most recent MIA cohorts and will be the focus of future publications, allowing us to explore the emergence of social, cognitive, and in vivo brain changes in the same animals. Indeed, the subtle impairments of cognitive performance exhibited by this latest cohort of MIA-treated NHPs align with the premorbid phase of schizophrenia, characterized by attentional and other cognitive deficits in later childhood and adolescence (133) that become more severe over time (134). The cognitive tasks used in that study were also chosen for their translatability to clinical work, as evidenced by impairments in these

domains at various stages of disease progression (135–137). Given that our NHP cohort is still at the early stages of development, behavioral differences between groups may be more subtle and continue to evolve (138).

Investigations at multiple levels indicate widespread dysfunction and altered organization of the PFC in schizophrenia and strongly implicate the primate DLPFC (139). Our recent work demonstrates that MIA-treated NHPs display reduced PFC volumes at 3.5 to 4 years of age (41), a period that coincides roughly with observations of reduced gray matter volume in adolescents with schizophrenia (140,141) and may serve as a biomarker of neurodevelopmental risk (142). Though postmortem investigations from MIA-treated NHPs provide only a snapshot in time, cellular (61) and molecular (35) differences indicate important changes in the adolescent brain in MIA-exposed NHP PFC that may share characteristics with psychiatric illness. However, the majority of postmortem studies in schizophrenia are carried out in adults; postmortem studies of MIA-exposed NHPs provide an important opportunity to evaluate cellular and molecular changes before symptoms appear. Additional research into the longitudinal effects of MIA on the brain has the potential to elucidate broader long-term consequences with relevance to altered neurodevelopment across the human life span. As noted above, schizophrenia is a highly heterogeneous disorder with multiple comorbidities, including medications and environmental influences. Research using postmortem brain tissue from individuals with schizophrenia provides insight into the cellular and molecular outcomes of the disorder, but is also complicated by the heterogeneous life history of each individual. Rodent studies provide a controlled environment from which to consider the etiology and course of schizophrenic features, but they are limited by substantial differences in PFC structure and function. NHPs, who share the unique architecture of the brain and developmental trajectory with humans, provide an invaluable compromise in a controlled environment to model features of schizophrenia longitudinally across the life span, for tremendous insight into potential etiologies such as MIA, and to develop strategies that intervene before symptoms worsen during the vulnerable period of adolescence. The MIA model may also provide insight into the complex developmental epigenetic mechanisms that link early MIA with schizophrenia etiology in late adolescence and early adulthood (143). Indeed, rodent models have identified transcriptomic and epigenomic mechanisms that mediate the downstream effects of MIA in rodent models, including PFC-specific alterations (144). Interestingly, transgenerational changes in MIA offspring behavior have been documented through multiple mouse generations (145,146). These effects were specific to offspring of males born to MIA-treated mothers, indicating that paternal sperm methylation may have been the source of this transgenerational effect. Our future NHP models will explore these transcriptomic and epigenomic mechanisms in a species more closely related to humans.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the University of California, Davis, Conte Center (National Institute of Mental Health Grant Nos. P50MH106438 and P50MH106438-06 [to MDB]) and the University of California, Davis, MIND Institute Intellectual and Developmental Disabilities Research Center (Eunice Kennedy Shriver National Institute of Child Health and Human Development Grant No. P50HD103526). SG was supported by the UC Davis Training Program in Learning, Memory, and Plasticity (Grant No. T32 MH112507).

We thank collaborators of the University of California, Davis, Conte Center and MIND Institute Intellectual and Developmental Disabilities Research Center for conversations on the topic and Anurupa Kar and Felicia Carbajal for assistance in preparing the manuscript.

REFERENCES

1. Brown AS, Meyer U (2018): Maternal immune activation and neuropsychiatric illness: A translational research perspective. Am J Psychiatry 175:1073–1083. [PubMed: 30220221]
2. Han VX, Patel S, Jones HF, Dale RC (2021): Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat Rev Neurol 17:564–579. [PubMed: 34341569]
3. Han VX, Patel S, Jones HF, Nielsen TC, Mohammad SS, Hofer MJ, et al. (2021): Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. Transl Psychiatry 11:71. [PubMed: 33479207]
4. Bauman MD, Van de Water J (2020): Translational opportunities in the prenatal immune environment: Promises and limitations of the maternal immune activation model. Neurobiol Dis 141:104–864.
5. Gumusoglu SB, Stevens HE (2019): Maternal inflammation and neurodevelopmental programming: A review of preclinical outcomes and implications for translational psychiatry. Biol Psychiatry 85:107–121. [PubMed: 30318336]
6. Kentner AC, Bilbo SD, Brown AS, Hsiao EY, McAllister AK, Meyer U, et al. (2019): Maternal immune activation: Reporting guidelines to improve the rigor, reproducibility, and transparency of the model. Neuropsychopharmacology 44:245–258. [PubMed: 30188509]
7. Tarantal AF, Hartigan-O'Connor DJ, Noctor SC (2022): Translational utility of the nonhuman primate model. Biol Psychiatry Cogn Neurosci Neuroimaging 7:491–497. [PubMed: 35283343]
8. Bauman MD, Buss C (2022): Maternal proinflammatory processes and fetal neurodevelopment: Integrating clinical and preclinical research approaches and identifying knowledge gaps that warrant future collaboration. Biol Psychiatry Cogn Neurosci Neuroimaging 7:444–446. [PubMed: 35534095]
9. Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M, et al. (2018): Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. Biol Psychiatry 83:109–119. [PubMed: 28754515]
10. Rasmussen JM, Graham AM, Entringer S, Gilmore JH, Styner M, Fair DA, et al. (2019): Maternal interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. Neuroimage 185:825–835. [PubMed: 29654875]
11. Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, et al. (2018): Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nat Neurosci 21:765–772. [PubMed: 29632361]
12. Ramirez JSB, Graham AM, Thompson JR, Zhu JY, Sturgeon D, Bagley JL, et al. (2020): Maternal interleukin-6 is associated with macaque offspring amygdala development and behavior. Cereb Cortex 30:1573–1585. [PubMed: 31665252]
13. NIMH Director's Message: A hypothesis-based approach: The use of animals in mental health research. Available at: https://www.nimh.nih.gov/about/director/messages/2019/a-hypothesis-based-approach-the-use-of-animals-in-mental-health-research. Accessed January 5, 2022.
14. Chang SW, Brent LJ, Adams GK, Klein JT, Pearson JM, Watson KK, et al. (2013): Neuroethology of primate social behavior. Proc Natl Acad Sci U S A. 110(Suppl 2):10387–10394. [PubMed: 23754410]
15. Platt ML, Seyfarth RM, Cheney DL (2016): Adaptations for social cognition in the primate brain. Philos Trans R Soc Lond B Biol Sci 371:20150096. [PubMed: 26729935]
16. Carlen M (2017): What constitutes the prefrontal cortex? Science 358:478–482. [PubMed: 29074767]
17. Preuss TM, Wise SP (2022): Evolution of prefrontal cortex. Neuropsychopharmacology 47:3–19. [PubMed: 34363014]

18. Preuss TM (1995): Do rats have prefrontal cortex? The Rose-Woolsey-Akert program reconsidered. J Cogn Neurosci 7:1–24. [PubMed: 23961750]
19. Bystron I, Blakemore C, Rakic P (2008): Development of the human cerebral cortex: Boulder Committee revisited. Nat Rev Neurosci 9:110–122. [PubMed: 18209730]
20. Rakic P (1995): Radial versus tangential migration of neuronal clones in the developing cerebral cortex. Proc Natl Acad Sci U S A 92:11323–11327. [PubMed: 8524778]
21. Sidman RL, Rakic P (1973): Neuronal migration, with special reference to developing human brain: A review. Brain Res 62:1–35. [PubMed: 4203033]
22. Finlay BL, Darlington RB (1995): Linked regularities in the development and evolution of mammalian brains. Science 268:1578–1584. [PubMed: 7777856]
23. Petanjek Z, Judas M, Kostovic I, Uylings HB (2008): Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. Cereb Cortex 18:915–929. [PubMed: 17652464]
24. Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HB, Rakic P, et al. (2011): Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A 108:13281–13286. [PubMed: 21788513]
25. Gibson KR (1991): Myelination and behavioral development: A comparative perspective on questions of neoteny, altnciality and intelligence. In: Gibson KR, Petersen AC, editors. Brain Maturation and Cognitive Development. New York: Routledge.
26. Machado CJ, Bachevalier J (2003): Non-human primate models of childhood psychopathology: The promise and the limitations. J Child Psychol Psychiatry 44:64–87. [PubMed: 12553413]
27. Levitt P (2003): Structural and functional maturation of the developing primate brain. J Pediatr 143:S35–S45. [PubMed: 14597912]
28. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, McArthur MJ, et al. (2012): Prolonged myelination in human neocortical evolution. Proc Natl Acad Sci U S A 109:16480–16485. [PubMed: 23012402]
29. Chew LJ, Fusar-Poli P, Schmitz T (2013): Oligodendroglial alterations and the role of microglia in white matter injury: Relevance to schizophrenia. Dev Neurosci 35:102–129. [PubMed: 23446060]
30. Whitford TJ, Ford JM, Mathalon DH, Kubicki M, Shenton ME (2012): Schizophrenia, myelination, and delayed corollary discharges: A hypothesis. Schizophr Bull 38:486–494. [PubMed: 20855415]
31. Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, Patterson PH (2014): Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. Biol Psychiatry 75:332–341. [PubMed: 24011823]
32. Machado CJ, Whitaker AM, Smith SE, Patterson PH, Bauman MD (2015): Maternal immune activation in nonhuman primates alters social attention in juvenile offspring. Biol Psychiatry 77:823–832. [PubMed: 25442006]
33. Rose DR, Careaga M, Van de Water J, McAllister K, Bauman MD, Ashwood P (2017): Long-term altered immune responses following fetal priming in a non-human primate model of maternal immune activation. Brain Behav Immun 63:60–70. [PubMed: 27876552]
34. Bauman MD, Lesh TA, Rowland DJ, Schumann CM, Smucny J, Kukis DL, et al. (2019): Preliminary evidence of increased striatal dopamine in a nonhuman primate model of maternal immune activation. Transl Psychiatry 9:135. [PubMed: 30979867]
35. Page NF, Gandal MJ, Estes ML, Cameron S, Buth J, Parhami S, et al. (2021): Alterations in retrotransposition, synaptic connectivity, and myelination implicated by transcriptomic changes following maternal immune activation in nonhuman primates. Biol Psychiatry 89:896–910. [PubMed: 33386132]
36. Kordower JH, Piecinski P, Rakic P (1992): Neurogenesis of the amygdaloid nuclear complex in the rhesus monkey. Brain Res Dev Brain Res 68:9–15. [PubMed: 1521327]
37. Ogren MP, Racic P (1981): The prenatal development of the pulvinar in the monkey: 3H-Thymidine autoradiographic and morphometric analyses. Anat Embryol (Berl) 162:1–20. [PubMed: 7283168]

38. Brand S, Rakic P (1979): Genesis of the primate neostriatum: [3H] Thymidine autoradiographic analysis of the time of neuron origin in the rhesus monkey. Neuroscience 4:767–778. [PubMed: 113693]
39. Rakic P, Nowakowski RS (1981): The time of origin of neurons in the hippocampal region of the rhesus monkey. J Comp Neurol 196:99–128. [PubMed: 7204668]
40. Rakic P (1988): Specification of cerebral cortical areas. Science 241:170–176. [PubMed: 3291116]
41. Vlasova RM, Iosif AM, Ryan AM, Funk LH, Murai T, Chen S, et al. (2021): Maternal immune activation during pregnancy alters postnatal brain growth and cognitive development in nonhuman primate offspring. J Neurosci 41:9971–9987. [PubMed: 34607967]
42. Kalin NH, Shelton SE (1998): Ontogeny and stability of separation and threat-induced defensive behaviors in rhesus monkeys during the first year of life. Am J Primatol 44:125–135. [PubMed: 9503124]
43. Owren MJ, Dieter JA, Seyfarth RM, Cheney DL (1993): Vocalizations of rhesus (*Macaca mulatta*) and Japanese (*M. fuscata*) macaques cross-fostered between species show evidence of only limited modification. Dev Psychobiol 26:389–406. [PubMed: 8270122]
44. Kalin NH, Shelton SE, Snowdon CT (1992): Affiliative vocalizations in infant rhesus macaques (*Macaca mulatta*). J Comp Psychol 106:254. [PubMed: 1395495]
45. Gilbert MH, Baker KC (2011): Social buffering in adult male rhesus macaques (*Macaca mulatta*): Effects of stressful events in single vs. pair housing. J Med Primatol 40:71–78. [PubMed: 21371035]
46. Winslow JT, Noble PL, Lyons CK, Sterk SM, Insel TR (2003): Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. Neuropsychopharmacology 28:910–918. [PubMed: 12700704]
47. Fairbanks LA (2001): Individual differences in response to a stranger: Social impulsivity as a dimension of temperament in vervet monkeys (*Cercopithecus aethiops sabaeus*). J Comp Psychol 115:22–28. [PubMed: 11334215]
48. Kinnally EL, Whiteman HJ, Mason WA, Mendoza SP, Capitanio JP (2008): Dimensions of response to novelty are associated with social engagement and aggression in adult male rhesus macaques (*Macaca mulatta*). J Comp Psychol 122:195–203. [PubMed: 18489235]
49. Kimoto S, Makinodan M, Kishimoto T (2019): Neurobiology and treatment of social cognition in schizophrenia: Bridging the bed-bench gap. Neurobiol Dis 131:104315. [PubMed: 30391541]
50. Lutz C, Well A, Novak M (2003): Stereotypic and self-injurious behavior in rhesus macaques: A survey and retrospective analysis of environment and early experience. Am J Primatol 60:1–15.
51. Hannibal DL, Bliss-Moreau E, Vandeleest J, McCowan B, Capitanio J (2017): Laboratory rhesus macaque social housing and social changes: Implications for research. Am J Primatol 79:1–14.
52. Cassidy LC, Hannibal DL, Semple S, McCowan B (2020): Improved behavioral indices of welfare in continuous compared to intermittent pair-housing in adult female rhesus macaques (*Macaca mulatta*). Am J Primatol 82:e23189. [PubMed: 32890432]
53. Hennessy MB, Chun K, Capitanio JP (2017): Depressive-like behavior, its sensitization, social buffering, and altered cytokine responses in rhesus macaques moved from outdoor social groups to indoor housing. Soc Neurosci 12:65–75. [PubMed: 26801639]
54. Guma E, Plitman E, Chakravarty MM (2019): The role of maternal immune activation in altering the neurodevelopmental trajectories of offspring: A translational review of neuroimaging studies with implications for autism spectrum disorder and schizophrenia. Neurosci Biobehav Rev 104:141–157. [PubMed: 31265870]
55. Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, et al. (2010): Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. Biol Psychiatry 67:965–973. [PubMed: 20079486]
56. Carter CS, Lesh TA, Iosif AM, Tanase C, Vlasova RM, Styner M, et al. (2020): T33. Neuroimmune mechanisms of psychiatric disorders: Longitudinal evaluation of diffusion measures of extracellular free water in a nonhuman primate model of maternal immune activation. Schizophr Bull 46(Suppl_1):S244.

57. Lesh TA, Maddock RJ, Howell A, Wang H, Tanase C, Ragland JD, et al. (2021): Extracellular free water and glutathione in first-episode psychosis–a multimodal investigation of an inflammatory model for psychosis. Mol Psychiatry 26:761–771. [PubMed: 31138893]
58. Lyall AE, Pasternak O, Robinson DG, Newell D, Trampush JW, Gallego JA, et al. (2018): Greater extracellular free-water in first-episode psychosis predicts better neurocognitive functioning. Mol Psychiatry 23:701–707. [PubMed: 28348381]
59. Pasternak O, Westin CF, Bouix S, Seidman LJ, Goldstein JM, Woo TU, et al. (2012): Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J Neurosci 32:17365–17372. [PubMed: 23197727]
60. Di Biase MA, Katabi G, Piontkewitz Y, Cetin-Karayumak S, Weiner I, Pasternak O (2020): Increased extracellular free-water in adult male rats following in utero exposure to maternal immune activation. Brain Behav Immun 83:283–287. [PubMed: 31521731]
61. Weir RK, Forghany R, Smith SE, Patterson PH, McAllister AK, Schumann CM, et al. (2015): Preliminary evidence of neuropathology in nonhuman primates prenatally exposed to maternal immune activation. Brain Behav Immun 48:139–146. [PubMed: 25816799]
62. Cook SC, Wellman CL (2004): Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J Neurobiol 60:236–248. [PubMed: 15266654]
63. Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, et al. (2004): Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125:1–6. [PubMed: 15051139]
64. Giovanoli S, Engler H, Engler A, Richetto J, Feldon J, Riva MA, et al. (2016): Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia. Transl Psychiatry 6:e772. [PubMed: 27045842]
65. Giovanoli S, Engler H, Engler A, Richetto J, Voget M, Willi R, et al. (2013): Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. Science 339:1095–1099. [PubMed: 23449593]
66. Kipp BT, Nunes PT, Galaj E, Hitchcock B, Nasra T, Poynor KR, et al. (2021): Adolescent ethanol exposure alters cholinergic function and apical dendritic branching within the orbital frontal cortex. Neuroscience 473:52–65. [PubMed: 34450212]
67. Gulledge AT, Kampa BM, Stuart GJ (2005): Synaptic integration in dendritic trees. J Neurobiol 64:75–90. [PubMed: 15884003]
68. Hausser M, Spruston N, Stuart GJ (2000): Diversity and dynamics of dendritic signaling. Science 290:739–744. [PubMed: 11052929]
69. Jaffe DB, Carnevale NT (1999): Passive normalization of synaptic integration influenced by dendritic architecture. J Neurophysiol 82:3268–3285. [PubMed: 10601459]
70. Magee JC (2000): Dendritic integration of excitatory synaptic input. Nat Rev Neurosci 1:181–190. [PubMed: 11257906]
71. Reyes A (2001): Influence of dendritic conductances on the input-output properties of neurons. Annu Rev Neurosci 24:653–675. [PubMed: 11520915]
72. Ferrante M, Migliore M, Ascoli GA (2013): Functional impact of dendritic branch-point morphology. J Neurosci 33:2156–2165. [PubMed: 23365251]
73. Vanderschuren LJ, Trezza V (2014): What the laboratory rat has taught us about social play behavior: Role in behavioral development and neural mechanisms. Curr Top Behav Neurosci 16:189–212. [PubMed: 24338663]
74. Gibbs RA, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, Scherer S, et al. (2004): Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature 428:493–521. [PubMed: 15057822]
75. Haddad FL, Patel SV, Schmid S (2020): Maternal immune activation by poly I:C as a preclinical model for neurodevelopmental disorders: A focus on autism and schizophrenia. Neurosci Biobehav Rev 113:546–567. [PubMed: 32320814]
76. Careaga M, Murai T, Bauman MD (2017): Maternal immune activation and autism spectrum disorder: From rodents to nonhuman and human primates. Biol Psychiatry 81:391–401. [PubMed: 28137374]

77. Vuillermot S, Luan W, Meyer U, Eyles D (2017): Vitamin D treatment during pregnancy prevents autism-related phenotypes in a mouse model of maternal immune activation. Mol Autism 8:9. [PubMed: 28316773]

78. Vitor-Vieira F, Vilela FC, Giusti-Paiva A (2021): Hyperactivation of the amygdala correlates with impaired social play behavior of prepubertal male rats in a maternal immune activation model. Behav Brain Res 414:113503. [PubMed: 34331970]

79. Weiser MJ, Mucha B, Denheyer H, Atkinson D, Schanz N, Vassiliou E, et al. (2016): Dietary docosahexaenoic acid alleviates autistic-like behaviors resulting from maternal immune activation in mice. Prostaglandins Leukot Essent Fatty Acids 106:27–37. [PubMed: 26703213]

80. Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, et al. (2017): Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. Nature 549:528–532. [PubMed: 28902840]

81. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. (2013): Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155:1451–1463. [PubMed: 24315484]

82. Mueller FS, Scarborough J, Schalbetter SM, Richetto J, Kim E, Couch A, et al. (2021): Behavioral, neuroanatomical, and molecular correlates of resilience and susceptibility to maternal immune activation. Mol Psychiatry 26:396–410. [PubMed: 33230204]

83. Braun AE, Carpentier PA, Babineau BA, Narayan AR, Kielhold ML, Moon HM, et al. (2019): "Females are not just 'protected' males": Sex-specific vulnerabilities in placenta and brain after prenatal immune disruption. eNeuro 6:ENEURO.0358-19.2019.

84. Nunez Estevez KJ, Rondon-Ortiz AN, Nguyen JQT, Kentner AC (2020): Environmental influences on placental programming and offspring outcomes following maternal immune activation. Brain Behav Immun 83:44–55. [PubMed: 31493445]

85. Reed MD, Yim YS, Wimmer RD, Kim H, Ryu C, Welch GM, et al. (2020): IL-17a promotes sociability in mouse models of neurodevelopmental disorders. Nature 577:249–253. [PubMed: 31853066]

86. Carlezon WA Jr, Kim W, Missig G, Finger BC, Landino SM, Alexander AJ, et al. (2019): Maternal and early postnatal immune activation produce sex-specific effects on autism-like behaviors and neuroimmune function in mice. Sci Rep 9:16928. [PubMed: 31729416]

87. Giovanoli S, Notter T, Richetto J, Labouesse MA, Vuillermot S, Riva MA, et al. (2015): Late prenatal immune activation causes hippocampal deficits in the absence of persistent inflammation across aging. J Neuroinflammation 12:221. [PubMed: 26602365]

88. Labouesse MA, Dong E, Grayson DR, Guidotti A, Meyer U (2015): Maternal immune activation induces GAD1 and GAD2 promoter remodeling in the offspring prefrontal cortex. Epigenetics 10:1143–1155. [PubMed: 26575259]

89. Li W, Chen M, Feng X, Song M, Shao M, Yang Y, et al. (2021): Maternal immune activation alters adult behavior, intestinal integrity, gut microbiota and the gut inflammation. Brain Behav 11:e02133. [PubMed: 33793085]

90. Li W, Sun F, Guo X, Hu Y, Ding S, Ding M, et al. (2020): Behavioral abnormalities and phosphorylation deficits of extracellular signal-regulated kinases 1 and 2 in rat offspring of the maternal immune activation model. Physiol Behav 217:112805. [PubMed: 31954148]

91. O'Leary C, Desbonnet L, Clarke N, Petit E, Tighe O, Lai D, et al. (2014): Phenotypic effects of maternal immune activation and early postnatal milieu in mice mutant for the schizophrenia risk gene neuregulin-1. Neuroscience 277:294–305. [PubMed: 24969132]

92. Zhang Z, van Praag H (2015): Maternal immune activation differentially impacts mature and adult-born hippocampal neurons in male mice. Brain Behav Immun 45:60–70. [PubMed: 25449671]

93. Imai K, Kotani T, Tsuda H, Nakano T, Ushida T, Iwase A, et al. (2018): Administration of molecular hydrogen during pregnancy improves behavioral abnormalities of offspring in a maternal immune activation model. Sci Rep 8:9221. [PubMed: 29907804]

94. Batinic B, Santrac A, Divovic B, Timic T, Stankovic T, Obradovic A, et al. (2016): Lipopolysaccharide exposure during late embryogenesis results in diminished locomotor activity and amphetamine response in females and spatial cognition impairment in males in adult, but not adolescent rat offspring. Behav Brain Res 299:72–80. [PubMed: 26620494]

95. Fujita Y, Fujita A, Ishima T, Hirai A, Suzuki S, Suganuma H, et al. (2020): Dietary intake of glucoraphanin during pregnancy and lactation prevents the behavioral abnormalities in the offspring after maternal immune activation. Neuropsychopharmacol Rep 40:268–274. [PubMed: 32463181]

96. Gray A, Tattoli R, Dunn A, Hodgson DM, Michie PT, Harms L (2019): Maternal immune activation in mid-late gestation alters amphetamine sensitivity and object recognition, but not other schizophrenia-related behaviours in adult rats. Behav Brain Res 356:358–364. [PubMed: 30145278]

97. Lipina TV, Zai C, Hlousek D, Roder JC, Wong AH (2013): Maternal immune activation during gestation interacts with Disc1 point mutation to exacerbate schizophrenia-related behaviors in mice. J Neurosci 33:7654–7666. [PubMed: 23637159]

98. Mattei D, Ivanov A, Ferrai C, Jordan P, Guneykaya D, Buonfiglioli A, et al. (2017): Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. Transl Psychiatry 7:e1120. [PubMed: 28485733]

99. Meyer U, Feldon J, Schedlowski M, Yee BK (2006): Immunological stress at the maternal-foetal interface: A link between neurodevelopment and adult psychopathology. Brain Behav Immun 20:378–388. [PubMed: 16378711]

100. Osborne AL, Solowij N, Babic I, Lum JS, Huang XF, Newell KA, et al. (2019): Cannabidiol improves behavioural and neurochemical deficits in adult female offspring of the maternal immune activation (poly I:C) model of neurodevelopmental disorders. Brain Behav Immun. 81:574–587. [PubMed: 31326506]

101. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH (2007): Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27:10695–10702. [PubMed: 17913903]

102. Abazyan B, Nomura J, Kannan G, Ishizuka K, Tamashiro KL, Nucifora F, et al. (2010): Prenatal interaction of mutant DISC1 and immune activation produces adult psychopathology. Biol Psychiatry 68:1172–1181. [PubMed: 21130225]

103. Breach MR, Dye CN, Joshi A, Platko S, Gilfarb RA, Krug AR, et al. (2021): Maternal allergic inflammation in rats impacts the offspring perinatal neuroimmune milieu and the development of social play, locomotor behavior, and cognitive flexibility. Brain Behav Immun 95:269–286. [PubMed: 33798637]

104. Canetta S, Bolkan S, Padilla-Coreano N, Song LJ, Sahn R, Harrison NL, et al. (2016): Maternal immune activation leads to selective functional deficits in offspring parvalbumin interneurons. Mol Psychiatry 21:956–968. [PubMed: 26830140]

105. Gogos A, Sbisa A, Witkamp D, van den Buuse M (2020): Sex differences in the effect of maternal immune activation on cognitive and psychosis-like behaviour in Long Evans rats. Eur J Neurosci 52:2614–2626. [PubMed: 31901174]

106. Lins BR, Hurtubise JL, Roebuck AJ, Marks WN, Zabder NK, Scott GA, et al. (2018): Prospective analysis of the effects of maternal immune activation on rat cytokines during pregnancy and behavior of the male offspring relevant to schizophrenia. eNeuro 5:ENEURO.0249-18.2018.

107. Murray BG, Davies DA, Molder JJ, Howland JG (2017): Maternal immune activation during pregnancy in rats impairs working memory capacity of the offspring. Neurobiol Learn Mem 141:150–156. [PubMed: 28434949]

108. Zhao X, Tran H, DeRosa H, Roderick RC, Kentner AC (2021): Hidden talents: Poly (I:C)-induced maternal immune activation improves mouse visual discrimination performance and reversal learning in a sex-dependent manner. Genes Brain Behav 20:e12755. [PubMed: 34056840]

109. Bates V, Maharjan A, Millar J, Bilkey DK, Ward RD (2018): Spared motivational modulation of cognitive effort in a maternal immune activation model of schizophrenia risk. Behav Neurosci 132:66–74. [PubMed: 29553777]

110. Deane AR, Potemkin N, Ward RD (2021): Mitogen-activated protein kinase (MAPK) signalling corresponds with distinct behavioural profiles in a rat model of maternal immune activation. Behav Brain Res 396:112876. [PubMed: 32846206]

111. Nakamura JP, Gillespie B, Gibbons A, Jaehne EJ, Du X, Chan A, et al. (2021): Maternal immune activation targeted to a window of parvalbumin interneuron development improves

spatial working memory: Implications for autism. Brain Behav Immun 91:339–349. [PubMed: 33096253]

112. Zhang Y, Cazakoff BN, Thai CA, Howland JG (2012): Prenatal exposure to a viral mimetic alters behavioural flexibility in male, but not female, rats. Neuropharmacology 62:1299–1307. [PubMed: 21376064]
113. Bergdolt L, Dunaevsky A (2019): Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. Prog Neurobiol 175:1–19. [PubMed: 30590095]
114. Bicks LK, Koike H, Akbarian S, Morishita H (2015): Prefrontal cortex and social cognition in mouse and man. Front Psychol 6:1805. [PubMed: 26635701]
115. Liu Y, Konopka G (2020): An integrative understanding of comparative cognition: Lessons from human brain evolution. Integr Comp Biol 60:991–1006. [PubMed: 32681799]
116. Crum WR, Sawiak SJ, Chege W, Cooper JD, Williams SCR, Vernon AC (2017): Evolution of structural abnormalities in the rat brain following in utero exposure to maternal immune activation: A longitudinal in vivo MRI study. Brain Behav Immun 63:50–59. [PubMed: 27940258]
117. Piontkewitz Y, Arad M, Weiner I (2012): Tracing the development of psychosis and its prevention: What can be learned from animal models. Neuropharmacology 62:1273–1289. [PubMed: 21703648]
118. Smolders S, Notter T, Smolders SMT, Rigo JM, Brone B (2018): Controversies and prospects about microglia in maternal immune activation models for neurodevelopmental disorders. Brain Behav Immun 73:51–65. [PubMed: 29870753]
119. Anticevic A, Lisman J (2017): How can global alteration of excitation/inhibition balance lead to the local dysfunctions that underlie schizophrenia? Biol Psychiatry 81:818–820. [PubMed: 28063469]
120. Gao R, Penzes P (2015): Common mechanisms of excitatory and inhibitory imbalance in schizophrenia and autism spectrum disorders. Curr Mol Med 15:146–167. [PubMed: 25732149]
121. Coiro P, Padmashri R, Suresh A, Spartz E, Pendyala G, Chou S, et al. (2015): Impaired synaptic development in a maternal immune activation mouse model of neurodevelopmental disorders. Brain Behav Immun 50:249–258. [PubMed: 26218293]
122. Paylor JW, Lins BR, Greba Q, Moen N, de Moraes RS, Howland JG, et al. (2016): Developmental disruption of perineuronal nets in the medial prefrontal cortex after maternal immune activation. Sci Rep 6:37580. [PubMed: 27876866]
123. Gonzalez-Burgos G, Miyamae T, Pafundo DE, Yoshino H, Rotaru DC, Hoftman G, et al. (2015): Functional maturation of GABA synapses during postnatal development of the monkey dorsolateral prefrontal cortex. Cereb Cortex 25:4076–4093. [PubMed: 24904071]
124. Erickson SL, Lewis DA (2002): Postnatal development of parvalbumin- and GABA transporter-immunoreactive axon terminals in monkey prefrontal cortex. J Comp Neurol 448:186–202. [PubMed: 12012429]
125. Li Y, Missig G, Finger BC, Landino SM, Alexander AJ, Mokler EL, et al. (2018): Maternal and early postnatal immune activation produce dissociable effects on neurotransmission in mPFC-amygdala circuits. J Neurosci 38:3358–3372. [PubMed: 29491010]
126. Caballero A, Granberg R, Tseng KY (2016): Mechanisms contributing to prefrontal cortex maturation during adolescence. Neurosci Biobehav Rev 70:4–12. [PubMed: 27235076]
127. Klune CB, Jin B, DeNardo LA(2021): Linking mPFC circuit maturation to the developmental regulation of emotional memory and cognitive flexibility. Elife 10:e64567. [PubMed: 33949949]
128. Volk DW, Chitrapu A, Edelson JR, Roman KM, Moroco AE, Lewis DA (2015): Molecular mechanisms and timing of cortical immune activation in schizophrenia. Am J Psychiatry 172:1112–1121. [PubMed: 26133963]
129. Jaaro-Peled H, Sawa A (2020): Neurodevelopmental factors in schizophrenia. Psychiatr Clin North Am 43:263–274. [PubMed: 32439021]
130. Pinkham AE, Harvey PD, Penn DL (2018): Social cognition psychometric evaluation: Results of the final validation study. Schizophr Bull 44:737–748. [PubMed: 28981848]

131. Bortolon C, Capdevielle D, Raffard S (2015): Face recognition in schizophrenia disorder: A comprehensive review of behavioral, neuroimaging and neurophysiological studies. Neurosci Biobehav Rev 53:79–107. [PubMed: 25800172]

132. Ryan AM, Freeman SM, Murai T, Lau AR, Palumbo MC, Hogrefe CE, et al. (2019): Non-invasive eye tracking methods for New World and Old World monkeys. Front Behav Neurosci 13:39. [PubMed: 30890923]

133. McCutcheon RA, Reis Marques T, Howes OD (2020): Schizophrenia–an overview. JAMA Psychiatry 77:201–210. [PubMed: 31664453]

134. Guo JY, Ragland JD, Carter CS (2019): Memory and cognition in schizophrenia. Mol Psychiatry 24:633–642. [PubMed: 30242229]

135. Harvey PD, Isner EC (2020): Cognition, social cognition, and functional capacity in early-onset schizophrenia. Child Adolesc Psychiatr Clin N Am 29:171–182. [PubMed: 31708046]

136. Dickstein D, Schaefer J, Weinberger DR (2013): The multifacted “global” cognitive impairment profiles in schizophrenia. In: Harvey PD, editor. Cognitive Impairment in Schizophrenia. New York: Cambridge University Press, 24–49.

137. Harvey PD, Bowie CR (2016): Cognition in severe mental illness: Schizophrenia, bipolar disorder, and depression. In: Husain M, Schott JM, editors. Oxford Handbook of Cognitive Neurology and Dementia. Oxford: Oxford University Press, 463–470.

138. Weed MR, Bryant R, Perry S (2008): Cognitive development in macaques: Attentional set-shifting in juvenile and adult rhesus monkeys. Neuroscience 157:22–28. [PubMed: 18805462]

139. Smucny J, Dienel SJ, Lewis DA, Carter CS (2022): Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia. Neuropsychopharmacology 47:292–308. [PubMed: 34285373]

140. Schwarz E, Doan NT, Pergola G, Westlye LT, Kaufmann T, Wolfers T, et al. (2019): Reproducible grey matter patterns index a multivariate, global alteration of brain structure in schizophrenia and bipolar disorder. Transl Psychiatry 9:12. [PubMed: 30664633]

141. Keshavan MS, Collin G, Guimond S, Kelly S, Prasad KM, Lizano P (2020): Neuroimaging in schizophrenia. Neuroimaging Clin N Am 30:73–83. [PubMed: 31759574]

142. Ursini G, Punzi G, Langworthy BW, Chen Q, Xia K, Cornea EA, et al. (2021): Placental genomic risk scores and early neurodevelopmental outcomes. Proc Natl Acad Sci U S A 118: e2019789118. [PubMed: 33558239]

143. Srivastava A, Dada O, Qian J, Al-Chalabi N, Fatemi AB, Gerretsen P, et al. (2021): Epigenetics of schizophrenia. Psychiatry Res 305:114218. [PubMed: 34638051]

144. Woods RM, Lorusso JM, Potter HG, Neill JC, Glazier JD, Hager R (2021): Maternal immune activation in rodent models: A systematic review of neurodevelopmental changes in gene expression and epigenetic modulation in the offspring brain. Neurosci Biobehav Rev 129:389–421. [PubMed: 34280428]

145. Weber-Stadlbauer U, Richetto J, Labouesse MA, Bohacek J, Mansuy IM, Meyer U (2017): Transgenerational transmission and modification of pathological traits induced by prenatal immune activation. Mol Psychiatry 22:102–112. [PubMed: 27021823]

146. Weber-Stadlbauer U, Richetto J, Zwamborn RAJ, Slieker RC, Meyer U (2021): Transgenerational modification of dopaminergic dysfunctions induced by maternal immune activation. Neuropsychopharmacology 46:404–412. [PubMed: 32919409]

147. Amodeo DA, Lai C-Y, Hassan O, Mukamel EA, Behrens MM, Powell SB (2019): Maternal immune activation impairs cognitive flexibility and alters transcription in frontal cortex. Neurobiol Dis 125:211–218. [PubMed: 30716470]

148. Spann MN, Monk C, Scheinost D, Peterson BS (2018): Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. J Neurosci 38:2877–2886. [PubMed: 29487127]

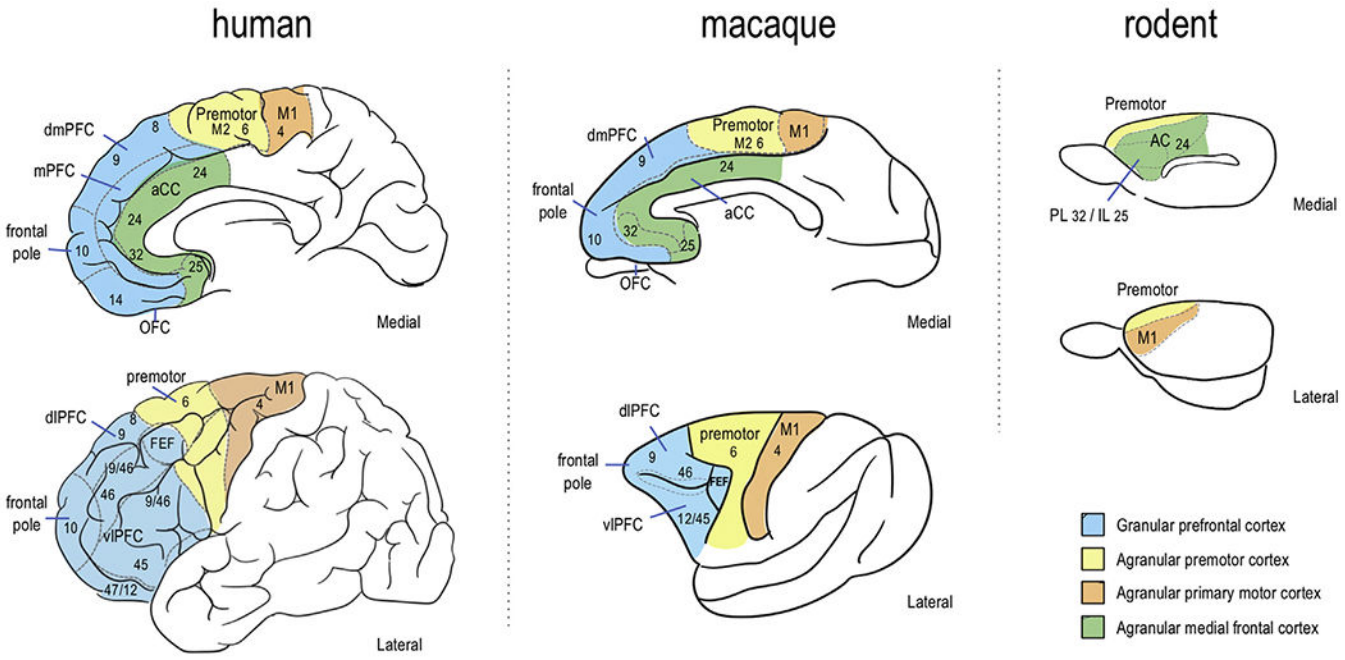

Figure 1.

Organization of the PFC in the human, macaque, and rat brain. Expansion and elaboration of PFC regions has been a hallmark of primate evolution, including territories involved in executive function, such as BAs 9 and 46 of the dlPFC, language and speech production (BA 44/45), and socio-emotional processing (BAs 47/12, 10, 11, and 13). Granular cortices, defined by the presence of a clear layer IV, represent canonical PFC territories with unique functional architectonics that subserve complex multimodal processing. Agranular territories more closely resemble the ventromedial PFC and aCC (BAs 24 and 32) of the primate brain and serve as a critical interface for integration of limbic and sensory information. aCC, anterior cingulate cortex; BA, Brodmann area; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial PFC; FEF, frontal eye fields; M1, primary motor area; M2, supplementary motor area; mPFC, medial PFC; OFC, orbitofrontal cortex; vlPFC, ventrolateral PFC. [Macaque and rodent illustrations were adapted with permission from Preuss and Wise (17).]

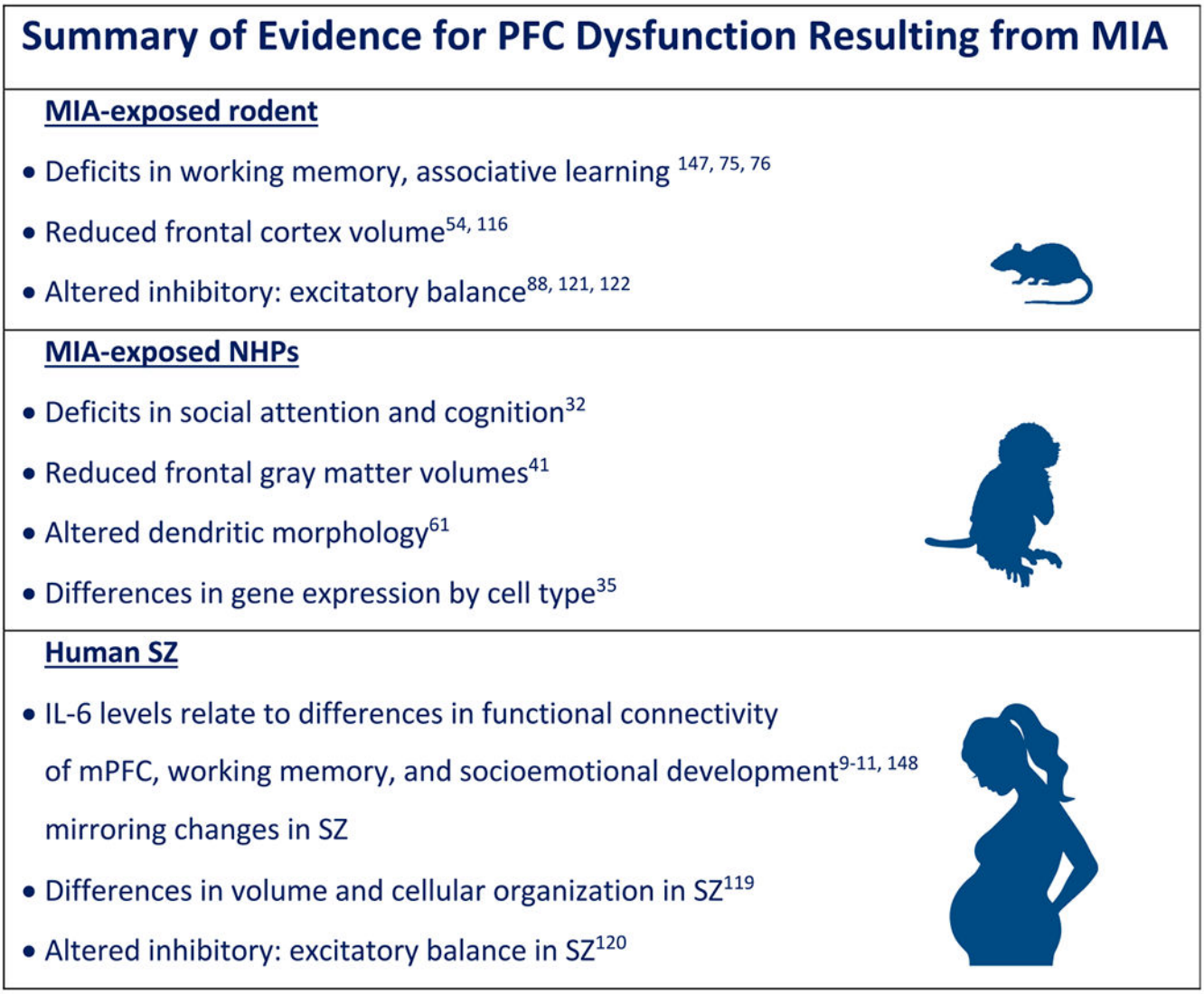

Figure 2.

Evidence of PFC dysfunction in schizophrenia populations and preclinical MIA models. A rapidly growing literature from rodent MIA models paired with decades of human schizophrenia studies highlights changes in PFC-related behavior and underlying neurobiology in the animal model and the clinical population. Although the NHP MIA model literature is less extensive compared with the rodent MIA literature owing to the time and resources required to generate each cohort, emerging findings from NHP MIA offspring also include changes in social and cognitive development, reductions in frontal gray and white matter, altered dorsolateral PFC dendritic morphology, and gene expression. MIA, maternal immune activation; NHP, nonhuman primate; PFC, prefrontal cortex.