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Maternal immune activation alters infant attentional processing in a nonhuman primate model

J.A. Hubbard [a,*], S. Chen [b], A.M. Iosif [b], A.M. Ryan [a], T. Murai [a], C.E. Hogrefe [a], T.A. Lesh [c], J. Smucny [c], R.J. Maddock [c], C.M. Schumann [d,e], T.D. Hanks [f,g], J. Van de Water [h], A.K. McAllister [g,i,j], C.S. Carter [g,k], A. Paukner [l], J.P. Capitanio [a], M.D. Bauman [a,d,m,**,1]

[a] California National Primate Research Center, University of California Davis, California, 95616, USA
[b] Department of Public Health Sciences, School of Medicine, University of California Davis, Sacramento, CA, 95817, USA
[c] Department of Psychiatry and Behavioral Sciences, School of Medicine, University of California Davis, Sacramento, CA, 95817, USA
[d] The MIND Institute, School of Medicine, University of California Davis, Sacramento, CA, 95817, USA
[e] Department of Cell Biology and Human Anatomy, School of Medicine, University of California Davis, Davis, CA, 95616, USA
[f] Department of Neurology, School of Medicine, University of California Davis, Sacramento, CA, 95817, USA
[g] Center for Neuroscience, University of California Davis, Davis, CA, 95618, USA
[h] Department of Rheumatology, Allergy and Clinical Immunology, School of Medicine, University of California Davis, Sacramento, CA, 95817, USA
[i] Department of Biology, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA
[j] Department of Translational Neuroscience, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA
[k] Department of Psychiatry and Human Behavior, School of Medicine, University of California Irvine, Irvine, CA, 92697, USA
[l] Department of Comparative Psychology, Nottingham Trent University, Nottingham, UK
[m] Department of Physiology and Membrane Biology, School of Medicine, University of California Davis, Davis, CA, 95616, USA

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ABSTRACT

Maternal infection during pregnancy has been linked to the emergence of neurodevelopmental disorders. Preclinical animal models of maternal immune activation (MIA) have provided critical mechanistic links between maternal cytokines and alterations in offspring brain and behavioral development. While most preclinical work on MIA used rodent models, nonhuman primate (NHP) models have strong translational potential due to their greater similarity with humans. Previous NHP MIA models have replicated rodent findings of atypical offspring behavior emerging as animals mature, but few studied MIA-induced alterations in infancy. Here, we present a unique contribution on early milestones of attention in males using a rhesus monkey NHP MIA model. During an assessment of imitation conducted at 1 week-old, MIA-exposed offspring deviated from species-typical abilities to imitate social signals from human demonstrators. During a visual paired comparison task at 1 month, MIA-exposed offspring looked longer at novel abstract stimuli than control animals. A similar response was observed at 3–4 months when MIA-exposed offspring looked longer at novel monkey faces than control animals. The atypical response to novel social stimuli exhibited by MIA-exposed offspring appears contingent on how different the novel stimuli looked compared to the familiar stimuli, where MIA animals looked longer at easy discriminations compared to control animals. These results indicate that attentional processes in MIA-exposed offspring may be disrupted early in development, potentially resulting in longer visual stimuli processing times. Disruption of early attentional processes in the NHP MIA model may provide translational insights to identify children impacted by gestational exposure to maternal infections.

1. Introduction

Epidemiological and clinical evidence has identified a diverse range of chronic and acute inflammatory conditions during pregnancy that are associated with an increased risk of offspring neurodevelopmental disorders (Bauman and Buss, 2022; Han et al., 2021a,b). Maternal infection

* Corresponding author.
** Corresponding author. California National Primate Research Center, University of California Davis, California, 95616, USA.
E-mail addresses: jahubbard@ucdavis.edu (J.A. Hubbard), mdbauman@ucdavis.edu (M.D. Bauman).
[1] Permanent Address: The MIND Institute, Bioscience Building 1416, 2805 50th Street, Sacramento, CA 95817.

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during pregnancy has emerged as a particular area of interest due to a global increase in emerging infectious diseases (Jones et al., 2008). Although the vast majority of women who experience infection during pregnancy will go on to have neurotypical offspring, mounting epidemiological evidence suggests that for some pregnancies, maternal infection may increase the likelihood of offspring neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder, schizophrenia (SZ) and Tourette syndrome (TZ) (Meyer, 2019). The diversity of maternal viral and bacterial infections (such as rubella, influenza, herpes simplex, cytomegalovirus, toxoplasmosis and others) associated with offspring neurodevelopmental disorders suggests that maternal immune response is the critical link between maternal infection and altered fetal neurodevelopment (Kim et al., 2024; Han et al., 2021a,b). However, understanding the mechanisms by which maternal infection influences offspring development in humans is challenging to disentangle both logistically and ethically due to a myriad of factors human offspring may be exposed to.

Preclinical models of maternal immune activation (MIA) offer a system for testing hypotheses and identifying causal relationships with significant translational potential for human studies (Bauman and Van de Water, 2020). In these animal models, pregnant dams are experimentally exposed to an immune challenge at a specific time during gestation, and MIA-exposed offspring are compared to control offspring. However, the experimental manipulation of MIA can vary across models and studies due to differences in gestational age, immunogen, and dose, resulting in different advantages and disadvantages when selecting a particular model (Kentner et al., 2019). Using rodent and nonhuman primate (NHP) models, causal relationships have been identified between maternal infection and behavioral abnormalities that mirror those indicative of ASD and SZ in humans (Brown and Meyer, 2018; Careaga et al., 2017; Estes and McAllister, 2016). MIA-exposed rodents exhibit behavioral abnormalities such as disruptions to communication, abnormal social behaviors, and increased repetitive behaviors (Meyer, 2013; Jouda et al., 2019). Previous research has shown that rodent MIA offspring also show differences in cognitive performance, such as deficits in working memory, cognitive flexibility, and sensorimotor gating (the ability to filter out extraneous information to focus attention and avoid overstimulation) (Meyer, 2013). However, a recent review of the effects of MIA on rodent learning and memory shows variation and conflicting directionality in these results, suggesting that these relationships may be more complex and potentially context-dependent (Sal-Sarria et al., 2024). This indicates that more research is warranted on how MIA influences the development of species-typical attentional processes, particularly in the early stages and across development.

Although rodent MIA models have provided foundational mechanistic insights (for review see Guma et al., 2019; Gumusoglu and Stevens, 2019; Woods et al., 2021), NHP models are valuable analogs due to their physiological and phylogenetic similarity with humans. Additionally, NHPs show unique similarities with humans, such as higher social complexity and diversity of behavioral repertoires. NHPs also share with humans a heavy reliance on visual stimuli compared to olfactory stimuli, as well as morphological similarities such as increased neural cortical folding, placental structure, gestational timelines, and offspring neurodevelopmental stages (Tarantal et al., 2022). NHP MIA models show parallels with preclinical rodent MIA models such as MIA offspring exhibiting changes in brain and behavior that parallel features of human neurodevelopmental disorders (reviewed in Ryan and Bauman, 2022). Initial studies in MIA-exposed rhesus monkey (*Macaca mulatta*) offspring revealed alterations in species-typical social behavior (Bauman et al., 2014) and abnormal gaze patterns to salient social information (Machado et al., 2015). In a recent assessment of cognitive development, MIA offspring showed subtle differences when performing memory and cognitive flexibility tests when tested as juveniles and subadults (Vlasova et al., 2021). Although the MIA-exposed NHPs from this study exhibit reductions in the frontal cortex as early as 6 months of age (Vlasova et al., 2021), it is not known if behavioral differences emerge at these early developmental timepoints.

Early attentional capabilities are crucial for social or cognitive development (Hunnius, 2007), including the ability to understand and respond to social signals (Simpson et al., 2014). Although there has been much debate over whether human and NHP share neonatal imitation capabilities, mounting evidence suggests that these attentional capacities are conserved (Gross, 2006). Human infants between 12 and 21 days old (Meltzoff and Moore, 1977), and as early as the first day of life (Heimann, 2022; Nagy et al., 2020) can imitate both facial and manual gestures from other humans (Davis et al., 2021). NHPs, such as rhesus macaques, also exhibit evidence of neonatal imitation as early as the first day of life, with a peak in imitation at day 3 (Ferrari et al., 2006). Neonatal imitation is theorized to be crucial for mother-infant bonding and has been shown to have a variety of positive social and cognitive developmental outcomes for rhesus macaques (Dettmer et al., 2016; Ferrari et al., 2009; Kaburu et al., 2016; Wooddell et al., 2018). Importantly, neonatal imitation may promote affiliation in subjects at risk for developing abnormal social behaviors. For example, nursery-reared rhesus infants were found to look longer and lip smacked more at a human experimenter both during imitation and after being imitated, suggesting that neonatal imitation may mediate adverse developmental outcomes for at risk infants (Sclafani et al., 2014). Although no study to date has assessed neonatal imitation in a MIA model, these assessments may provide insight into early attentional processes implicated in human neurodevelopmental disorders (Ashinoff and Abu-Akel, 2021; Heimann and Holmer, 2021).

Our overarching goal was to explore early behavioral markers of attention in a cohort of MIA-exposed NHPs that exhibit subtle cognitive deficits in late adolescence paired with volumetric reductions in prefrontal cortex (Vlasova et al., 2021), aberrant dopaminergic signaling (Smucny et al., 2023), evidence of neuroinflammation (Lesh et al., 2023) and altered brain metabolites (Maddock et al., 2024). In this study, we focused on how MIA influences attentional processes across early development in NHPs. The behavioral assessments were chosen to coincide with time points relevant for NHP early development as well as with other scheduled procedures to reduce stress associated with separating the infant from the dam. We used two assessments to measure attentional and cognitive processes in infant macaques: neonatal imitation and a novelty preference paradigm, the visual paired comparison test (VPC). Imitation was assessed at 1 week of age due to evidence in the literature suggesting this is an innate rather than learned trait that peaks within the first few days of life. VPC was assessed at 1 month to represent a time point between imitation and the 3–4 months' time point, which occurs in the middle of the pre-weaning phase (0–6 months of age). During the imitation paradigm, modeled after a series of studies conducted by Paukner and colleagues (Dettmer et al., 2016; Ferrari et al., 2006, 2009; Kaburu et al., 2016; Sclafani et al., 2014; Simpson et al., 2014), subjects were measured on their ability to imitate social signals from a human demonstrator. The VPC test was used to assess an individual subject's recognition memory, as measured by a visual preference for a novel stimulus compared to familiar stimuli (Basile et al., 2024). Although we expected all subjects to prefer novel images, we hypothesize that if attentional processes are disrupted in MIA offspring, this could result in alterations to imitative abilities and visual attention on the VPC task. This could result in MIA animals showing reduced novelty preference compared to control animals due to attentional or discriminatory deficits. Alternatively, MIA animals could show heightened novelty preference compared to controls which could be due to longer processing times and/or a deficit for disengaging attention, a process sometimes referred to as "sticky attention" in the human literature (Sacrey et al., 2013). Furthermore, some NHP studies on general visual discrimination have found differences in performance depending on the similarity between stimuli as a measure of "easy" vs. "hard" discriminations (Ahissar and Hochstein, 1997; Fragaszy, 1981; Washburn and Putney, 2001). We hypothesize that if MIA-exposed

offspring experience attentional deficits, that this may be further influenced by discrimination difficulty. We explore whether fixations on the novel stimulus differ based on MIA treatment and discrimination difficulty (easy vs. hard discriminations), and whether those fixation patterns are consistent over early developmental timepoints.

2. Methods

All experimental procedures were developed in consultation with the veterinary and behavioral staff at the California National Primate Research Center and protocols were approved by the University of California, Davis Institutional Animal Care and Use Committee. Detailed methods on animal selection, MIA procedure and validation, and overall project testing regime are provided in Vlasova et al. (2021).

2.1. Maternal administration of poly ICLC

Twenty-eight multiparous adult female rhesus monkeys carrying a male fetus were assigned to one of two experimental groups: 1) MIA, or 2) control animals (CON). Pregnant dams assigned to the MIA group (N = 14) were injected with 0.25 mg/kg synthetic double-stranded RNA (poly ICLC) (Oncovir, Inc., Washington, DC) via intravenous injection on gestational days 43, 44, and 46. In this study, MIA induction was confirmed by the presence of transient sickness behaviors, including reduced appetite and fever, accompanied by a strong pro-inflammatory cytokine response as indexed by the change in IL-6 from baseline (Vlasova et al., 2021). Pregnant dams assigned to the control group were either injected with sterile saline (N = 10) or left untreated (N = 4). These experiments were conducted before the NIH requirement to consider sex as a biological variable. Since the emergence of neurodevelopmental disorders in offspring appears to be heavily male-skewed or show heightened or earlier onset of symptoms in males (TZ: Baizabal-Carvallo and Jankovic, 2023; SZ: Leung and Chue, 2000; ASD: Loomes et al., 2017), all offspring chosen for this study (N = 28) were male.

2.2. Rearing conditions

As dams exhibit sickness behaviors during MIA-induction, research staff cannot remain blind to treatment conditions during the gestational manipulation. When the offspring were born four months later, they received unique dye marks to facilitate behavioral coding, independent of dam treatment identification, and all infant-dam pairs were relocated to a single project housing room. No other identifying information regarding treatment was present on cages, data collection forms, or recorded videos. Infants were raised indoors in separate cages with their mothers who had visual access to other animals in the room. At approximately 2–3 weeks of age, stable social groups were formed, consisting of four mother-infant pairs (two MIA, two CON) plus one adult male. Social groups were formed and continued for 3 h daily until infants were weaned. The infants were weaned from their mothers at approximately 6 months old and paired with an age-matched peer from their social group in an adjacent cage. Daily 3 h social groups continued after weaning until 18 months of age with the same four offspring, the same adult male, and the addition of an adult female. Subjects were fed twice daily (Lab Diet #5047, PMI Nutrition International), and provided with forage scratch daily and fresh produce biweekly. Access to water was provided *ad libitum* along with several enrichment devices. All infants were temporarily separated from their dams and transported to an adjacent building for behavioral assessments.

2.3. Neonatal imitation test – 1 week

During a single test session, a human demonstrator generated facial expressions towards infants who were handheld by another experimenter. All sessions were video recorded, and infants were tested at seven days old (± 1 day). The assessment was divided into two conditions: lip smack and tongue protrusion (Fig. 1). Lip smack is important in social signaling for rhesus macaques, often used between mothers and infants as well as other group members during affiliative interactions. The second gesture, tongue protrusion, is not thought to bear any social significance for rhesus macaques. Lip smack demonstration consisted of slightly opening and closing the mouth rapidly in ~5 s bursts; the tongue protrusion demonstration consisted of opening the mouth with maximal extension and retraction of the tongue. Each assessment consisted of a baseline period in which the human demonstrator first showed a neutral facial expression for 40 s, followed by a stimulus period (20 s) and a still period (20 s). One facial gesture was displayed throughout the stimulus period, and the neutral facial expression was resumed during the still period. There was a total of 3 stimulus periods and two still periods per condition (Table S1 in S1). To detect evidence of imitation using this assessment, a typical response would be for subjects to increase their production of matching facial gestures during experimental periods (stim or still) when compared to the initial baseline, thereby reflecting the subject's ability to selectively respond to socially relevant cues. Still periods serve as intermittent but consistent reference points across conditions, allowing researchers to examine behavior within the context of a facial interaction but in the absence of a stimulus. All sessions were coded by a single observer (AP) for the frequency of lip smack and tongue protrusion gestures produced by infants. Coder reliability was established prior to video coding at greater than 90 %.

2.4. Abstract visual paired comparison test – 1 month

During a single test session, abstract black and white illustrations (Fagan Test of Infant Intelligence; Infantest Corporation, Cleveland, OH) were presented to infants who were handheld by an experimenter. All sessions were video recorded, and infants were tested at 35 days old (± 3 days). Images were temporarily mounted on an opaque trifold so they could be easily changed between trials in a session (Fig. 2). The trifold accommodated the video camera with a hole in the center to record the gaze of infant subjects. One experimenter held the infant approximately 36 cm from the trifold and switched the stimuli across trials, while a second experimenter operated the video camera and recorded infant fixation times using a stopwatch. The room was darkened before testing aside from an overhead lamp to illuminate the testing trifold. Subjects had 1 min to acclimate to the room conditions prior to testing. Before familiarization and between each trial the infant's head was covered with a small towel to control trial start and end times.

Within a testing session, each subject experienced four problem sets with different visual stimuli. Each problem set contained two trials, for a total of eight trials per single testing session. Before each problem set, the subjects experienced a familiarization by presenting two identical stimuli and were required to look at either image for a cumulative 20 s. After the 20-s familiarization period, trial 1 began with one of the stimuli being replaced with a novel stimulus on the right or left side in a randomized fixed order for all subjects. Once the subject first fixated on a stimulus, a 10 s stopwatch was used to denote the length of the trial, but unlike the familiarization trial these 10 s were not cumulative. After trial 1, the location of the stimuli was reversed and recorded in the same way for trial 2. After trial 2, there was a 30 s delay before a second problem set of visual stimuli was introduced, which restarted the process of familiarization, test trial 3 and test trial 4. After testing, the videos were scored by a single observer (CH) using The Observer XT software (Version 12.0, Noldus Inc., Leesburg, VA, USA) for the frequency and duration of looking at the novel and familiar stimuli. Coder reliability was established prior to video coding for durations of looking time at greater than 85 %.

2.5. Social visual paired comparison test – 3–4 months

All infants were temporarily separated from their dams at 3–4

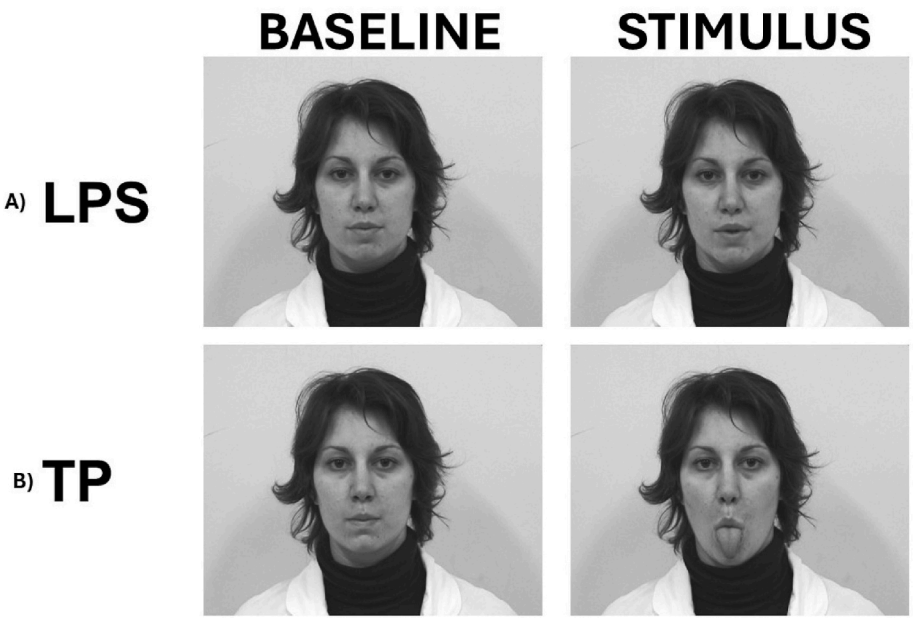

Fig. 1. Neonatal imitation conditions include lip smacking (A) and tongue protrusion (B). Figure adapted from Paukner et al., 2017); licensed under CC BY 4.0. A portion of original figure was used and modified for clarity.

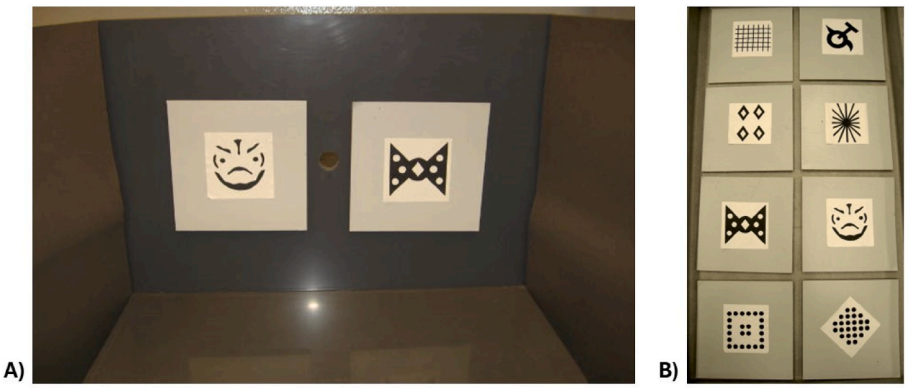

Fig. 2. Abstract visual paired comparisons test, showing the test setup (A) and stimuli sets in the fixed order of presentation (B).

months of age for approximately 25 h as a part of the BioBehavioral Assessment (BBA) at the California National Primate Research Center (CNPRC). The BBA program has been conducted at the CNPRC since 2001 and has assessed thousands of animals across various rearing conditions, including outdoor-reared, indoor mother-reared, and indoor nursery-reared. The BBA program consists of a battery of tests designed to assess an infant's behavioral and physiological reactivity, one of which is the visual paired comparisons test (for details on BBA, see Capitanio, 2021). During this test, infants were transferred from their holding cage to the test cage, which was approximately 68.5 cm from the viewing monitor. The room was darkened during testing, and the images were presented on the monitor with a camera centered on the viewing monitor to capture subject responses. The infant was given a 30 s habituation period before any stimuli were presented. After habituation, still pictures of neutral faces and body postures of rhesus monkeys of varying ages and sexes were presented during a single test session that was video recorded (Fig. 3). Two pictures were always presented at a time, with each picture occupying either the left or right third of the screen, with each picture measuring 19.6 cm × 22.8 cm with a white space between measuring 25.4 cm. Details on how stimuli videos were created, cage sizing, and equipment specifications can be found in Sclafani et al. (2016). A single observer coded all videos using Observer XT software (Noldus Inc., Leesburg, VA, USA). Coder reliabilities were established prior to video coding at greater than 85 % (Sclafani et al., 2016).

Throughout the session, seven discrete problem sets or blocks were presented, with three trials per block: a familiarization trial, trial 1 with a novel stimulus introduced on a side of the screen in a fixed order (Table S2 in S1), and trial 2 with the novel stimulus location reversed on the screen compared to trial 1. A tone of 1000 Hz was presented 250 ms before trials to orient the animal towards the viewing screen. During the familiarization trial, two identical images were presented on a screen for 20 s. After familiarization, the screen went blank for a 5 s intertrial interval before trial 1 began, where the location of the novel stimulus replaced one of the identical images and was presented for 8 s. For trial 2, the same images from trial 1 were presented but in reverse positions on the screen for 8 s. This procedure continued for all problem sets or blocks until each subject experienced sets 1–7. Problem sets were always presented in the same order, with an inter-set interval of 5 s to match intertrial intervals.

Since subjects were unrestrained in the test cage, we cannot assume they looked at the familiarization stimuli or test stimuli for the full 20 or 8 s, respectively. As a result, we calculated the proportion of time the subject looked at the novel stimulus and excluded sessions where the

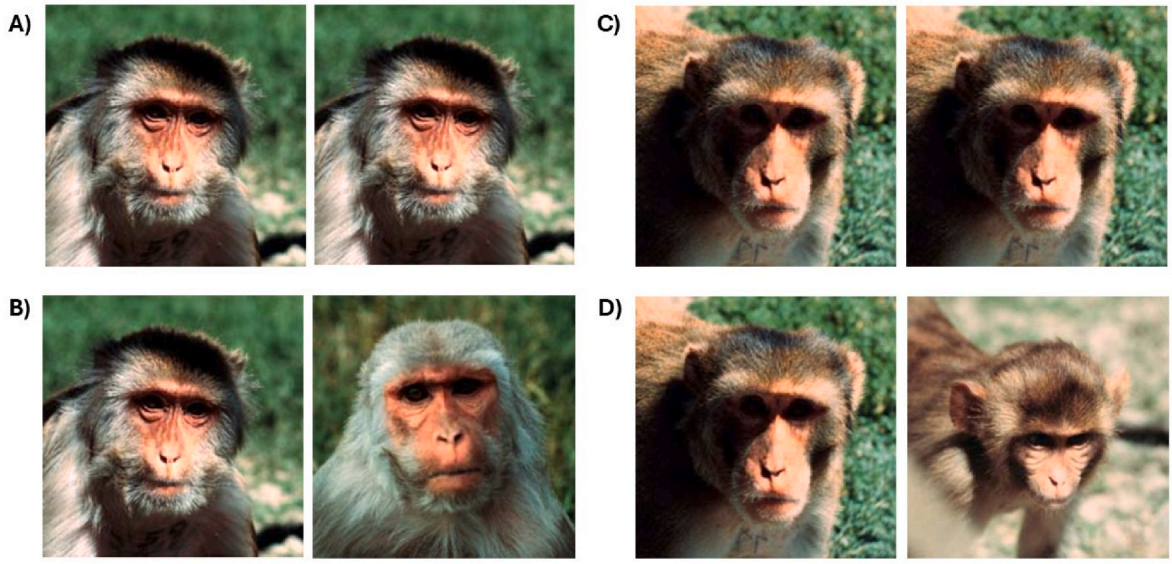

Fig. 3. Examples of easy and hard problem stimuli provided during the social visual paired comparisons test. During familiarization trials (A for problem 1 & C for problem 2), infants were presented with two identical unfamiliar monkey faces. During subsequent recognition trials (B for problem 1 & D for problem 2), infants were presented with the same monkey face from the immediately preceding familiarization trial and a novel face. Faces with similar features were categorized as hard problems (B), while faces with dissimilar features were categorized as easy problems (D). The full stimuli set provided can be found in the supplemental material of Sclafani et al. (2016).

subject had a value of zero during the familiarization trial. Proportions of looking at novel stimuli were calculated within a block by summing the time looking at the novel stimulus across test trials 1 and 2 divided by the sum of time looking at both novel and familiar stimuli across both test trials 1 and 2. These calculated proportions were then averaged across the problem sets with valid data per subject to get an overall proportion of time looking at novel stimuli across sets. The problem sets were then categorized into "easy" vs. "hard" discriminations based on their visual similarity (e.g., shading, orientation). These distinctions were informally corroborated through blinded categorizations by colleagues familiar with rhesus macaques of varying ages and sizes, resulting in three easy and four hard problems.

2.5.1. Statistical analysis

Statistical analysis was conducted using generalized linear mixed-effect models with appropriate choices for the link and variance functions, with random effects included as needed to account for clustering (McCulloch and Searle, 2004). We used negative binomial regression with a log link and log-transformed observation time as an offset to account for overdispersion when analyzing imitation counts. For proportions of looking time during the VPC tests we used beta regression with a logit link as it is well-suited for modeling variables that are continuous and bounded between 0 and 1, such as proportions, rates, or probabilities. The primary models included a fixed effect for group (MIA and CON, or MIA, CON and the colony database group IMR (indoor mother-reared), as defined in section 2.6.4 below. In these models, estimated group differences are expressed on the log scale (negative binomial regression) and on the logit scale (beta regression). By exponentiating this estimated difference, we obtained a ratio for greater interpretability. For the negative binomial models, this ratio represents the incidence rate ratio (IRR), i.e., the ratio of the outcome rate in one group compared to the reference group, after adjusting for different exposure times. For the beta regression models, this represents a ratio of the odds (OR) for the proportion being modeled. All model assumptions were validated visually and analytically. Model selection was conducted using goodness of fit metrics such as the corrected Akaike Information Criterion (AICc), which adjusts for small sample sizes. Models were considered a better fit if they reduced the AICc by 2 or more points. Models within 2 AICc points of each other were considered similarly fit and were further explored post-hoc. All tests were two-sided and conducted with an alpha level of 0.05, and statistical analyses were performed in SAS OnDemand version 9.4 (SAS Institute Inc., Cary, NC).

2.5.2. Imitation 1 week

Counts of imitation at the 1-week time point were analyzed both within a condition (expressions of lip smack within the lip smack condition), as well as across conditions (expressions of lip smack between the lip smack and tongue protrusion conditions). These counts were modeled using a series of repeated measures negative binomial regression models, including those with a fixed effect for treatment (MIA, CON), time period (Baseline, Stimulus, Still), condition type (lip smack, tongue protrusion), and their interactions selected based on AICc. To account for within-animal dependence, random intercepts were included in these models. Although all twenty-eight animals were tested, one test video was compromised, resulting in twenty-seven animals being included in this analysis (MIA = 13, CON = 14).

2.5.3. Abstract visual paired comparison task – 1 month

The proportion of looking time at novel stimuli for the one-month time point was analyzed using a beta regression model with a fixed effect for treatment (MIA, CON). Although all 28 animals were tested, one test video was compromised, resulting in twenty-seven animals being included in this analysis (MIA = 13, CON = 14).

2.5.4. Social visual paired comparison task – 3–4 months

Since subjects for the MIA project were assessed during BBA using standardized CNPRC methods, we took this opportunity to compare our project animals to other monkeys in the wider colony. Considering that rearing condition can have significant influences on behavior (Vandeleest et al., 2011), we chose a comparison group based on similarity in social rearing to our study animals. Out of the 5500+ infants who underwent the BBA assessment, we selected males from the indoor mother-reared social condition (IMR, N = 184). Although this rearing condition was most similar to our project animals (MIA and CON), our project animals received additional socialization through the formation of daily social groups. Thus, we used this comparison group to assess

how our treated project animals (MIA) perform compared to a larger colony-wide dataset of similarly reared controls, given the limitations of our sample size when comparing project animals only. The proportion of looking time at novel stimuli for the three-to-four-month time point was analyzed using a series of beta regression models, including those with a fixed effect for treatment (MIA, CON, IMR), problem type (easy, hard), and their interaction. To account for within-animal correlation between problem types, random intercepts were included in the models.

2.5.5. Attention across early development

The proportion of looking time at novel stimuli at the three to four-month time point was analyzed using a series of beta regression models, including those with a fixed effect for treatment (MIA or CON), the proportion of looking time at novel stimuli at the one-month time point (early attention), and their interaction.

3. Results

A summary of all model comparisons is provided in Supplementary materials (Tables S3–S11 in S1), along with the effect sizes and significance levels discussed in the text below.

3.1. Imitation 1 week

At the one-week time point, MIA and control animals exhibited subtle differences in imitation patterns across time periods. The best-fit model was within 2 AICc points of the null model, suggesting it has a similar fit to the data (Table S3 in S1). However, a similar fit rather than worse fit to the null may suggest subtle differences that are worthy of further investigation. Due to an overall significant interaction between treatment and time period ($p = 0.021$ Table S4 in S1), we used linear contrasts to examine the differences between periods (baseline, stimulus, still) for each group based on the fitted models. Post-hoc comparisons revealed MIA animals showed a 49 % reduction in the rate of imitation during stimulus periods compared to baseline (IRR = 0.51, 95 % CI [0.28, 0.91], $p = 0.024$). Control animals, however, showed a 41 % reduction in the rate of imitation during still periods compared to stimulus periods (IRR = 0.59, 95 % CI [0.36, 0.97], $p = 0.038$, Fig. 4, Table S5 in S1). We also found subtle evidence that within an imitation session the main effects model performed similarly to the null model, indicating that all subjects may produce the lip smack response more often than the tongue protrusion response ($\beta = 0.51$, $p = 0.008$, Table S5 in S1).

3.2. Abstract visual paired comparison task – 1 month

At the one-month time point, all animals preferred novel images over familiar images, with significant differences between treatment groups. On average, subjects spent more time looking at novel images (58 %) than looking at familiar images (42 %) ($t(26) = 3.43$, $p = 0.002$). However, MIA and control animals showed differences in performance on the VPC task, where MIA animals showed a 51 % increase in odds for proportional looking time at novel stimuli compared to CON animals (OR = 1.51, 95 % CI [1.05, 2.16], $p = 0.027$; Fig. 5, Table S6 in S1).

3.3. Social visual paired comparison task – 3–4 months

At the three-to-four-month time point, all animals preferred novel images over familiar images, with significant differences between treatment groups that were dependent on problem difficulty. On average, project subjects spent more time looking at novel images (68 %) than looking at familiar images (32 %) ($t(26) = 8.25$, $p < 0.0001$). However, MIA and control animals showed differences in performance on the VPC task that were dependent upon problem difficulty. This was evident in the two best-performing models, where one model included main effects of treatment and problem difficulty as fixed effects, whereas

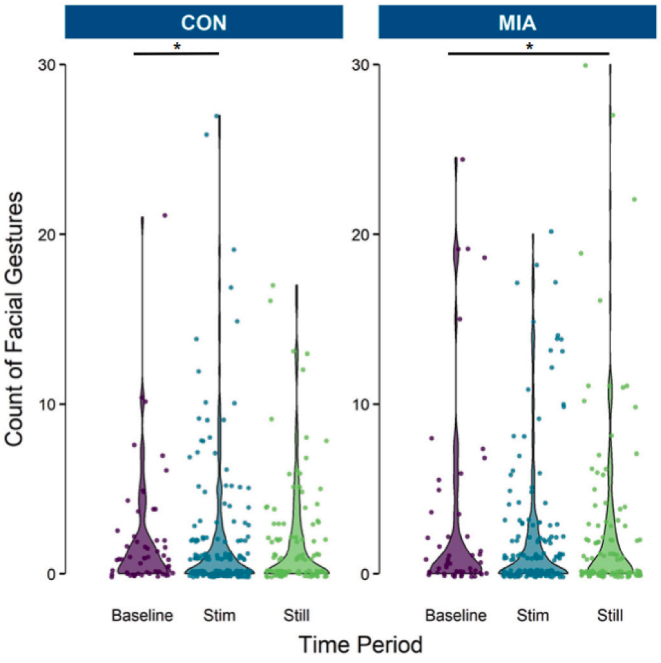

Fig. 4. Count of producing facial gestures indicative of imitation by treatment group (Control vs. MIA) across time periods: initial baseline (prior to signaling), stimulus (providing either a lip smack or tongue protrusion signal), and still (neutral face between signaling). The counts at baseline were divided by 2 to adjust for the doubled exposure times of baseline compared to other periods. We found that the interaction between treatment and time period was significant ($p = 0.021$), where MIA animals showed a 49 % reduction in the rate of producing facial gestures indicative of imitation during stimulus periods compared to baseline. In contrast, control animals showed a 41 % reduction in the rate of producing facial gestures indicative of imitation during still periods compared to stimulus periods. Note that * represents $p < 0.05$.

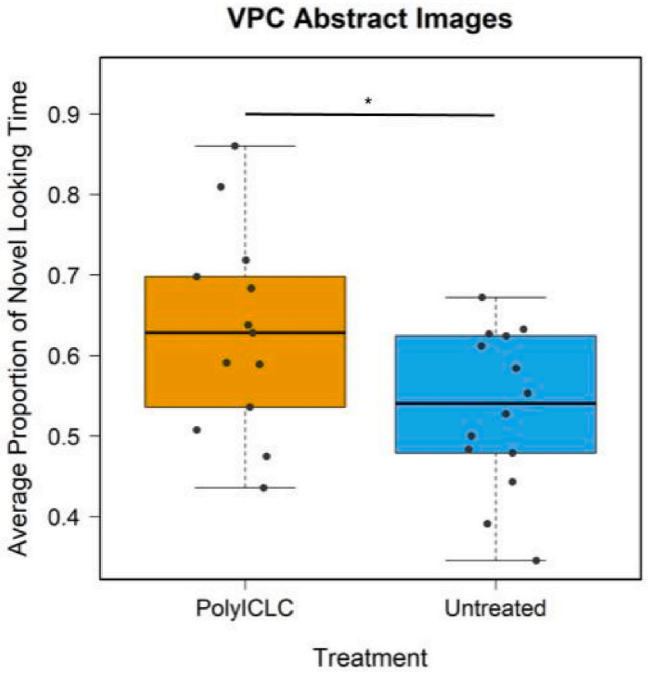

Fig. 5. Average proportion of looking time at novel abstract stimuli compared to familiar stimuli across all problem sets by treatment group. Although all animals preferred novel abstract images over familiar images ($p = 0.002$), MIA animals showed a 51 % increase in odds for proportional looking time at novel stimuli compared to CON animals. Note that * represents $p < 0.01$.

the other model further included the interaction between treatment and problem difficulty. In the main effects model where we tested all three groups, we found that MIA animals showed a 73 % increase in their odds for proportional looking time at novel stimuli compared to IMR controls (OR = 1.73, 95 % CI [1.31, 2.30], p = 0.0002; Fig. 6a, Table S7 in S1), but did not significantly differ compared to CON offspring (OR = 1.36, 95 % CI [0.93, 1.98], p = 0.111; Fig. 6a). However, after excluding the IMR controls in the analysis this effect became marginal (OR = 1.39, 95 % CI [0.97, 1.99], p = 0.071; Fig. S1 and Table S9 in S1).

When looking at the effect of problem type across all three groups on the average proportion of novel looking time, we found that there were significant differences between problem types, where during easy problems subjects showed a 24 % increase in odds for proportional looking time at novel stimuli compared to hard problems (OR = 1.24, 95 % CI [1.09, 1.40], p = 0.001; Fig. S2 and Table S7 in S1). When we investigated the interaction between problem type and treatment, we found no significant effects, indicating that the difference between CON and MIA did not depend on problem difficulty (p = 0.143; Fig. 6b). There was a marginal difference, however, between MIA and IMR controls where MIA animals tended to show a larger difference in looking time at novel stimuli between easy vs. hard problem types compared to IMR controls (p = 0.056; Fig. 6b). Considering the limitation of our sample size in detecting interaction terms and the fact that the interaction model was similarly fit (within 2 AICc points) to the model when both variables were included as main effects, we explored these data further by stratifying the analysis by problem type. When we examined easy problems, or highly different stimulus pairs, we found significant treatment group differences (F-test (2, 209) = 7.33 p = 0.0008). Specifically, for easy problems MIA animals showed higher odds in the proportion of looking time at novel stimuli compared to CON animals (OR = 1.73, 95 % CI [1.00, 3.00], p = 0.0501; Fig. 6b) and IMR controls (OR = 2.19, 95 % CI [1.45, 3.32], p = 0.0003; Fig. 6b–Table S8 in S1) despite the null model showing a better fit to these data. However, when we examined hard problems, or highly similar stimulus pairs, we found no significant differences (F-test (2, 208) = 2.08, p = 0.127; Fig. 6b–Table S9 in S1). Interestingly, after removing the IMR controls, the interaction model was significantly better fit compared to the model including only main effects of treatment and problem type. This model showed that the difference between CON and MIA animals was higher for easy problems compared to hard problems (p = 0.008; Fig. 3 and Table S10 in S1).

3.4. Attention across early development

Due to our longitudinal dataset, we also tested for behavioral consistency in subject performance on the VPC task over time. One model significantly outperformed the null model, whereas two other models were similarly fit between both the best fit model and the null model. The best fit model was the model that included treatment as a fixed effect, echoing a similar finding in Section 3.3, where MIA-subjects tended to have higher proportions of looking time at novel stimuli on the VPC task at the 3–4-month time point (OR = 1.42, p = 0.068). However, it is noteworthy that both the main effects model and interaction model, including treatment and the proportion of looking time at novel stimuli during the one-month VPC task, performed similarly to the null model and the univariate model containing treatment only. In the main effects model, when early attention on the VPC task was controlled for, the effect of treatment became significant (OR = 1.66, p = 0.021, Table S11 in S1).

4. Discussion

Here we demonstrate that MIA-exposed NHP offspring exhibit differences in attention towards imitation and novel stimuli across three time points in early development. During the first week of life, we found evidence for a treatment group by time period interaction effect on imitation. Specifically, MIA-exposed offspring imitated less during stimulus periods (when the human demonstrator produced facial expressions) compared to baseline (when the human demonstrator produced a neutral expression prior to signaling). In contrast, control subjects imitated more during stimulus periods compared to still periods. These changes in imitation may reflect differences in the ability to disengage, shift and engage visual attention as indexed by performance on the visual paired comparison test (VPC). At one month of age, MIA-exposed offspring looked proportionally longer at novel abstract stimuli compared to controls. Additionally, at three to four months of age MIA-exposed offspring attended to novel social stimuli longer than both within-project controls (CON) and a larger database of similarly-reared colony controls (IMR). Collectively, these findings suggest that infant MIA subjects experienced changes to attentional processes, resulting in differences in imitation and performance on the VPC task.

Our results largely mirror cognitive findings from rodent MIA model studies where researchers have found overall deficits to working memory, attention, and sensory processing (Sal-Sarria et al., 2024). Although

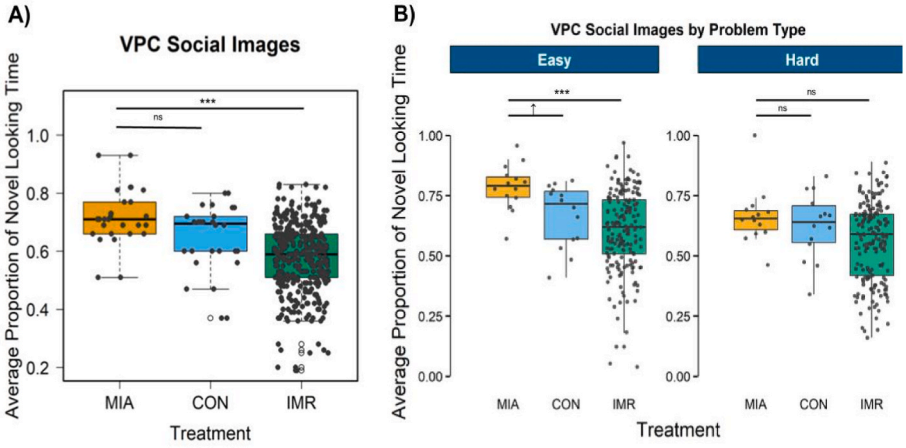

Fig. 6. a) Average proportion of looking time at novel social stimuli compared to familiar stimuli across all problem sets by treatment group. MIA animals showed a 73 % increase in the odds of looking proportionally longer at novel stimuli compared to IMR controls, but this difference was not observed when compared to CON project controls. b) Average proportion of looking time at novel stimuli compared to familiar stimuli by problem type and treatment type. For easy problems MIA animals showed higher odds in the proportion of looking time at novel stimuli compared to CON animals (73 %, p = 0.0501) and IMR controls (119 %, p = 0.0003). For hard problems no group differences were observed (p = 0.127). Note that *** represents $p < 0.001$ and arrows represent trends ($0.56 < p < 0.1$) using MIA as the reference category.

most rodent MIA studies have focused on behavioral changes that emerge or worsen as the animals mature (for review, Bergdolt and Dunaevsky, 2019), the protracted period of neurodevelopment in the rhesus macaque model allows us to explore the early emergence of atypical behaviors. Additionally, NHPs have specialized musculatures that enable them to produce complex social signals not available to non-primate species, providing us with a unique opportunity to evaluate facial signal imitation in the NHP model (Burrows, 2008). Here, we report that MIA-exposed offspring exhibit an atypical response to an early imitation assessment at 1 week of age. Infant macaque imitative skills are likely modulated by underlying differences in visual attention (Simpson et al., 2014) and may be further influenced by arousal or other factors. These attentional behaviors are likely mediated by neurological underpinnings, including mirror neurons that reinforce imitation by firing both when an animal performs a behavior and when it observes another performing the same behavior (Ferrari et al., 2009; Molenberghs et al., 2009). In typically developing rhesus macaque offspring, the mirror neuron system shows evidence of activation when mother-reared infants perform imitative gestures towards their mothers when compared to nursery-reared infants (Vanderwert et al., 2015). It is possible that MIA exposure may disrupt mother-infant gaze patterns that can further influence imitative patterns when tested with a human observer. However, prior investigators have found that arousal alone cannot explain neonatal imitation abilities in typically developing rhesus monkeys (Paukner et al., 2017). Contrastingly, our results suggest that MIA treatment may influence differences in baseline propensity to produce facial gestures without receiving a prompt by a human demonstrator compared to periods where they are prompted. Control animals showed species typical responses to produce fewer social signals during still periods compared to stimulus periods, whereas MIA animals produced fewer social signals during stimulus periods compared to the baseline period. This suggests that MIA animals likely possess comparable imitative abilities to CON subjects, yet they express their imitation with a delay or show evidence of carry-over effects. MIA subjects show higher baseline rates of social signaling that are reduced when demonstrators produce social signals during stimulus periods. A reduction in imitation during stimulus periods rather than still periods may indicate that MIA animals require greater processing time while observing social signals, resulting in delayed production of imitative signals themselves. This interpretation is consistent with other attentional deficits described here such as the aberrant response to novelty preference exhibited by MIA-exposed offspring. When imitation was conducted at 7 days of age, a neonatal assessment was also conducted to determine gross physical and developmental motor differences across treatment groups. As previously reported in Vlasova et al. (2021), we did not find any statistically significant differences between groups. However, the scores for visual orientation (which required the subject to orient their head toward a light stimulus) showed lower mean performance for MIA subjects compared to CON subjects. Although more data is warranted to determine if these differences are true and translationally relevant, this pattern may suggest that MIA subjects may experience divergences from CON subjects early in life that may contribute to differences in attentional processes later in development.

Some studies have employed novelty preference paradigms to evaluate differences in attention and recognition memory among MIA subjects. Rodent novelty preference assessments, however, often use different methods such as physical exploration of a novel object in an arena rather than following the attention of a demonstrator towards novel images. These differences in methodology are likely due to perceptual differences of how rodents and primates explore the world, with rodents being primarily olfactory-based compared to primates who are primarily visually based. Despite these methodological differences, rodent studies using novelty preference paradigms have found that MIA offspring differ from controls, with some studies reporting deficits in novelty preference (Ibi et al., 2009; Ozawa et al., 2006), while others showed a heightened preference towards novel objects (Golan et al., 2005; Ito et al., 2010). Reports of hypersensitivity to a novel object in MIA-exposed offspring were associated with alterations in hippocampal cell counts, slice physiology, and c-Fos expression (Bergdolt and Dunaevsky, 2019; Golan et al., 2005; Ito et al., 2010). Although MIA models have made great strides towards understanding the impacts on offspring in biological, neurological and behavioral outcomes, an exciting step for future studies on MIA includes integration across these domains to better identify potential mechanisms and causal relationships. This integration has already begun to appear in the literature within animal MIA models, both rodent and NHPs. An integration across animal MIA models to assess outcome similarity, however, may yield greater translational potential for informing human interventions for MIA exposed offspring.

While VPC paradigms are often presented as a simple test of recognition memory, converging evidence suggests that VPC measures both memory and other non-mnemonic factors, including novelty preference, habituation, motivation, and other processes (Basile et al., 2024). VPC paradigms have found increased preference for novel stimuli in a Rett syndrome model using adolescent cynomolgus macaques (*Macaca fascicularis*) (Zhang et al., 2019). Similarly, a study investigating developmental outcomes of fetal alcohol exposure in rhesus macaques found that offspring who were exposed to alcohol in utero showed an increased preference for novel stimuli using the same methodologies as used in this study for the one-month assessment (Golub et al., 2014). Eye tracking studies have yielded similar findings, showing that human children diagnosed with Rett syndrome also exhibit an increased preference for novel stimuli (Rose et al., 2019). Here, we observed a similar pattern in MIA-exposed NHPs early in development. In the human literature, there is evidence that young children diagnosed with ASD also exhibit a heightened preference for novelty, which has in part been attributed to a prolonged latency to disengage attention, which has also been referred to as "sticky attention" (Nayar et al., 2022; Sabatos-DeVito et al., 2016; Sacrey et al., 2013). This study provides a novel and critical bridge between rodent, NHP and human MIA literature in assessments of attention and memory and may indicate a potential mechanism for other NHP cognitive findings, such as deficits in cognitive flexibility (Vlasova et al., 2021). However, there are several methodological aspects that may be important influences on VPC performance, including stimulus type (abstract vs. social images), data collection methods (involuntary attention at 1 month vs. voluntary attention at 3–4 months), and stimuli order or location. This suggests that the lack of predictability from our early one-month time point to the later 3-to-4-month time point may be due to differences in stimulus preference or methodology across assessments rather than reflecting developmental differences. More studies are warranted, however, to tease apart the relationship between stimuli preference, methodological differences in protocol, and biological differences in attention across development in infant NHPs.

In addition to the effect of experimental treatment, we found that discrimination difficulty between images influenced performance on the VPC task, where all subjects attended to novel stimuli significantly longer on easy problems where images had greater dissonance compared to harder problems where images shared similar features. Differences in performance based on task difficulty have been assessed using different cognitive paradigms and often result in altered performance on difficult tasks (Ahissar and Hochstein, 1997; Fragaszy, 1981; Washburn and Putney, 2001). However, the effect of problem difficulty on performance appeared to be modulated by experimental treatment. Specifically, MIA subjects attended to novel stimuli significantly longer during easy problems compared to project controls. However, when MIA subjects were compared to both CON and colony controls (IMR), we found that this interaction between treatment and problem difficulty became non-significant. This may suggest that the high level of variation in the IMR data may influence the model's ability to detect differences compared to the current study with a smaller sample size ($N_{IMR} = 184$, $N_{MIA} = 13$, $N_{CON} = 14$). Although we had limited power to detect interaction effects, stratified analyses revealed that task difficulty may

play a role. This dependence on task difficulty for the treatment effect is a novel finding that has not yet explored in the NHP MIA model. These results suggest that task difficulty, based on visual similarity, is an important consideration when detecting relevant differences in attention or cognition between MIA and control subjects. Finally, despite showing consistent results regarding effects of treatment on attention, we did not find that early measures of attention collected at the one-month time point predicted later measures at the 3-to-4-month time point. However, we did find subtle indications that the relationship between early measures on the VPC task and later measures may depend upon treatment group, which warrants further investigation and larger sample sizes to detect such potential effects in studies on attention in MIA subjects. The inability to detect significant differences across early development may be due to the type of stimuli (abstract vs. social) used in the two VPC assessments. We know that social interest can change across development as evidenced by greater attention to social images compared to nonsocial images, and reduced latency to orient to social stimuli as individuals age (Maylott et al., 2020).

Although we are at the earliest stages of exploring underlying neurobiological mechanisms in the NHP MIA model, our *in vivo* neuroimaging studies in these same animals revealed reductions in the frontal and prefrontal cortex (Vlasova et al., 2021), aberrant dopaminergic signaling (Smucny et al., 2023), evidence of neuroinflammation (Lesh et al., 2023) and altered brain metabolites (Maddock et al., 2024) that may contribute to alterations in attention, motivation, learning, and memory. These neuroimaging results suggest that neural mechanisms essential to disengage, shift and engage visual attention are compromised in the MIA exposed offspring (Lee et al., 2018; Noudoost and Moore, 2011; Petersen and Posner, 2012; Yamaguchi et al., 2017). In addition to the neurobiological changes associated with MIA exposure, these effects may be modulated by task difficulty (Boudreau et al., 2006), as evidenced by our results which show that VPC performance depends on both exposure to MIA and stimulus similarity. Future studies are underway to explore underlying cellular and molecular changes, providing additional mechanistic insight into the behavioral phenotype.

Our results indicate altered patterns of imitation and heightened responses to novelty on the VPC task across early development in NHPs. Although these findings provide an important translational bridge between rodent MIA models and patient populations, there are unique limitations associated with NHP models. One major limitation of this study is that we lack longitudinal data on attentional abilities in this cohort of macaques beyond the early developmental period. However, due to logistical constraints associated with conducting pre-clinical studies with NHPs we restricted these assessments to early development where we expected divergences in groups to emerge. We encourage future studies to expand on these early findings and test the longevity of these results into adolescence and adulthood in macaques. Another major limitation of this study is that these results were only tested in males and do not consider how MIA exposure may influence female responses. Considering that many neurodevelopmental disorders of interest to the MIA model show sex differences in the emergence of disorders (ASD) or onset of symptoms (SZ), it is crucial to assess how MIA exposure influences later behavior and physiology in both sexes (Coiro and Pollak, 2019). In a recent review on the effects of MIA on learning and memory, it was found that a majority of studies reported sex differences, with only males showing cognitive deficits or showing relatively greater deficits than females (Sal-Sarria et al., 2024). Additionally, differences in imitation abilities for ASD patients may be more pronounced in men, due to women being able to "camouflage" autistic traits by imitating neurotypical behaviors (Allely, 2019). Thus, while our results are relevant for extrapolation to other male MIA offspring, it is unclear whether these effects would be transferrable to female offspring. However, considering results from previous studies on learning and memory, MIA effects in female offspring attention may be similar to, or an attenuated version of, what we observed in males in the present study. Sex as a biological variable is a focus of our ongoing NHP MIA model and will be addressed in future publications.

In conclusion, the alterations in early attentional capabilities exhibited by the MIA-exposed offspring align with changes in attention, sensory processing capabilities, impulsiveness, social behavior, and communication observed across many neurodevelopmental disorders (Grzadzinski et al., 2011; Hattori et al., 2006). Indeed, differences in early social attention are a hallmark feature of ASD that may impact social development trajectories (Braithwaite et al., 2020; Falck-Ytter et al., 2023; Mundy and Bullen, 2022). Several studies have reported impairments of attention disengagement in autistic individuals that parallel our findings (Bryson et al., 2018; Landry and Bryson, 2004). Studies focused on attentional differences are important because they may be critical for understanding subsequent downstream changes in the MIA model such as alterations to social behavior and communication since these conspecific interactions are likely driven, at least in part, by the attention of the participants interacting. If MIA subjects show deficits to, or abnormal increases in, attention this could influence whether they are attending too much or too little to their conspecific partners, resulting in deviations from species-typical social behavior and communication patterns. Understanding early markers of attention in the MIA model may help better understand risk and resilience to prenatal immune challenge (Meyer, 2019) and provide screening tools for early indicators of emerging neurodevelopmental disorders, allowing health care providers crucial interventions for at-risk human infants early in development when interventions are more effective.

CRediT authorship contribution statement

J.A. Hubbard: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **S. Chen:** Writing – original draft, Formal analysis, Data curation. **A.M. Iosif:** Writing – original draft, Formal analysis, Data curation. **A.M. Ryan:** Writing – review & editing, Data curation. **T. Murai:** Writing – review & editing, Data curation. **C.E. Hogrefe:** Writing – review & editing, Data curation. **T.A. Lesh:** Writing – review & editing, Funding acquisition, Conceptualization. **J. Smucny:** Writing – review & editing, Funding acquisition, Conceptualization. **R.J. Maddock:** Writing – review & editing, Funding acquisition, Conceptualization. **C.M. Schumann:** Writing – review & editing, Funding acquisition, Conceptualization. **T.D. Hanks:** Writing – review & editing, Funding acquisition, Conceptualization. **J. Van de Water:** Writing – review & editing, Funding acquisition, Conceptualization. **A.K. McAllister:** Writing – review & editing, Funding acquisition. **C.S. Carter:** Writing – review & editing, Funding acquisition, Conceptualization. **A. Paukner:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **J.P. Capitanio:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **M.D. Bauman:** Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Data statement

Data from the experiments outlined in this manuscript are available from the author upon request.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101075.

Data availability

Data will be made available on request.

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