Archival Report

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Maternal Immune Activation in Nonhuman Primates Alters Social Attention in Juvenile Offspring

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ABSTRACT

BACKGROUND: Sickness during pregnancy is associated with an increased risk of offspring neurodevelopmental disorders. Rodent models have played a critical role in establishing causal relationships and identifying mechanisms of altered brain and behavior development in pups prenatally exposed to maternal immune activation (MIA). We recently developed a novel nonhuman primate model to bridge the gap between human epidemiological studies and rodent models of prenatal immune challenge. Our initial results demonstrated that rhesus monkeys given the viral mimic synthetic double-stranded RNA (polyinosinic:polycytidylic acid stabilized with poly-l-lysine) during pregnancy produce offspring with abnormal repetitive behaviors, altered communication, and atypical social interactions.

METHODS: We utilized noninvasive infrared eye tracking to further evaluate social processing capabilities in a subset of the first trimester MIA-exposed offspring ($n = 4$) and control animals ($n = 4$) from our previous study.

RESULTS: As juveniles, the MIA offspring differed from control animals on several measures of social attention, particularly when viewing macaque faces depicting the fear grimace facial expression. Compared with control animals, MIA offspring had a longer latency before fixating on the eyes, had fewer fixations directed at the eyes, and spent less total time fixating on the eyes of the fear grimace images.

CONCLUSIONS: In the rhesus monkey model, exposure to MIA at the end of the first trimester results in abnormal gaze patterns to salient social information. The use of noninvasive eye tracking extends the findings from rodent MIA models to more human-like behaviors resembling those in both autism spectrum disorder and schizophrenia.

Keywords: Autism spectrum disorders, Immunology, Macaque, Nonhuman primate, Poly IC, Schizophrenia, Social attention.

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The prenatal environment and, in particular, the maternal immune system may have a profound effect on fetal neurodevelopment (1–4). In humans, exposure to infections during pregnancy may increase the risk of giving birth to a child who will later develop an autism spectrum disorder (ASD) or schizophrenia (SZ) (5–14). Animal models have demonstrated that exposing pregnant dams to prenatal challenges, such as influenza (15–18) or the bacterial endotoxin lipopolysaccharide (19–22), produce offspring with behavioral abnormalities and neuropathology relevant to both SZ and ASD. The diversity of infections associated with alterations in neurodevelopment suggests that the maternal immune response, rather than a specific pathogen, drives changes in fetal brain development. The emerging maternal immune activation (MIA) hypothesis has been directly tested in animal models by artificially activating the immune system of pregnant rodents with the viral mimic, synthetic double stranded RNA (polyinosinic:polycytidylic acid [poly IC]), a toll-like receptor-3 agonist that stimulates an inflammatory response in the absence of a specific pathogen (23). Rodent pups born to dams treated with poly IC at mid gestation demonstrate behavioral abnormalities, neuropathology, and altered gene expression relevant to both ASD and SZ [reviewed in (24–28)].

It is important to emphasize that sickness during pregnancy is not uncommon (29,30), and clearly, not all women who experience infection during pregnancy have children later diagnosed with a neurodevelopmental disorder (31). A number of factors, including genetic susceptibility, the intensity and timing of the infection, and exposure to additional postnatal challenges, all may influence the degree to which the prenatal immune challenge alters neurobehavioral development (32). Translational animal models provide a powerful tool to systematically examine how these factors contribute to offspring pathophysiology following MIA. In the rodent MIA model, the effects of poly IC on brain and behavior development appear to be mediated by the maternal cytokine response, in particular interleukin-6 (33,34), and exacerbated by postnatal environmental stressors (35).

While rodent models have provided compelling evidence for a causal relationship between MIA and aberrant brain and behavioral development in the offspring (36–40), there are limitations in relying solely on rodent models to study complex

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human brain disorders. Nonhuman primates, such as the rhesus macaque (*Macaca mulatta*), can provide a more direct comparison with human brain and behavior pathologies to determine the clinical relevance of the MIA model to human neurodevelopmental disorders (41–43). Previous primate models have documented changes in brain and behavior development of macaque offspring following third trimester exposure to influenza or lipopolysaccharide (18,19); however, the effects of MIA at earlier gestational time points have not been explored. We have developed a novel, nonhuman primate model of maternal immune activation using a modified form of poly IC (poly IC stabilized with poly-l-lysine [poly ICLC]) that is recognized by the primate immune system and induces a transient innate inflammatory response (44,45). Pregnant rhesus monkeys injected with poly ICLC at the end of either the first or second trimester produce offspring with abnormal motor stereotypies and repetitive behaviors (46). While both first and second trimester MIA offspring produced fewer affiliative vocalizations than control animals, only the first trimester MIA offspring showed signs of atypical social interactions with unfamiliar peers. Given that both ASD and SZ are characterized by changes in social cognition and emotion (47), as well as altered visual attention devoted to facial expressions (48,49), we initiated a series of noninvasive eye-tracking studies to provide further insight into the nature of the social impairments observed in the MIA offspring. Here, we present the initial results from these eye-tracking studies demonstrating abnormal patterns of social attention in the macaque offspring exposed to MIA in the first trimester.

METHODS AND MATERIALS

All experimental procedures were developed in collaboration with the veterinary, animal husbandry, and environmental enrichment staff at the California National Primate Research Center 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. Additional methodological details are provided in Supplement 1.

Subjects and Living Conditions

Noninvasive eye tracking was used to evaluate social attention in a subset of juvenile macaque monkeys from our previous study (46) before puberty, when the animals were approximately 2.5 years of age. All control (CON) ($n = 4$) and first trimester MIA exposed male animals ($n = 5$) were selected to participate in the current series of experiments to follow-up on the social behavior differences described in our earlier report. One of the MIA animals did not habituate to the testing procedures and was therefore dropped from the study, yielding a final sample size of $n = 4$ for the MIA group. The MIA offspring were born to dams injected with .25 mg/kg synthetic double-stranded RNA (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 43, 44, and 46. CON offspring were born to dams injected with saline at these same time points or at the end of the second trimester (gestational days 100, 101, and 103) or had no manipulation at all during pregnancy. Preliminary analyses revealed that the behavioral profiles of the male saline-treated control monkeys ($n = 1$ first trimester, $n = 2$ second trimester) and the male untreated control monkey ($n = 1$) were very similar and thus pooled to form a single control group. While we detected no differences in first trimester, second trimester, and untreated control animals in our previous report (46), it is important to note that repeated, daily prenatal stress has been shown to alter neurobehavioral development in nonhuman primates (50–54). To minimize the influence of prenatal stress, MIA and saline-control dams were preselected for their willingness to receive intravenous injections and followed identical procedures for routine ultrasounds, housing, and prenatal care.

Noninvasive Eye Tracking

All data collection occurred while the animals sat in a modified primate chair with a slanted top (Crist Instrument Co., Inc., Damascus, Maryland). Visual stimuli were presented to each monkey using a personal computer running the Eprime 2.0 Professional software package (Psychology Software Tools, Pittsburgh, Pennsylvania). All gaze data were collected using the Eye-Trac 6 .NET User Interface program (Applied Science Laboratories Bedford, Massachusetts) on a separate personal computer.

Experiment 1: Facial Expressions

The animal viewed 40 color photographs of unfamiliar adult male and female macaque facial expressions that are used for social communication. These facial expressions included neutral ($n = 10$), lipsmack ($n = 10$), fear grimace ($n = 10$), and open-mouth threat ($n = 10$). Each face stimulus was presented for 5 seconds and was preceded and followed by a blank, black screen (5 seconds). The experimental animals saw the same 40 facial expression stimuli on each of the 5 days of this experiment but in a random order each day. Figure 1A shows a schematic of an eye-tracking trial and Figure 1B shows examples of facial expression categories.

Experiment 2: Facial Expressions Embedded in Complex Scenes

Similar to experiments involving patients with ASD (55), the animals viewed 50 color photographs showing 10 different nature scenes. Each nature scene was seen five times during a testing session, once each with a neutral, lipsmack, fear grimace, or threat face embedded at a random spatial location and once without any embedded face (Figure 2). The experimental animals saw the same 50 images on each of the 5 days of this experiment but in a random order each day. These stimuli were presented in the same trial structure and for the same duration as the stimuli used for experiment 1.

Data Analysis

Each animal's total fixation duration, total frequency of fixations, average fixation duration, average gaze dwell duration, and average pupil diameter were measured for each stimulus in experiments 1 and 2 using the ASL Results Plus software package (Applied Science Laboratories). This software also

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