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Altered dendritic morphology in dorsolateral prefrontal cortex of nonhuman primates prenatally exposed to maternal immune activation

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Abstract

Women who contract a viral or bacterial infection during pregnancy have an increased risk of giving birth to a child with a neurodevelopmental or psychiatric disorder. The effects of maternal infection are likely mediated by the maternal immune response, as preclinical animal models have confirmed that maternal immune activation (MIA) leads to long lasting changes in offspring brain and behavior development. The present study sought to determine the impact of MIA-exposure during the first or second trimester on neuronal morphology in dorsolateral prefrontal cortex (DLPFC) and hippocampus from brain tissue obtained from MIA-exposed and control male rhesus monkey (*Macaca mulatta*) during late adolescence. MIA-exposed offspring display increased neuronal dendritic branching in pyramidal cells in DLPFC infra- and supragranular layers relative to controls, with no significant differences observed between offspring exposed to maternal infection in the first and second trimester. In addition, the diameter of apical dendrites in DLPFC infragranular layer is significantly decreased in MIA-exposed offspring relative to controls, irrespective of trimester exposure. In contrast, alterations in hippocampal neuronal morphology of MIA-exposed offspring were not evident. These findings demonstrate that a maternal immune

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

challenge during pregnancy has long-term consequences for primate offspring dendritic structure, selectively in a brain region vital for socioemotional and cognitive development.

Keywords

Animal model; Poly IC; Neuroimmunology; Schizophrenia; Autism; NHP; Neuroanatomy; Golgi; Maternal immune activation

1. Introduction

Decades of epidemiological evidence strongly support a link between exposure to a variety of maternal infections and increased risk for offspring neurodevelopmental disorders (NDDs), including schizophrenia (SZ) and autism spectrum disorder (ASD) (Brown and Meyer, 2018; Canetta et al., 2016; Han et al., 2021; Jiang et al., 2016; Lins, 2021). Sero-epidemiological studies that utilize archived or prospectively collected maternal biospecimens suggest that the maternal immune response, rather than a specific infectious agent, is the critical link between maternal infections and altered offspring neurodevelopment (Abdallah et al., 2013, 2012; Allswede et al., 2020, 2016; Brown et al., 2004; Buka et al., 2001; Goines et al., 2011; Jones et al., 2017). Indeed, even in the absence of an acute inflammatory event triggered by infection, variation in maternal cytokine levels during pregnancy have been associated with changes in infant brain growth, functional connectivity, and behavioral development (Rasmussen et al., 2019; Rudolph et al., 2018). Collectively, these studies suggest that changes in maternal cytokines during pregnancy can have long-lasting consequences, ranging from no impact to subtle differences in infant brain and behavioral development, to severe NDDs. Understanding the neurobiological mechanisms linking maternal infection with changes in offspring neurodevelopment is essential to developing novel therapeutic interventions and will require a collaborative effort between clinical and preclinical research endeavors.

Preclinical animal models of maternal immune activation (MIA) provide important translational tools for understanding the mechanisms by which altered brain development may lead to pathologies in brain function, neurotransmission and, ultimately, behavior (Estes and McAllister, 2016; Woods et al., 2021). In spite of significant challenges associated with methodological variability, offspring born to MIA-treated dams exhibit many reproducible changes in brain and behavioral development relevant to human NDDs (Kentner et al., 2019). The vast majority of MIA models have used rodent systems to provide foundational knowledge of the neurodevelopmental consequences of MIA exposure (Bergdolt and Dunaevsky, 2019; Brown and Meyer, 2018; Careaga et al., 2017). There are, however, limitations to relying solely on rodent model systems to explore the association between maternal infection and altered offspring neurodevelopment. Studies in nonhuman primates provide the opportunity to examine developmental differences in a model with greater similarity to humans in placental structure and pregnancy physiology (Carter, 2020, 2007; Grigsby, 2016; Rutherford, 2013) as well as gestational timelines and fetal brain development (Clancy et al., 2007; Molnar and Clowry, 2012). Given the extensive expansion and elaboration of the neocortex in primate evolution (Allman, 1990; Kaas, 2012, 2006;

Northcutt and Kaas, 1995) and particularly the prefrontal cortex (Krasnegor et al., 1997; Petrides and Pandya, 2002; Teffer and Semendeferi, 2012; Uylings and van Eden, 1991), as well as derived patterns of subregional organization and connectivity in the hippocampus (Vanier et al., 2019; Wang and Barbas, 2018), a nonhuman primate model offers a unique opportunity to study the effects of MIA on these highly complex brain regions.

To help bridge the gap between preclinical rodent models and human clinical populations, our research team has developed the first polyinosinic-polycytidylic acid (Poly I:C) based nonhuman primate MIA model in the rhesus macaque (*Macacca mulatta*). Pregnant rhesus monkeys injected with a modified form of Poly I:C (Poly ICLC) during gestation exhibit signs of immune response, such as elevated cytokine levels including IL-6 which likely contributes to altered fetal brain development (Gallagher et al., 2013; Smith et al., 2007). In offspring from a small nonhuman primate cohort of Poly ICLC-treated rhesus macaque mothers used to establish dosing, preliminary histopathological findings revealed differences in dendritic morphology in the prefrontal cortex (Weir et al., 2015). Specifically, apical dendrites in MIA-exposed offspring displayed reduced trunk diameter and an increased number of oblique dendrites as compared to controls. Following dosing studies, a larger cohort of MIA-exposed offspring was generated to compare the timing (first versus second trimester) of the prenatal immune exposure. Behavioral testing and observation of the offspring of these animals indicated aberrant behaviors, including abnormal social interactions, repetitive behaviors, and reduced affiliative vocalizations, that emerge in the first two years of life in the MIA-exposed offspring (Bauman et al., 2014). As juveniles (approximately 2.5 years of age) the first trimester-exposed MIA offspring display abnormal gaze patterns characterized by reduced attention to salient social cues (Machado et al., 2015) as compared to age-matched controls.

Though preclinical models are models of a specific neurodevelopmental insult, and not of any specific disease or disorder (Silverman et al., 2022), it is nevertheless valuable to consider postmortem studies from human clinical populations where strong evidence has implicated MIA as a potential factor in their etiology, particularly where neurobiological observations may overlap. In late adolescence, the MIA-exposed offspring utilized in the present study demonstrated elevated presynaptic dopamine levels in the striatum as indexed by [18F] fluoro-1-m-tyrosine (FMT) (Bauman et al., 2019). This is consistent with findings in patients with schizophrenia, who display increased presynaptic dopamine levels relative to controls (Howes et al., 2013, 2009). Alterations to spine density are additionally a consistent finding in adult patients with schizophrenia (Glausier and Lewis, 2013) and may relate to alterations in neuropil including synaptic loss (Glantz et al., 2006; Osimo et al., 2019).

In the present study, we analyzed neuron morphology in our cohort of MIA-exposed offspring to determine how the maternal immune response during pregnancy may affect long-term brain development. Specifically, we targeted the morphology of pyramidal neurons in the dorsolateral prefrontal cortex (DLPFC; BA9/46) and hippocampus (CA3 region, Fig. 1) in the male offspring of MIA-treated mothers who received a modified form of Poly ICLC treatment in either the first or second trimester of gestation. We further sought to determine whether the *timing* of MIA exposure during pregnancy differentially

impacts long-term changes in dendritic morphology in the DLPFC and hippocampus of MIA exposed offspring.

2. Methods

All experimental procedures were developed in collaboration with the veterinary, animal husbandry, and environmental enrichment staff at the California National Primate Research Center (CNPRC) and approved by the University of California, Davis Institutional Animal Care and Use Committee. All attempts were made (in terms of social housing, enriched diet, use of positive reinforcement strategies, and minimizing the duration of daily training/testing sessions) to promote the psychological well-being of the animals that participated in this research. Detailed methods from this cohort are available in our previous publications (Bauman et al., 2019, 2014; Rose et al., 2017; Weir et al., 2015) and have been updated below to reflect newly developed MIA model reporting guidelines (Kentner et al., 2019).

2.1. Subjects and maternal immune activation (MIA) protocol

The MIA offspring were born to dams injected with 0.25 mg/kg synthetic double-stranded RNA (polyinosinic:polycytidylic acid [Poly I:C] stabilized with poly-L-lysine [Poly ICLC]; Oncovir, Inc., Washington, DC) via intravenous injection while temporarily restrained by trained technicians at the end of the first trimester on gestational days (GD) 43, 44, 46 or at the end of the second trimester on GD 100, 101, 103. Control offspring were born to dams injected with saline at these time points or had no manipulation at all during pregnancy. Dams injected with poly ICLC exhibited a transient increase in IL-6 levels, temperature and sickness behaviors as previously reported (Bauman et al., 2014). The present study included 13 male offspring; comprised of first trimester MIA exposed (MIA1; $n = 5$), second trimester MIA exposed (MIA2; $n = 4$), and control animals born to dams that were either injected with saline at the same gestational timepoints in the first ($n = 1$) or second trimester ($n = 2$) or were untreated ($n = 1$).

2.2. Rearing conditions and husbandry

All infants were born at term, raised with their mothers, and provided three hours daily access to a social group consisting of four mother-infant pairs and one adult male to facilitate species-typical social development. Infants were raised in individual cages with their mothers, where they had continuous visual access to other animals. Infants were weaned at 6 months of age but continued daily peer group interactions through approximately 2 years of age. At the time of tissue collection, all animals were housed indoors in social MIA/control pairs 24 h per day, 7 days per week. These pairs occupied two adjacent, age-appropriate laboratory cages where they had visual access to other animals. Animal rooms were maintained at 17.78–28.89 °C and on a 12/12 light/dark cycle (lights on at 0600). Subjects were fed twice daily (Lab Diet #5047, PMI Nutrition International Inc, Brentwood, MO), provided with fresh produce biweekly, had access to water ad libitum and a variety of enrichment devices. Animals participated in a variety of behavioral tests throughout development as described in behavioral (Bauman et al., 2014; Machado et al., 2015; Rose et al., 2017) and neuroimaging (Bauman et al., 2019) studies.

2.3. Tissue processing

At 3.5–4 years of age, the brain was perfused with saline, extracted, the cerebellum and brainstem removed, and the cerebrum bisected through the sagittal sulcus into the right and left hemispheres. Right hemisphere blocks were frozen in liquid nitrogen vapor and retained for use in future analyses. Blocks of tissue approximately x-mm including BA9/46 and the hippocampus from the left hemisphere were wrapped in gauze and placed in Golgi-Cox solution for 12 weeks. Blocks were rinsed and dehydrated in graded concentrations of ethanol, embedded in parlodion, and cut into 150 um sections on a sliding microtome. Sections were prepared for 10 min in a solution of ammonium hydroxide, followed by 5 min in Kodak developer solution. Sections were then rinsed and dehydrated in serial concentrations of ethanol, cleared in xylenes, mounted on slides using DPX, and coverslipped.

2.4. Data collection and morphometric analyses

All data was collected by a single rater (R.K.W.) blinded to treatment condition using a Zeiss microscope (Imager Vario Z2) with a motorized stage equipped with transducers on the XYZ-axes. Neurons were identified at 5× magnification and evaluated at 20× magnification using previously described inclusion criteria (Bianchi et al., 2013; Hrvoj-Mihic et al., 2017; Jacobs et al., 2001; Travis et al., 2005; Weir et al., 2015). Briefly, dendritic trees were traced only if they met the following criteria: 1) the neuron was complete within a single section, 2) neurons possessed fully impregnated, unobscured processes with no breaks, 3) neuronal somata were centrally located within the z-axis of the section, and 4) apical dendrites were in an orientation perpendicular to the pial surface (Fig. 2). Neurons that met inclusion criteria were traced at high magnification (100x) with an oil immersion lens using the computer-assisted tracing software system NeuroLucida (MBF Biosciences, Williston, VT). Basal dendrites, which showed no significant morphological differences between treated and controlled subjects in our previous work, were not measured for DLPFC neurons.

2.4.1. DLPFC pyramidal neurons—At least 10 neurons per case (a minimum of 2 neurons per section across 5 sections, 230 neurons in total) were identified in Layer III along the dorsal limb of the principal sulcus in BA9/46 (Fig. 1) at 5× magnification and evaluated at 20× magnification for the inclusion criteria described above. Apical dendritic arbors were traced at high magnification (100×) in their entirety, and additional morphological measures were collected, including soma area (μm^2), total length of dendrites (μm), number of dendritic segments (defined as a section of dendrite between branching nodes or between a branch point and the end of the dendrite, an indication of branching frequency), and spine density (number of spines per μm).

Thirty neurons per case were selected from each of supragranular layers II/III and infragranular layers V/VI of the principal sulcus of the dorsal limb of the DLPFC. Measurements for all 780 neurons were taken from a 30 μm section of primary apical dendrite located 100 ± 10 μm from the apex of the soma. Neurons were selected using the following inclusion criteria: 1) neurons displayed a clearly defined apical trunk free of early bifurcations in the initial 30 μm segment, 2) there were no bends, kinks, or breaks in the

apical trunk, and 3) the initial 30 μm segment included no branching points for oblique dendrites. Soma area (μm^2), diameter of the apical dendrite at its emergence from the soma, and number of spines on the 30 μm segment were also measured. The number of oblique dendrites along the total length of the apical dendrite was also noted.

2.4.2. Hippocampal neurons—A target of 10 neurons per case (1–2 neurons per section across 5 sections per case, 118 total neurons in total) were identified from the CA3 region of the hippocampus (Fig. 1) at 5× magnification and evaluated at 20× for the exclusion criteria described above. Neurons were traced and measures collected similarly to DLPFC neurons.

2.5. Statistical analysis

Statistical analyses were conducted within a generalized linear mixed-effects models framework (McCullagh and Nelder, 1989). This framework allowed us to account for the clustered design (with multiple neurons measured per animal) and to accommodate dependent variables that are normally distributed (e.g., dendrite diameter and length, cell body area, etc.) and counts (number of spines). Transformations were employed to improve normality for some variables. We used a log link and Poisson function to model the number of spines and identity link and a normal variance function for the rest of the variables. For each dependent variable we fitted a model with a main effect for group (Control, Poly 1, MIA2) and used a compound-symmetric covariance structure to account for the within-animal dependence. The covariance structure was allowed to vary across groups if suggested by diagnostic analyses. Kenward-Roger procedure was used to estimate degrees of freedom. All models were validated both graphically and analytically. Following a significant main effect of group, pairwise group differences were assessed using Tukey-Kramer's adjustment for multiple comparisons. Hypothesis tests were two-sided; p-values <0.05 were considered statistically significant. All analyses were implemented using PROC MIXED and GLIMMIX in SAS Version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Our findings were consistent with our previous study showing increased branching of apical dendrites in the infragranular DLPFC, as well as decreased diameter of apical dendrite trunks, in the DLPFC in MIA-exposed offspring (Weir et al., 2015). Results further indicate that the timing of MIA exposure—during the end of the first and second trimester—is sufficient to reproduce the phenotype, with no significant differences between first- and second-trimester exposed groups. We additionally examined the morphology of pyramidal neurons in the hippocampus but found no significant differences between MIA-exposed offspring and controls.

3.1. DLPFc

The group effect was significant for apical dendrite diameter in infragranular layers ($F_{2,10} = 7.68$, $P = 0.01$), but not for supragranular layers ($F_{2,10} = 2.11$, $P = 0.17$). Pairwise comparisons adjusted for multiple comparisons further revealed significant differences in group means of apical dendrite diameter in infragranular layers between MIA1 and control

(estimated difference −0.34, SE = 0.11, $P = 0.03$) and between MIA2 and control groups (estimated difference −0.42, SE = 0.11, $P = 0.01$), but not between MIA1 and MIA2 ($P = 0.77$). The group effect was significant for oblique dendrite branching in both infragranular ($F_{2,10} = 11.18$, $P = 0.003$) and supragranular layers ($F_{2,10} = 8.73$, $P = 0.006$). Post-hoc testing revealed significant differences in oblique dendrite count in infragranular layers between MIA1 and control (estimated difference 0.14, SE = 0.03, $P = 0.003$) and between MIA2 and control groups (estimated difference 0.12, SE = 0.04, $P = 0.01$), but not between MIA1 and MIA2 ($P = 0.76$). Similarly, there were significant differences in oblique dendrite count in supragranular layers between MIA1 and control (estimated difference 0.14, SE = 0.04, $P = 0.01$) and between MIA2 and control groups (estimated difference 0.15, SE = 0.04, $P = 0.01$), but not between MIA1 and MIA2 ($P = 0.97$). Table 1 provides descriptive statistics for DLPFC neuron measures including apical dendrite diameter and number of oblique dendrites for MIA-exposed offspring and controls and summarizes the results of the analyses and Fig. 3 presents the data.

Supplementary Table S1 provides descriptive statistics for DLPFC neurons for MIA-exposed offspring and controls and summarizes the results of the analyses. No significant group differences were observed for total cell body area ($F_{2,5.39} = 0.50$, $P = 0.63$), dendritic length ($F_{2,11.1} = 0.50$, $P = 0.62$), or spine number ($F_{2,4.16} = 0.87$, $P = 0.48$) or for dendritic spine density ($F_{2,10.4} = 0.85$, $P = 0.46$).

3.2. Hippocampus

No significant group effects were observed for cell body area ($F_{2,5.29} = 0.36$, $P = 0.72$), or basal dendrite length ($F_{2,10.1} = 2.40$, $P = 0.14$), Similarly, no significant group effects were observed for apical dendrite length ($F_{2,10} = 0.13$, $P = 0.88$), spine number ($F_{2,4.02} = 1.15$, $P = 0.40$), or density ($F_{2,10} = 1.43$, $P = 0.28$). While total dendritic spine number ($F_{2,9.55} = 4.10$, $P = 0.052$) approached significance, no differences in spine density were observed ($F_{2,10.1} = 1.0$, $P = 0.40$; see Supplemental Table S2 for detailed results).

4. Discussion

Here we present evidence of altered dendritic morphology in DLPFC, but not hippocampus, in late adolescent rhesus monkeys at 3.5–4 years of age that were prenatally exposed to MIA. Specifically, MIA-exposure during either the first or second trimester was associated with more extensive oblique dendritic branching in both infra- and supragranular layers and reduced diameter of apical dendrites in infragranular layers in DLPFC, relative to unexposed adolescent offspring. These findings reproduce our preliminary results from a prior small dosing cohort which showed similar alterations in dendritic morphology in DLPFC (Weir et al., 2015) in animals exposed to MIA at a single timepoint at the end of the first trimester. Transcriptomic analyses (Page et al., 2021) performed in tissue blocks from the same cohort of first- and second-trimester MIA-exposed NHP offspring analyzed here showed evidence for differences in gene expression in both PFC and hippocampus, with the greatest differences observed in hippocampus. Although we did not observe altered morphology in hippocampal neurons, spine number or density at this time point, it is possible that changes may be found at a later timepoint in development. The impact of MIA on dendritic spine

development has been recently reviewed elsewhere (Pekala et al., 2021). In brief, in rodent models, the length and complexity of dendrites were reduced in the cortex and hippocampus (Baharnoori et al., 2009; de Cossío et al., 2017; Li et al., 2014; Zhang and van Praag, 2015). In addition, the density of dendritic spines on pyramidal neurons in the cortex (Baharnoori et al., 2009; Coiro et al., 2015; de Cossío et al., 2017; Li et al., 2014) and granule cells in the DG (Abazyan et al., 2010; Li et al., 2014) was reduced in MIA offspring.

Here we will focus our discussion on the prefrontal cortex, as converging evidence from behavior, neuroimaging, and postmortem tissue studies highlight this as a region vulnerable to prenatal immune challenge in nonhuman primates (Hanson et al., 2022). In a longitudinal structural magnetic resonance imaging (MRI) study of a recent cohort, male monkeys exposed to MIA in the first trimester displayed a reduction in prefrontal cortical volume as early as 6 months of age (Vlasova et al., 2021) that persists until at least 3.5–4 years of age, suggesting that MIA-treated offspring deviate from typical brain developmental trajectories beginning in the early postnatal period. These early insults may alter the course of typical neurodevelopment with consequences reaching into adolescence and beyond, with significant potential to affect the development of complex, species-typical social and cognitive behavior. Social and cognitive deficits have been documented in MIA-exposed NHPs (Bauman et al., 2014; Machado et al., 2015; Vlasova et al., 2021), consistent with observations in rodent studies demonstrating deficits in behaviors associated with frontal lobe function, as well as altered neurodevelopment, neurotransmitter function, and brain cytokines in the frontal cortex (Bergdolt and Dunaevsky, 2019). Notably, the primate PFC is characterized by the elaboration of regions associated with higher-order cognition (Armstrong and Falk, 2012; Preuss, 2007), and differs from rodent PFC not just in size and complexity, but also in the presence of DLPFC (Preuss, 1995; Preuss and Wise, 2022), underscoring the importance of nonhuman primate studies.

Observations across the lifespan in behavior, physiology, and neurodevelopment, provide a glimpse into the neurobiological underpinnings of altered development in the nonhuman primate MIA model (see Table 2). MIA-exposed NHP offspring exhibited aberrant behavioral development (Bauman et al., 2014; Machado et al., 2015; Rose et al., 2017) as well as preliminary evidence of increased striatal dopamine from *in vivo* neuroimaging studies (Bauman et al., 2019). Importantly, brain tissue analyzed in our study was collected during late adolescence (Watts and Gavan, 1982) and may represent the early emergence of MIA-induced morphological changes. Similar to our findings, postmortem human brain tissue from schizophrenia patients also exhibit alterations in DLPFC dendritic morphology, with regional and laminar-specific effects in adult subjects (Garey et al., 1998; Glantz and Lewis, 2000; Kolluri et al., 2005). The typical emergence of major psychiatric conditions in late adolescence and early adulthood suggests that this time-period may be a key period for observing the effects of altered neurodevelopment in dynamically changing neural circuitry. Importantly, changes in neuronal morphology observed in the adult brain in neuropsychiatric disorders, such as loss of dendritic spines, may manifest as a part of a later course of progressive changes that may be observed at later stages in development.

We do not know if the subtle changes in dendritic morphology identified in MIA-exposed offspring were present early in development or emerged as the animals matured. In a

mouse study, dendritic length was significantly reduced in mPFC neurons of MIA-exposed offspring at P10 and 35, but returned to control values at P60 (Baharnoori et al., 2009). Rodent models offer significant advantages in evaluating multiple postmortem timepoints; given the practical considerations associated with the nonhuman primate model, we are severely constrained in the number of timepoints we can examine. However, the timing of brain tissue collection in late adolescence allowed us to identify perturbations to cellular morphology at a discrete but important timepoint for neurological development in the macaque, at 3.5–4 years, or roughly at the age of onset of sexual maturity in males (Bercovitch and Clarke, 1995). Adolescence is known to be a highly dynamic period of brain development and maturation, particularly in the PFC in macaques (Watts and Gavan, 1982) as well as in humans (Blakemore, 2012; Blakemore and Choudhury, 2006; Casey et al., 2008; Giedd, 2004). In humans, patterns of developmental changes in organization and connectivity likely contribute to vulnerability to psychosis onset in late adolescence and early adulthood (Lewis, 1997; Patel et al., 2021), albeit with sex-specific variation in age of onset (Walder et al., 2013).

With its protracted course of maturation, the prefrontal cortex may be especially vulnerable to prenatal insults such as MIA. Prior to embryonic day 40 (E40) in macaques (E42 in humans), symmetrical division of cortical progenitor cells establishes additional progenitor units, followed by the asymmetric division of progenitor cells, which in turn lead to the production of cortical columns (Sidman and Rakic, 1973; Rakic, 1988, 1995; Bystron et al., 2008). The inside-out columnar migration of cortical neurons occurs between E40-90, guided by radial glia, and results in the characteristic cytoarchitecture of each cortical region. Infragranular neurons arrive in layers V/VI of the prefrontal cortex at approximately E40-60. Neurons in the supragranular layers (layers II/II), with the longest distance to travel to their ultimate positions, are present from E80-90. The nearly-two-month-long period of neurogenesis and migration in the primate brain reflects its greater size and complexity (Finlay and Darlington, 1995), and sharply contrasts with the corresponding week-long period of neurogenesis and migration in the rodent. In the current study, MIA induction occurred in the late first trimester (E43, 44, 46) just prior to the migration of infragranular cells, or in the late second trimester (E100, 101, 103) after migration of supragranular neurons has completed, as they begin to mature in place. Although distinct abnormalities in primate DLPFC development have been reported following exposure to ionizing radiation in early versus midgestation (Selemon et al., 2013), the timing of prenatal immune challenge in the first or second trimester did not result in detectable differences in dendritic morphology between MIA-exposed groups by 3.5–4 years of age. The timing of MIA induction in this study targets particularly important developmental timepoints for corticogenesis and neuronal migration, but development and refinement of neuronal dendritic trees and their connections continues long into the postnatal period. Thus, early developmental insults may set the stage for altered neurodevelopment long past the period of initial maternal immune activation, resulting in aberrant morphology that we have observed at maturity in DLPFC neurons.

It is also plausible that MIA exposure early in life may not directly impact dendritic morphology but may predispose MIA-exposed offspring to additional postnatal events that shape neuron structure and function. For example, chronic stress leads to structural and

functional changes, including atrophy of apical dendrites in neurons of the medial prefrontal cortex (Cook and Wellman, 2004; Radley et al., 2004) and hippocampus (Lambert et al., 1998; Watanabe et al., 1992). This cohort of MIA-treated animals demonstrated behaviors including increased stereotypic behaviors as they matured (Rose et al., 2017) that have been associated with stress responses and coping mechanisms (Pomerantz et al., 2012). Ongoing cross-talk between the developing nervous and immune system may also contribute changes to apical dendritic morphology during both pre- and postnatal development. Other macaque species (*Macaca fascicularis*) infected with the simian immunodeficiency virus (SIV) postnatally show a reduced diameter of apical dendrites in layer V pyramidal cells in the frontal cortex (Montgomery et al., 1999), which is related to the duration of illness. Monkeys who were chronically infected with the virus for 2–3 years, as compared to those who had been infected for only 2.5–3 months, showed substantially greater reductions in apical dendrite diameter as compared to control animals, suggesting progressive degeneration of the apical dendrite in response to chronic infection. These results suggest that pro-inflammatory changes induced by viral infection can alter neuronal morphology beyond the period of prenatal development, although it is important to note that broader impacts of SIV infection may transcend the effects of neuroinflammation (Moretti et al., 2021; Obregon-Perko et al., 2020; Williams et al., 2016; Zink et al., 1998).

Blood samples collected at 1 and 4 years of age front the animals used in this study revealed long-lasting changes in immune system development of the MIA-treated offspring (Rose et al., 2017). At one year of age, MIA exposed offspring displayed elevated production of innate inflammatory cytokines at baseline and following stimulation. By four years of age, the MIA exposed offspring continued to display elevated IL-1b, with a pattern of increased production of *T*-cell helper type (TH)-2 cytokines, IL-4, and IL-13. Thus, evidence of long-lasting changes in immune system development in this cohort raises the possibility that MIA may continue to affect neurodevelopmental processes throughout offspring development in a progressive manner.

At a basic level, alterations to the morphology of pyramidal neurons may disrupt neuronal communication and the balance of excitatory and inhibitory signaling, which is a common hypothesis for dysfunction in a variety of neurodevelopmental and psychiatric disorders including ASD and schizophrenia (Canitano and Pallagrosi, 2017; Foss-Feig et al., 2017; Gao and Penzes, 2015; Kehrer et al., 2008; Marín, 2012; Rubenstein and Merzenich, 2003; Yizhar et al., 2011). Our recent transcriptomic study of the same cohort of MIA-treated primate offspring (Page et al., 2021) as the current study revealed differences in the expression of genes associated with neurotransmission, including down-regulation of genes associated with excitatory and inhibitory neurons and glutamatergic synapses. Dendritic structure determines the electrical properties of neurons (Gulledge et al., 2005; Häusser et al., 2000; Jaffe and Carnevale, 1999; Magee, 2000; Reyes, 2001), and thus, subtle changes to the morphology of apical dendrites may have significant consequences for membrane excitability and neuronal function. Biophysical models of oblique dendrites based on data from rodent CA1 pyramidal neurons (Ferrante et al., 2013) suggest a role for these projections in modulating signal propagation, such that the morphological variability of branch points may significantly alter synaptic activity by decreasing differential impedance, affecting cellular excitability. A variety of conditions are linked to alterations in the neuronal

morphology of apical dendritic branching patterns, with varying implications for cellular function. Oblique dendrites are known to be particularly vulnerable to the amyloid beta-induced blockage of A-type potassium channels in the early stages of Alzheimer's disease, increasing neuronal excitability, as evidenced by back-propagating action potentials (Morse et al., 2010). In a mouse model of Alzheimer's disease (Šišková et al., 2014), structural degeneration of dendritic trees lead to hyperexcitability and increased conversion to action potentials, leading to widespread dysfunction in neural circuitry. Taken together, it is likely that changes to the architecture of oblique dendrites of pyramidal neurons, as we observed in MIA-treated offspring, may contribute to systemic dysfunction of circuitry in the DLPFC.

5. Conclusions

Although the results of the present study extend the results of rodent MIA models into a species more closely related to humans, there are inherent logistical constraints to nonhuman primate studies, including relatively modest sample sizes and selection of only male offspring. We recognize that sex differences are emerging as a critical factor in MIA model studies (Coiro and Pollak, 2019) and future research will focus on the impact of MIA on the female nonhuman primate brain. Life history considerations, including long gestational periods and protracted developmental trajectories as compared to rodents, mean that each nonhuman primate cohort requires multiple years to mature. As such, our understanding of the cellular and molecular changes underlying altered neurodevelopment in the nonhuman primate model lags behind rapid progress in the rodent MIA model (Bergdolt and Dunaevsky, 2019). Further examination of archived brain tissue from the nonhuman primate MIA model nevertheless provides a critical opportunity to bridge the gap between rodent MIA models and human studies by highlighting the neurodevelopmental consequences of MIA in highly complex NHP brain circuitry. This is a particular advantage in animals that have been monitored across the lifespan for alterations in behavior, physiology, and neurodevelopment, and allows for comparisons to be made between these variables.

Alongside genetic and environmental factors, maternal infection during pregnancy, such as from influenza and COVID-19, may represent a significant risk factor for the development of autism and schizophrenia, as well as other related disorders by affecting brain development and neuronal morphology. The development of targeted interventions for maternal infection, including measures to reduce the deleterious effects of pro-inflammatory cytokines, strongly benefit from translational studies that support our understanding of maternal immune activation as a risk factor for neurodevelopmental and psychiatric disorders and their underlying neuroanatomical correlates. In particular, highlighting vulnerable circuits and systems at key developmental timepoints in the primate brain may provide vital insight for understanding the etiology and course of human psychiatric disorders that affect highly complex, uniquely derived circuitry.

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Data availability

Data will be made available on request.

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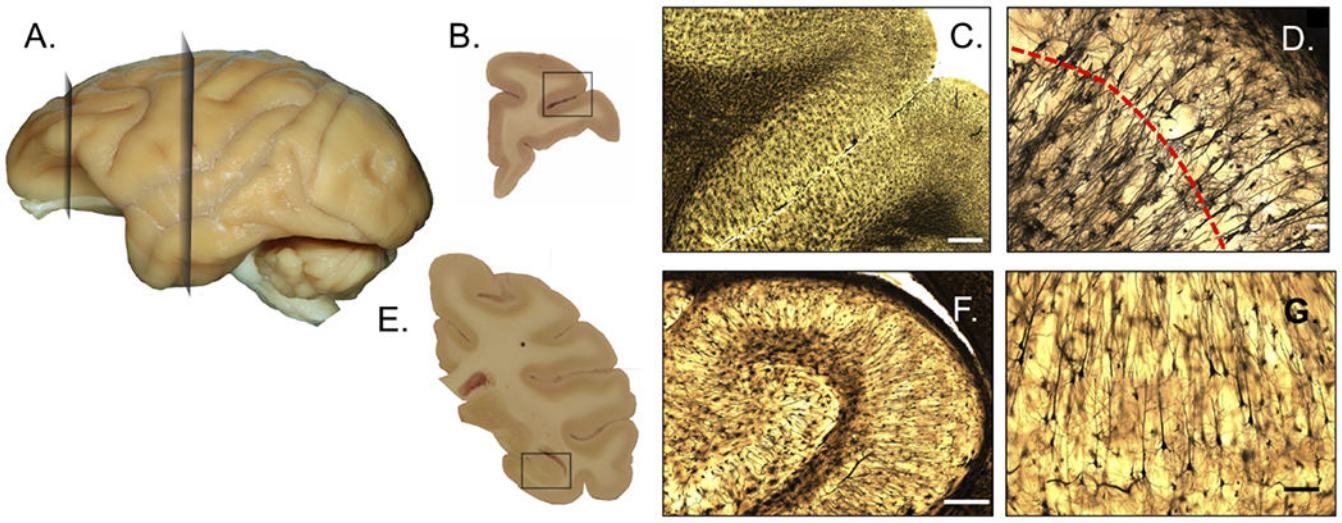

Fig. 1.

Regions of Interest Sampled. A. Whole macaque hemisphere with lines indicating where coronal blocks were sampled. B. Coronal block-face image of the prefrontal cortex. Box indicates the location of the principal sulcus. C. Photomicrograph of a 150 μM-thick Golgi stained section of BA46 principal sulcus. Scale bar (white) = 1000 μM. D. Photomicrograph of cortical layers in BA 46 along the principal sulcus of the DLPFC. Dotted line (red) demarcates the supragranular (upper) layers II/III and infragranular (lower) layers V/VI. E. Block face image of whole macaque hemisphere. Box indicates the region of temporal lobe containing the hippocampus. F. Photomicrograph of a 150 μM-thick Golgi stained section from the hippocampus at 5x magnification. Scale bar = 500 μM. G. Photomicrograph of cells in the CA3 region of the hippocampus at 10x magnification. Scale bar = 50 μM. Whole hemisphere and DLPFC block face image have been adapted from Weir et al. (2015).

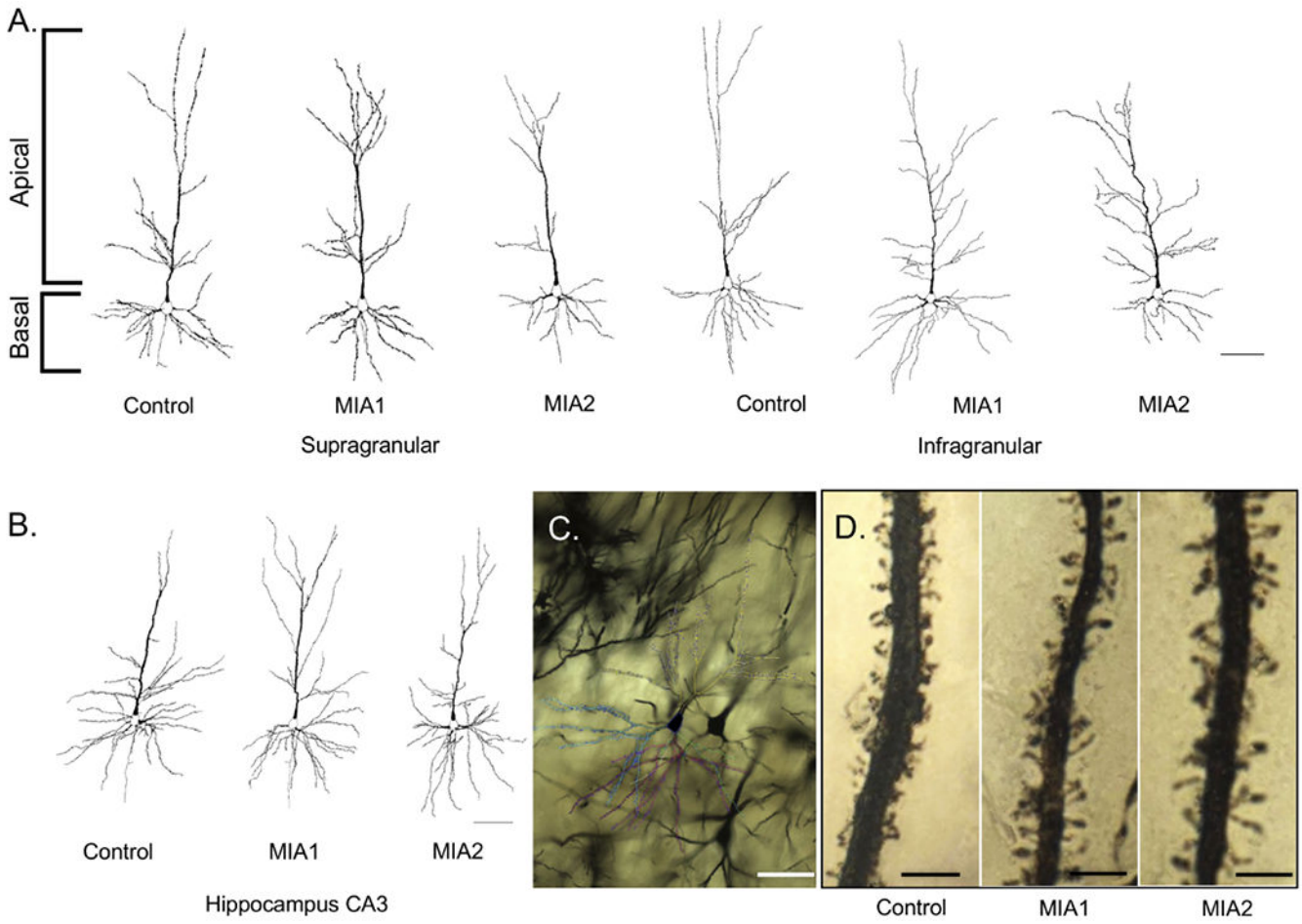

Fig. 2.

Examples of Golgi Stained Neurons in the DLPFC and Hippocampal CA3 regions. A. Representative tracings from the supra- and infragranular DLPFC in all three groups. Scale bar = 50 μm. B. Representative tracings from the CA3 region of the hippocampus in all three groups. Scale bar = 50 μm. C. Photomicrograph showing a traced Golgi stained neuron in situ in hippocampal CA3 region. Scale bar (white) = 50 μm. D. Photomicrographs (100x magnification) of apical dendritic segments from infragranular layers in DLPFC. Scale bar = 5 μm.

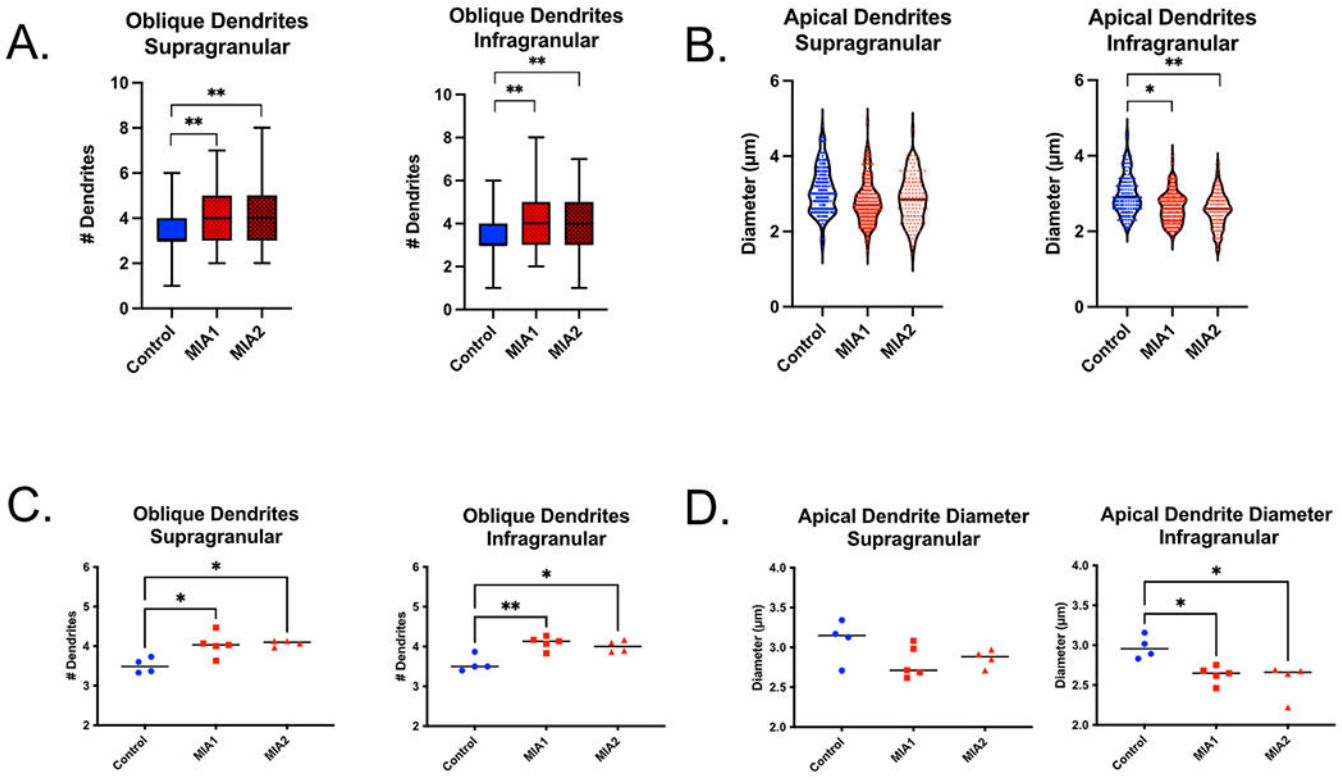

Fig. 3.

Graphs of apical dendrite measurements from DLPFC neurons. Single asterisks (*) indicate significant differences at a ≤ 0.05. Two asterisks (**) indicate significance at a ≤ 0.01. A. Counts of apical oblique dendrite numbers in supra- and infragranular DLPFC. Statistical analyses showed that oblique dendrite counts were significantly higher in both MIA groups as compared to controls in both supra- and infragranular layers. B. Diameter of apical dendritic segments measured 30 µm from the soma. No significant difference in apical dendrite diameter was found between groups in supragranular neurons measured. Both MIA groups showed significantly smaller neuron diameter as compared to controls. C. Graphs showing individual subject means for counts of apical oblique dendrite numbers in supra- and infragranular DLPFC. Ordinary One-way ANOVAs showed significant differences between control animals and both MIA groups measured in both supra- and infragranular layers. D. Graphs showing individual subject means for apical dendrite diameter in supra- and infragranular DLPFC. Ordinary One-way ANOVAs showed no significant differences between control animals and MIA treated offspring for apical dendrite diameter in supragranular DLPFC. Both MIA groups showed significantly smaller neuron diameter as compared to controls.

Table 1

Descriptive statistics and estimated group differences for DLPFC apical dendrite diameter and number of oblique spines for MIA-exposed offspring and controls.

	Control	MIA1	MIA2	MIA1 vs Control		MIA2 vs Control		MIA1 vs MIA2	
	Mean (*SD*)[a]	Mean (*SD*)[a]	Mean (*SD*)[a]	*Estimate* (*SE*)	*P*[b]	*Estimate* (*SE*)	*P*[b]	*Estimate* (*SE*)	*P*[b]
Infra									
Apical Dendrite Diameter[c]	2.97 (0.14)	2.63 (0.11)	2.56 (0.23)	−0.34 (0.11)	0.03*	−0.42 (0.11)	0.01**	0.08 (0.11)	0.77
Oblique Dendrites[d]	3.57 (0.21)	4.09 (0.16)	4.01 (0.15)	0.14 (0.03)	0.003***	0.12 (0.04)	0.01**	0.02 (0.03)	0.76
Supra									
Apical Dendrite Diameter[c]	3.09 (0.27)	2.82 (0.20)	2.86 (0.11)	−0.27 (0.14)	0.17	−0.22 (0.15)	0.31	−0.05 (0.14)	0.94
Oblique Dendrites[d]	3.51 (0.19)	4.04 (0.30)	4.08 (0.08)	0.14 (0.04)	0.01**	0.15 (0.04)	0.01**	−0.01 (0.04)	0.97

Abbreviations: MIA1 = 1st trimester exposed offspring; MIA2 = 2nd trimester exposed offspring; *SE* = standard error.

[a]Thirty neurons per animal were measured. Descriptive statistics represent means calculated from subject averages.

[b]Tukey-Kramer procedure for multiple comparisons was used to adjust *P*-values.

[c]Estimated group differences are from linear mixed-effects models with fixed effects for outcome group (MIA1, MIA2, Control), and using a compound-symmetric covariance to model within-animal dependence.

[d]Estimated group differences are from Poisson mixed-effects models with fixed effects for group (MIA1, MIA2, Control), and using a compound-symmetric covariance to model within-animal dependence.

Table 2

Summary of brain changes in MIA-treated primate offspring.

-1651064853Behavior00BehaviorBehaviorBehaviorBehaviorBehavior	Key findings from MIA-exposed offspring	Study Design	Citation
Behavior	• Increased repetitive behaviors • Decreased affiliative vocalizations • Inappropriate social interactions (1st trimester only)	Longitudinal behavioral study	Bauman et al., 2014 [b]
	• Innate cytokines positively correlate with stereotyped behaviors at year 2, while TH2-associated cytokines positively correlate with self-directed stereotypies at year 4.	Immune development and behavior	Rose et al., 2017 [b]
	• MIA-exposed offspring show increased latency to focus on eyes, decreased latency to focus on mouth	Eye tracking with facial expression stimuli	Machado et al., 2015 [b]
Imaging-17145-233824Imaging0ImagingImagingImagingImagingImaging	• Increased presynaptic striatal dopamine	PET study	Bauman et al., 2019 [b]
	• PFC shows volumetric decreases in gray and white matter • Subtle differences in cognitive performance	Structural MRI study; cognitive development	Vlasova et al., 2021 [c]
Postmortem-13197-25594Postmortem0PostmortemPostmortemPostmortemPostmortemPostmortem	• Decreased diameter of apical dendrites • Increased oblique dendrites Increased stereotypies (limited behavioral assessments)	Golgi pilot study of DLPFC, Layer II pyramidal neurons in dosing cohort	Weir et al., 2015 [a]
	• 266 genes are differently expressed in brain, highest number in hippocampus No differences observed between 1st and 2nd trimester exposed offspring	RNASeq in PFC, ACC, HC, V1	Page et al., 2021 [b]
	• Decreased diameter of apical dendrites in infragranular layers • Increased number of oblique dendrites • No differences observed between 1st and 2nd trimester exposed offspring	Golgi study of DLPFC pyramidal neurons, Hippocampal CA3 principal neurons in 1st and 2nd trimester MIA-exposed nonhuman primates	Present Study [b]

[a] Cohort 1: SFARI-funded dosing study.

[b] Cohort 2: SFARI-funded pilot study (animals used in present study).

[c] Cohort 3: NIH-Funded Conte Center.