



Early developmental changes in visual social engagement in infant rhesus monkeys

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ABSTRACT

Impairments in social interaction in Autism Spectrum Disorder (ASD) differ greatly across individuals and vary throughout an individual's lifetime. Yet, an important marker of ASD in infancy is deviations in social-visual engagement, such as the reliably detectable early deviations in attention to the eyes or to biological movement (Klin et al., 2015). Given the critical nature of these early developmental periods, understanding its neurobehavioral underpinnings by means of a nonhuman primate model will be instrumental to understanding the pathophysiology of ASD. Like humans, rhesus macaques 1) develop in rich and complex social behaviors, 2) progressively develop social skills throughout infancy, and 3) have high similarities with humans in brain anatomy and cognitive functions (Machado and Bachevalier, 2003). In this study, male infant rhesus macaques living with their mothers in complex social groups were eye-tracked longitudinally from birth to 6 months while viewing full-faced videos of unfamiliar rhesus monkeys differing in age and sex. The results indicated a critical period for the refinement of social skills around 4–8 weeks of age in rhesus macaques. Specifically, infant monkeys' fixation to the eyes shows an inflection in developmental trajectory, increasing from birth to 8 weeks, decreasing slowly to a trough between 14–18 weeks, before increasing again. These results parallel the developmental trajectory of social visual engagement published in human infants (Jones & Klin, 2013) and suggest the presence of a switch in the critical networks supporting these early developing social skills that is highly conserved between rhesus macaque and human infant development.

1. Introduction

Social-visual attention, defined as directing visual attention to socially relevant information, such as looking at other people's faces, in particular the eyes, and attention to gestures, body posture, or action, is a fundamental ability of all primate species and considered to be the basis for social cognition (Baron-Cohen et al., 1997; Emery, 2000). As a visually orienting ability in socially gregarious species, social-visual attention is considered a primary selective pressure in the evolution of the primate brain (Chance and Jolly, 1970; Dunbar and Shultz, 2007). On a very fundamental level, social-visual attention is critical for understanding and interpreting social contingencies and intention of others, and allows for the flexible modification of behavior based on that information. As an example, rhesus macaques evaluate information regarding dominance through the observation of social interactions and

then adjust their own aggressive and affiliative behavior accordingly (Deaner et al., 2005), which is essential for survival. In humans, social information includes a variety of nonverbal cues, such as eye contact or gestures that are often significant to establish joint attention in children and adults and to navigate in large and complex society (Emery, 2000). Using the gaze of another to alter one's own landscape of saliency is a basic tenet for understanding more complex social contingencies that may emerge later in ontogeny or phylogeny, such as theory of mind (Baron-Cohen, 1992). In studies with human adults, social-visual attention is known to engage extensive brain areas of the human social and attentional networks, including the amygdala, lateral intraparietal cortex, medial prefrontal cortex, and superior temporal sulcus (Sato et al., 2011; Kampe et al., 2001; Wang et al., 2011; Akiyama et al., 2007; Okada et al., 2008). Electrophysiology, inactivation, and fMRI studies in adult rhesus macaques have also implicated the amygdala,

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superior temporal sulcus, and lateral intraparietal cortex when monkeys monitor the gaze of another individuals demonstrating a conservation in the neural substrates of social-visual attention (Mosher et al., 2011; Kamphuis et al., 2009; Roy et al., 2014). Unfortunately, the developmental trajectory of neural basis of social-visual engagement in infancy remains unexplored. Due to the difficulty of acquiring frequent neuroimaging data in human infants over a short period of time, we must rely on the use of animal models to better characterize the development of social-visual engagement and its neural underpinning. Such information may be invaluable to better understand the neural origins of developmental disorders associated with profound inability to develop normal social skills, such as ASD.

Rhesus macaques are an ideal model for studying the development of early social-visual behavior given (1) the rich and complex social structure in which they develop and navigate, (2) the similarity in the development of brain structures and cognitive functions compared to humans, and (3) in both species, the visual system is the primary method by which individuals navigate the world (Machado and Bachevalier, 2003). Kuwahata et al. (2004) found that infant monkeys reliably preferred face-like schematic configurations over any other pattern by 1 month of age. Similarly, Lutz et al. (1998) determined that a preference for face-like drawings over distorted pen drawings of rhesus macaque faces emerged at 6 weeks of age. Although this preference seems to develop after birth, there is evidence to suggest an innate mechanism for face detection and preference. Specifically, it has been noted that infant monkeys that are reared without exposure to any faces for 6–24 months will quickly develop a facial preference to the first face or face-like stimuli they regularly witness (Sugita, 2008). Face scanning behavior continues to develop in the first 3 months of life. Parr et al. (2016) showed an initial strong preference for conspecific over heterospecific faces at birth, whereas attention to heterospecific faces significantly increase at around 5 weeks of age. Another study conducted with the same animals also indicated that infant monkeys develop a preference for direct gaze that emerges in the first 3 months, and that viewing patterns towards direct faces versus indirect faces showed different developmental timelines. That is, infant monkeys' fixations to the eyes were first equivalent in duration for both gaze types in the first 2 months, but thereafter remained longer for the averted gaze faces than the direct faces (Muschinski et al., 2016).

In adulthood, gaze is crucial for survival within large social groups and is used to recruit allies or assert dominance (Maestriperi and Wallen, 1997; Emory, 2000). Currently, there are few studies that have explored the behavioral development of eye-looking in infancy for rhesus macaques, and those that had revealed significant limitations. Some studies used still drawing representations of faces (Lutz et al., 1998) rather than dynamic conspecific videos, which can contain more nuanced social signals to elicit looking behavior. Others were limited by poor temporal resolution, such that only 3 time points were studied in the first year (Mendelson et al., 1982), which may not accurately capture development during a time with rapid brain development. Given the importance of interpreting gaze in both humans and nonhuman primates and the progressive development of social skills required for normal social interactions, eye-looking represents an important foundation of social cognition. Here, we precisely characterized the progressive development of social visual attention in infant rhesus macaques that viewed videos of other unfamiliar monkeys across the first 6 months of life. The study was carefully designed to resolve several limitations of previous developmental studies in monkeys. First, a large sample size of 36 infant monkeys living with their mothers in large social groups served as subjects. Given the reported effects of different social rearing environments on the development of face-processing behaviors (Simpson et al., 2019a,b,c), the use of mother-reared infants in large social environments provides the closest approximation to natural development of social-visual attention. Second, fine grain developmental measures of social-visual attention were taken at 14 time points between postnatal Week 2 to Week 24 (6 months). Third, social-visual

attention to faces was measured with a paradigm that was originally intended to mimic an eye-tracking procedure used to trace the development of social-visual attention in human infants (Jones and Klin, 2013). The similarities in procedural design were intended to assess whether social-visual attention is a phylogenetically conserved mechanisms across primate species and to develop a rhesus macaque model that will allow us to investigate the neural bases of social-visual attention in primates.

2. Methods

2.1. Subjects

Two cohorts of infant rhesus monkeys were tested during the 2015 and 2016 birthing seasons. A total of 36 newborn male monkeys (*Macaca mulatta*), all living with their mothers in large, socially complex groups at Yerkes National Primate Research Center (YNPRC) Field Station (Lawrenceville, GA) at Emory were assigned to the study. Both mother and infant lived in large social groups containing over 100 individuals to preserve critical social aspects of natural rhesus monkey groups while allowing experimental control typical of less complex social conditions (Berard, 1989; Lovejoy and Wallen, 1988; Wallen, 2005). All infant-mother pairs remained socially housed within their original social groups for the duration of the study and infants were estimated full-term (>450 g) offspring of mid-ranking multiparous mothers. Rank was established through observations of antagonistic and agonistic behaviors that are well-established within each social compound (Bernstein, 1976), and we limited the study to mid-ranking families in order to limit the effects of rank on early life social experience. Although the goal of the study was to begin testing as soon after birth as possible, to assure that bonding between mothers and infants was not impacted by the procedures, each mother-infant pair had at least 3 days after birth prior to the first testing session. Infants were always tested with their mothers and both were immediately returned to their habitats after testing to continue bonding and interacting of members of their group. Infants did not participate in the study if (1) health complications necessitated regular veterinary care and removal from their social group, (2) required to be separated from their mother that did not begin naturally lactating, or (3) were rejected by their mother shortly after birth and did not receive proper maternal care. The greatest drop-off in subjects ($N = 9$) occurred in the first month of life, and a total of 23 out of 36 infants were tested at all time points of the study. For a summary of testing age distribution and averaged number of videos viewed at each age, see Table 1.

All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Emory University and followed the American Psychological Association standards for the ethical treatment of animals.

2.2. Eye-tracking procedures

Animals were tested at weeks 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 with previously established procedures that allow direct access to animals from their social groups for short periods of time (Herman et al., 2000; Maestriperi et al., 2006; McCormack et al., 2009). The mother-infant pairs were transferred to an onsite behavioral testing facility where the mother was first anesthetized (3–5 mg/kg⁻¹ telazol, i. m.). The pair was then carried to a dedicated testing chamber containing a reclining seat on which the mother could rest comfortably on her back while the infant was placed on her front, ventrum-ventrum. Attached to one wall of the testing chamber was a 19" (62.6 cm, 45.27° diagonal) computer monitor (1024 × 768 pixels) onto which experimental stimuli were presented. Underneath the monitor was an infrared eye-tracking camera (<http://www.iscan.com/60Hz>) mounted on a motorized gimbal, which allowed an experimenter to track the location of the infant's eye. The infant lay with his mother through the duration of the testing procedure, seated approximately 25" from the screen. Infants

Table 1

A summary of the amount of data collected from infants at each testing session. There was week-to-week variation in the monkeys that successfully calibrated and the number of clips that were used for analyses. Percentage of clips viewed with usable data remained high throughout the 14 testing sessions.

Session	Monkeys Tested	Monkeys Calibrated (% success)	Avg Age at Testing (weeks \pm s.d.)	Avg movies viewed	Percentage of Movies Analyzed (Movies Analyzed/Movies Collected)
1	36	8 (22 %)	0.82 \pm 0.15	5.34 \pm 2.45	76 % (32/42)
2	35	19 (54 %)	1.62 \pm 0.18	4.47 \pm 3.13	64 % (54/85)
3	33	15 (45 %)	2.69 \pm 0.22	7.80 \pm 2.73	76 % (84/110)
4	30	21 (70 %)	3.56 \pm 0.20	5.26 \pm 3.45	70 % (75/112)
5	27	20 (74 %)	4.61 \pm 0.23	5.70 \pm 3.34	74 % (86/117)
6	26	16 (62 %)	6.52 \pm 0.26	5.38 \pm 0.89	64 % (54/86)
7	24	18 (75 %)	8.64 \pm 0.21	5.78 \pm 3.14	90 % (93/103)
8	24	12 (50 %)	10.68 \pm 0.29	8.08 \pm 1.44	84 % (81/97)
9	23	14 (60 %)	12.76 \pm 0.28	7.21 \pm 3.77	91 % (92/101)
10	23	11 (48 %)	14.70 \pm 0.32	6.18 \pm 1.54	73 % (54/74)
11	23	9 (39 %)	16.63 \pm 0.33	4.00 \pm 1.32	86 % (31/36)
12	23	8 (35 %)	18.61 \pm 0.27	10.13 \pm 2.29	98 % (79/81)
13	23	12 (52 %)	20.61 \pm 0.26	5.75 \pm 3.74	86 % (59/69)
14	23	15 (65 %)	22.67 \pm 0.32	4.73 \pm 3.39	92 % (65/71)

acclimated to the darkened chamber quickly, attending to the screen following approximately 2–3 min after introduction. Following a 5-point calibration procedure, infants continued to watch videos of social rhesus macaques while freely nursing and maintaining contact with the mother (see details in Parr et al., 2016; Muschinski et al., 2016). In between video clips, a centering stimulus was presented during the intertrial interval and any changes in calibration accuracy would be easily detected in real time. If any changes in calibration accuracy occurred due to movement shifts in infant or mother position, the 5 calibration points were repeated to ensure reliable and accurate calibration throughout the testing session.

Testing sessions were restricted to 30 min to limit the mother's time under anesthesia. If all 5 calibration points was unsuccessful prior to 25 min, the session was rescheduled for a later time for a maximum of two session attempts per infant per timepoint. Yet, there was some individual variability in infant behaviors at each time point. That is, at the younger ages, infants had a tendency to fall asleep and had to be awoken to complete the sessions, whereas at the older ages, the infants became more active during the session and less attentive to the movies". Despite this individual variability on a session-by-session basis, infants typically completed calibration within 5 min of being introduced to the box and would complete viewing the session's respective playlists within 20 min after calibration. Stringent calibration procedures and standards ensured that, although not all infants were successfully calibrated at each time point and each video clips, the data collected following successful calibration provided high-quality and reliable eye-tracking data, as indicated by relatively high percentage of movies analyzed per session for the animals successfully calibrated (see Table 1). After testing, the mother-infant pair was placed in holding cage in an adjacent room to allow for recovery of the mother from anesthesia. When the mother was

fully alert, the pair was returned to their social group. Infants remained unconstrained and were free to move around, though infant was placed back onto the mother's ventrum when beginning to leave the mother and explore the box enclosure.

2.3. Stimuli

High quality digital videos depicting unfamiliar conspecifics filmed on the rhesus monkey breeding colony maintained by the Caribbean Primate Research Center (CPRC) in Cayo Santiago, Puerto Rico were used. The videos were cropped to 10 s in length and played with accompanying background sound and presented in 32-bit color. Close-up videos of both female and male monkeys from a range of ages were shown (see Fig. 1a). Videos showed scenes of a single monkey, with approximately equal representation of female and male, and juvenile and adult monkeys. For juvenile monkeys, animal's full body covered approximately 40 % of the screen video surface. For adult monkeys only animal's torso, arms, and head were visible and covered approximately 50 % of the screen video surface. Videos were selected to present neutral emotional facial expressions with no conspecific vocalizations to avoid emotional reactions from the infant and maintain a stable recording of

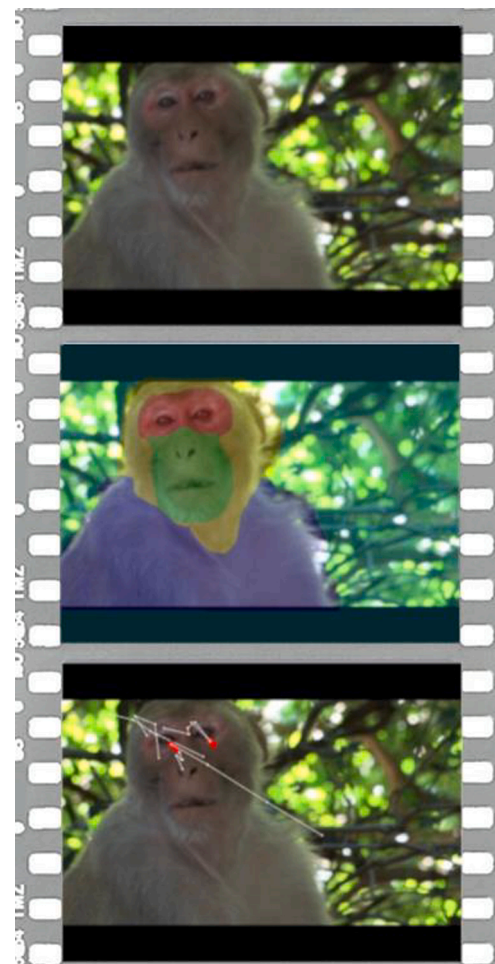


Fig. 1. (A) A sample of successive still frames from a movie showing a single adult macaque. (B) Manually outlined ROI superimposed on each still frame and showing the ROI borders of eye (red), mouth (green), head (yellow), and body (blue) regions. (C) Example of a scanpath for one monkey's viewing this video at 7 weeks – fixations are represented in red points and saccades are shown as white lines. The scanpath represents the viewing of the monkey of approximately 1 s before and after the example still image (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

the infant eyes; a total of 38 unique videos were created in this process. In between each video, a 2 s inter-trial interval with a centering stimulus (circular, chiming target on an otherwise blank screen) was presented to maintain infant's attention. For each testing session, a pseudorandom combination of repeated and novel videos was presented with an approximate 4:1 ratio, totaling 12 videos per session. If the infant was not attending to the screen during a video, it would be marked and repeated at the end when all videos had been presented (for a summary of averaged number of videos viewed at each session, see Table 1). A subset of stimuli (7 out of 38) were inverted to serve as comparison controls for changes in low-level perceptual effects and in perception, as inverted faces have been established to have different behavioral and neural responses when compared to upright faces in both humans and monkeys (Parr et al., 1999; Yin, 1969; Yovel and Kanwisher, 2005).

2.4. Data analysis

Analysis of eye movements and coding of fixation data were performed with software written in MATLAB (MathWorks). The first phase of analysis was an automated identification of non-fixation data, comprising blinks, saccades and fixations directed away from the presented screen. Saccades were identified by eye velocity using threshold of $30^\circ/\text{s}$. Eye movements identified as fixations were coded into four regions of interest that were defined within each frame of all video stimuli: eyes, mouth, head, and body (see Fig. 1B). The regions of interest were hand traced for all frames of the video and were stored as binary bitmaps (through software written in MATLAB, see Fig. 1B). Automated coding of fixation time to each region of interest then consisted of a numerical comparison of each infant's coordinate fixation data with the bitmapped regions of interest (Jones and Klin, 2013). Fixation time was cutoff at a minimum of 20 % of total trial duration. A fixation percentage for each region of interest was calculated by comparing the fixations for the particular region to the total number of recorded fixations for the entire clip. An example of scan paths is illustrated on Fig. 1C.

Statistical analyses were performed with R software, version 3.5.0 (R Core Team, 2018). Clips that had no fixations recorded were excluded. Locally weighted polynomial regression were conducted using a LOESS model (Cleveland, 1979; Cleveland and Devlin, 1988) to evaluate the relationship between age and fixation percentage to each region of interest. The benefit of a LOESS model is to allow for an evaluation of trajectories without making any assumptions on the underlying shape of the data. These LOESS models were used to examine the order of polynomial shape that could best describe the developmental trajectories of each region of interest. To further analyze the trajectory, several polynomial regressions of varying degrees determined from the LOESS model were then overlaid and goodness-of-fit (GOF) was evaluated with residual standard error, the polynomial regression that produced the best GOF was used as the developmental trajectory. Because some subjects could not be calibrated at each time point, there were missing data across the time points. To mitigate this limitation, we used within-subject polynomial models, such that general shape was first generated separately for each individual subject, then a model was produced to fit the entire population. To determine that any polynomial regression was different from chance, a model based moving block bootstrap was conducted (Politis and Romano, 1994), repeated 5000 times using 6 blocks per run, and a pseudorandomized length per block. A polynomial model regression of the previously determined degree (i. e., degree = 3 for eyes) was generated and from the regression was returned from each run. A histogram of these p-values was created and showed a relatively flat distribution with a tail at $p < 0.05$ (see Fig. 2). Therefore, we are confident that our regressions resulted in $p < 0.01$.

Because there were significantly fewer inverted videos shown during testing (only 2 clips per session), the inverted videos were binned into three 2-month periods to increase the power of data analyses. A within-subject ANOVA was performed between age group and clip type to

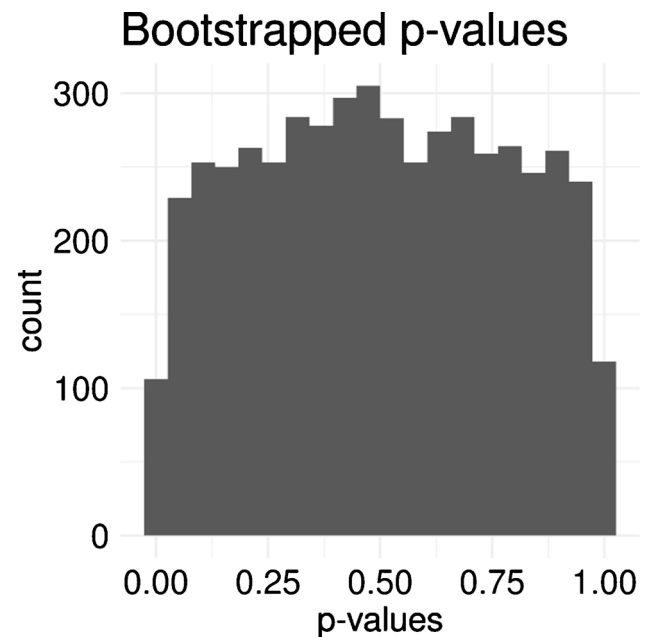


Fig. 2. An example histogram depicting the resulting p-values generated from a moving block bootstrapping of the data. In this example, the fixation percentage to the eye region was bootstrapped, and in each run a polynomial of degree 3 was fit on top of the data and p-value was generated. This was done 5000 times and resulting counts are shown on the y-axis.

determine any differences between viewing upright and inverted faces.

3. Results

Overall, of the time spent looking at the videos at each testing session, infant monkeys fixated on the eyes 25 %–50 % of the time, made saccades 29 %–35 % of the time and blinked 0.7 %–3.5 % of the time (See Supplemental Table 1). The fixation rate across the 14 sessions in the infant monkeys is in fact similar to the fixation rate reported in normally developing human infants from 2 to 6 months of age (35%–50%; Jones and Klin, 2013, see Fig. 3), though the human infants showed a slight but steady increase in eye fixations from 2 to 6 months but infant monkeys did not.

A LOESS model between percentage of fixation to the eye-region and the monkey's age in weeks was first conducted to estimate the shape of the data trajectory. From the regression, several degrees of polynomial regressions were fit, the third-degree polynomial provided the strongest GOF out of all models tested [$t(691) = 0.18$, $F(3, 691) = 4.203$, $p = 0.006$]. As shown in Fig. 3a, the developmental trajectory for attention to the eye-region shows an increase from 2 weeks until approximately 6 weeks. The attention then decreases to reach a trough at about 15 weeks when it begins to shift again and rise until 22 weeks. Additionally, analyses were performed on each annual cohort separately (2015, $n = 12$, and 2016, $n = 24$) and showed no differences between cohorts ($p = 0.74$), indicating a high degree of overlap in their trajectories and providing proof of internal reliability and reproducibility (see Fig. 4). Finally, analysis of the eye-region between inverted and upright faces showed significantly less attention to the eyes viewing inverted than upright faces ($F(1, 1146) = 4.854$, $p = 0.028$), confirming that the differences in viewing patterns at the different ages are due specifically to changes in face processing and not to lower level perceptual features.

In contrast to the eye region, the trajectory of fixation percentage to both the mouth and body regions started with the highest points in the first few weeks and gradually decreased over time. The LOESS models more closely resembled a second-degree polynomial, and fitting several polynomial regressions of varying degrees showed a second-degree

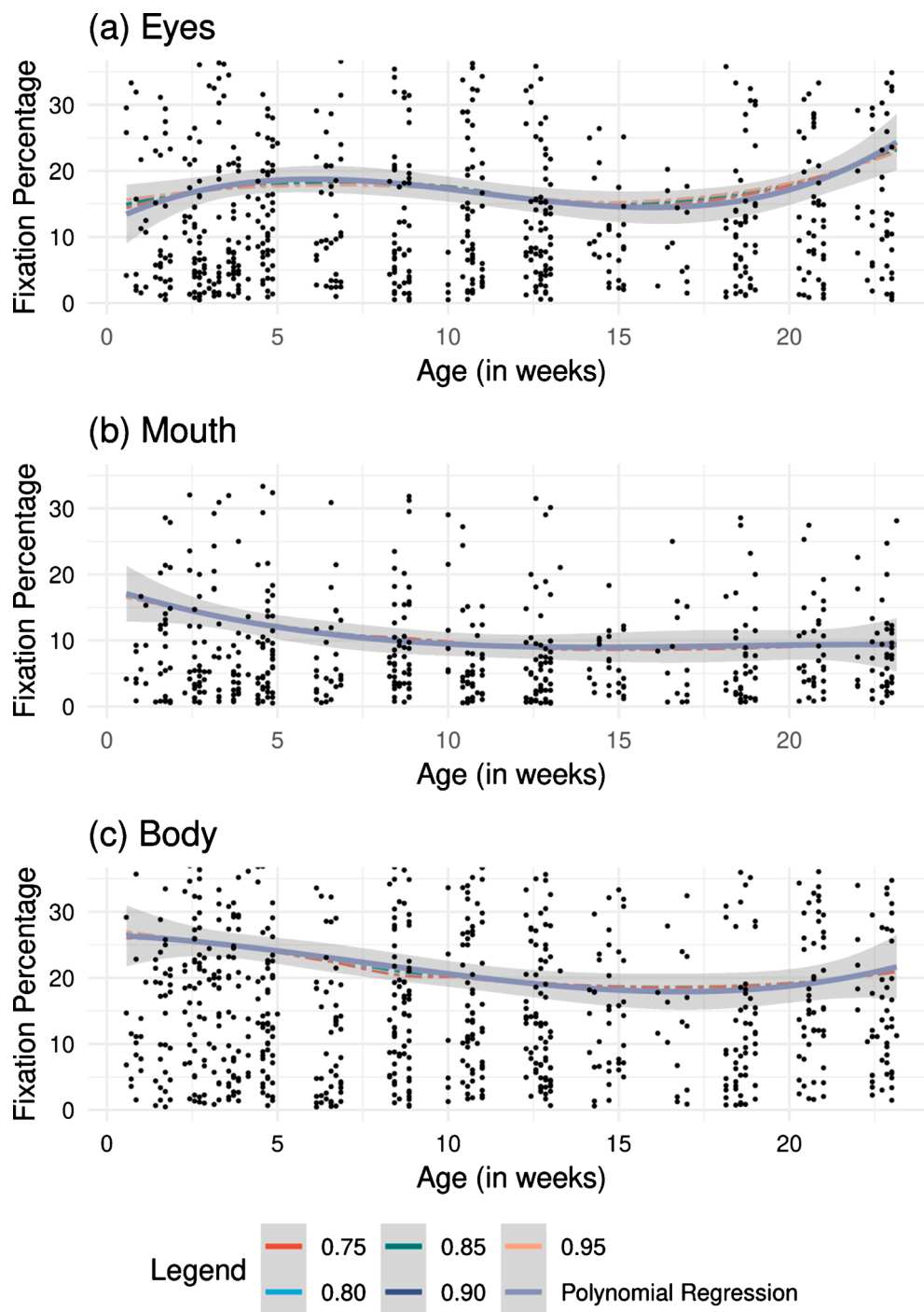


Fig. 3. The fixation percentage to the three regions of interest: (a) eyes, (b) mouth, and (c) body. The colored dashed lines on each graph represents the LOESS models of varying degrees of α (as indicated in legend) from 0.75 to 0.95. Imposed on top of the LOESS models is a polynomial regression, the shaded gray region surrounding the regression represents the 95 % confidence interval for the model.

polynomial provided the strongest GOF for both mouth and body regions. For the mouth region (see Fig. 3b), the polynomial provided a strong GOF [$t(530) = 0.03$, $F(2, 530) = 7.318$, $p = 0.0007$], with an inflection point of around 15 weeks when attention to the mouth region begins to increase slightly. Additionally, analysis of inverted clips showed significantly increased viewing to the mouths of inverted faces ($F(1,1144) = 16.079$, $p < 0.0001$).

The body region polynomial fit also provided a strong GOF [$t(842) = 0.02$, $F(2, 842) = 8.897$, $p = 0.0003$], with an inflection point of close to 17 weeks when attention begins to increase slightly again (Fig. 3c). The difference in trajectory between the eyes compared to the mouth and

body regions suggests that the third-degree polynomial is unique to the eye-region and not an overall shift in attentional patterns. For a summary of polynomial fitting for each region, see Table 2.

4. Discussion

This study assessed the developmental trajectory of visual attention to social stimuli in monkeys during the first 24 weeks of life using eye-tracking procedures and stimuli similar to those previously reported in human infants. The study obtained densely-sampled longitudinal eye-tracking data – infants were alert and attentive to experimental

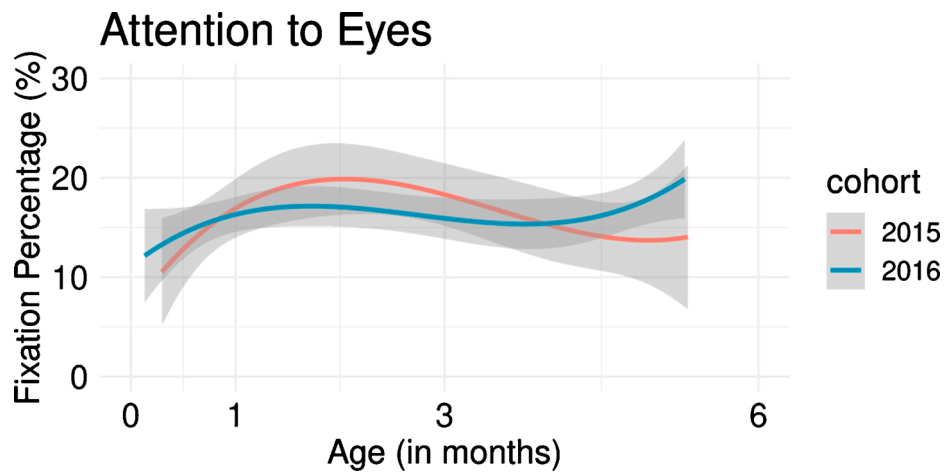


Fig. 4. Fixation percentage to the eye region separated between the two cohorts of infants tested over two separate years (2015, 2016). Shaded gray regions surrounding the regression lines represents the 95 % confidence interval for the each year model. The darker gray areas represent the overlap between the two cohorts.

Table 2

A summary of the amount of polynomial fitting used to describe the attention the Eyes, Mouth, and Body. Initial models were estimated using a LOESS model to determine the shape of the polynomial regression. The goodness-of-fit (GOF) was evaluated for the polynomial regression: in each case the degree of polynomial chosen yielded the highest F-statistic and adjusted R^2 values, with both the polynomial of one greater and one less degree having yielding a loss in GOF.

	Adjusted R2	F-statistic (df)	P value
Eyes			
1st degree	5.36e-05	1.037 (1, 636)	0.3088
2nd degree	0.002249	1.782 (2, 692)	0.1691
3rd degree	0.01366	4.203 (3, 691)	0.005838
4th degree	0.01231	3.162 (4, 690)	0.01368
Mouth			
1st degree	0.01612	9.717 (1, 531)	0.001925
2nd degree	0.0232	7.318 (2, 530)	0.0007327
3rd degree	0.02208	5.004 (3, 529)	0.001981
Body			
1st degree	0.01409	13.06 (1, 843)	0.0003193
2nd degree	0.01837	8.897 (2, 842)	0.001501
3rd degree	0.01813	6.196 (3, 841)	0.0003642

stimuli as evidenced by a high percentage of trials yielding usable data (see Table 1), and there was limited loss of data due to blinks or inattention, as a high percentage of data were usable fixation and saccade data. Additionally, our study leveraged the use of laboratory testing procedures in an environment that allowed for mother-reared infants to be raised in semi-naturalistic studies. The importance of maintaining these naturalistic aspects of infant social development is vital given the significant effects of different rearing conditions on the development of face processing in infancy (Simpson et al., 2019a,b,c). The results indicate 1) important and specific shifts in attentional looking patterns to the eyes, mouth and body; 2) strong preference for the eyes in upright versus inverted faces in the first 8–12 weeks of age; and 3) these patterns of visual attention were similar to those reported in human infants for the eyes but not for the mouth. These results will be discussed in turn.

4.1. Attention to the eyes

The findings indicated a sharp increase in attention to the eyes that reached a peak around 5–6 weeks of age, followed by a decline that reached a trough around 16 weeks before a continuous rise thereafter until the last age point assessed (i.e. 24 weeks). This developmental trajectory is in line with prior research indicating that infant macaques become sensitive to the direction of other faces at around 3–4 weeks,

suggesting a time period when more elaborate forms of face processing begin to come online during the first few weeks of life (Mendelson et al., 1982). By 5–6 weeks, the infants are actually showing an increased preference for direct-gaze faces over averted-gaze faces (Muschinski et al., 2016). Additionally, this time period coincides with a shift from strong preferential orientation to conspecifics' faces to heterospecifics' faces (Parr et al., 2016). Field studies in rhesus macaques have also shown that reciprocal face-face interactions between the infant and mother begin to dramatically increase and peak at close to 1 month (Ferrari et al., 2009), overlapping with our first inflection point in attention to the eyes. Thus, the development of critical mother-infant bonds that are being formed from birth to 5–6 weeks of age may also be based on the ability to focus attention to the eye-region of conspecifics and be dependent upon the prior maturation of more elaborate perceptual processing of face areas (see further discussion below). One possible explanation to the increases in attention to the eyes could also be related to perceptual development, as visual acuity significantly increased in the first weeks in infant monkeys and does not reach adult-like levels until 6 weeks (Boothe et al., 1980). However, this explanation seems unlikely given that, despite weaker visual acuity than adults, infant visual abilities are proficient enough as they can clearly discriminate between conspecific and heterospecific faces at birth (Parr et al., 2016). Additionally, a study of 3-week old monkeys with limited face experience suggests a robust face detection system early on (Simpson et al., 2013). Another comparative study between nursery-reared and mother-reared infant rhesus macaques have demonstrated the importance of early social experiences in age-related increases in attention during the first 13 weeks (Simpson et al., 2019a,b,c), further suggesting that the early developmental shifts in attention to the eyes we observed in our study are due to the early development of social-affective systems, supported by early social experience.

Following this peak, attention to the eyes progressively declines to reach a trough around 15–16 weeks. This decrease parallels a similar decrease in mother-infant mutual gaze as well as in face-direction preference observed by others (Muschinski et al., 2016). It also appears to follow the emergence of fear modulation with regard to different contexts during the same period (Kalin et al., 1991). Given that direct eye-contact can be an emotionally aversive stimuli for rhesus macaques, this reduction in attention to the eye-region may be due to the development and maturation of emotional-affective processes during infancy. Yet, our findings contrast with the earlier decrease in attention to eye-gaze observed in infants living in semi-natural settings (Ferrari et al., 2009) as well as in mother-infant mutual gaze (Dettmer et al., 2016). These differences could be accounted for by our selection of

emotionally neutral faces that may have been lacking important emotional cues to trigger gaze avoidance and resulted in a protracted emergence of an emotional-affective driven avoidance of direct eye contact. Indeed, if we hypothesize that early avoidance of direct eye contact is mediated by the development of emotional-affective systems, then we will predict that the use of stimuli depicting lip-smacking, fear grimace, or other emotionally salient facial expressions as those seen in real-time dyadic interactions between mother-infant may elicit earlier gaze aversion to emotionally and socially salient facial features that were absent in our stimuli.

From 16–24 weeks, attention to the eyes begin to increase again. Infants may begin to re-establish attention to the eye region as aversion to direct eye-contact subsides and the maturation of emotional regulation and attention to faces becomes more volitional than reflexive in nature. Specifically, the second increase to the eye region may reflect a shift from a reflexive avoidance towards direct eye-contact towards an increase in attention to averted gaze. The attention towards eyes modulated by head direction/orientation during averted gaze suggest that the second increase eye gaze is important for the support of gaze following that has been reported to emerge at around 6 months (Simpson et al., 2019a,b,c; Rosati et al., 2016).

It is also possible that changes in attention could be driven by low-level perceptual features, such as face-like configurations. Studies in both humans and monkeys have shown newborn innate attraction to face-like configurations of dots over other patterns (Goren et al., 1975; Valenza et al., 1996; Kuwahata et al., 2004). However, attention to the eye-region of inverted faces were significantly different from upright faces. Yet, since inverted faces maintain the same low-level perceptual information of the videos but disrupts face processing (Parr et al., 1999; Yin, 1969; Yovel and Kanwisher, 2005), we believe that the effects observed are specific to the social-attention to the eye region and not to low-level perceptual features or perceptual improvements over time.

4.2. Attention to the mouth and body

In comparison to attention to the eyes, attention to the mouth starts out relatively high at around 17 percent fixation to the area compared to the rest of the scene, but this attention to the mouth begins to decline to reach a trough around 15–16 weeks. The first couple of weeks in life is characterized by the emergence of reciprocal lipsmacking, a behavior that is correlated with later-life stress and emotional regulation (Kaburu et al., 2016). The early attention to the mouth region and resulting emergence of reciprocal lipsmacking may be an ethologically relevant form of social attention, but is later overshadowed by social cues of increasing valence later in life – for example, paying attention to the eyes while establishing mother-infant mutual gaze begins to overshadow reciprocal lipsmacking. The data also indicate a later inflection point at around 17 weeks when attention to the mouth appears to slightly increase again. This increase coincides with a time in development associated with a peak in fear-grimace display and willingness to leave the mother to explore (Suomi, 1984; Hinde and Spencer-Booth, 1967). The mouth of other rhesus macaques is a socially significant area of the face and macaque lipsmacking is believed to share a homologous developmental mechanism as human speech (Morrill et al., 2012). Additionally, lipsmacking in infancy is positively correlated with later life interest in social interaction (Paukner et al., 2013), and facial expressions are important in determining and establishing social hierarchies (de Waal and Luttrell, 1985). Attention to the mouth region is likely an important factor as infant monkey begin to leave their mother and explores and interacts with others in the social group. Similar to the eye-region, attention to the mouth region could be driven by low-level perceptual effects, especially given the movement of the mouth. Again, the significant difference in attention to the mouth region with respect to the inverted faces that maintain low-level perceptual effects while disrupting face processing. Changes in perception to inverted faces is that the mouth is in the location where the eyes are expected on the

face or that when face processing is disrupted through inversion, the movement present in the mouth region becomes the most salient area of the video. Still, these differences between the perception of inverted and upright mouths provides confidence that the developmental changes described are due to changes in social-attention and not general attention or perceptual improvements over time.

Attention to the body starts with the highest fixation percentage at around 30 percent then steadily declines throughout development, though continues to be a region of high fixation after the eyes. Given the neutral emotional valence of the videos as well as the close-up view that most videos had of the focal monkey, there were very few instances of the video monkey manipulating objects with hands that may have attracted attention of the infants. Therefore, the high fixation percentage to the body region may be due to the relative size of the region in comparison to those of the eye and mouth regions – there is simply more area of the video coded as the body. It is important to note, however, that percentage fixation towards the eyes matches that of the body shortly after 20 weeks and continues to trend upwards at the end of our observed timeframe (24 weeks), further strengthening the social significance of attention to the eye region at 6 months of age.

4.3. Comparison with to attention to face cues in human infants

To obtain additional information on the phylogenetic conservation of developmental changes in social visual engagement between primate species, we also compared the changes in attention to visual cues in infant monkeys presented here with those obtained from typically developing human infants (see Fig. 5). As mentioned in the introduction, to facilitate this comparison, the infant monkeys were behaviorally tested and the data analyzed using similar procedures as those used in human infants and were observed at ages (1 week to 24 weeks) that corresponded to the 2 months to 24 months age range used with the human infants (Jones and Klin, 2013). Despite slight methodological differences between species (i.e., human infants sat in a car seat with their mother seated nearby vs macaque infants placed on the ventrum of anaesthetized mothers), the current study preserved as many aspects of the human study as possible, including the use of similar equipment and software, similar preparation of experimental stimuli, and utilizing the same MatLab code for the processing of raw eye-tracking data. Additionally, the selection of time points for testing infant monkeys were chosen to closely match those from the human study. The high degree of similarity in the technical parameters and developmental time points between the two studies allowed for more direct comparisons between nonhuman primate and human studies. Yet, the procedural differences between species need to be considered when comparing the data.

The developmental trajectory of visual attention to the eyes of rhesus macaques closely parallels that shown in typically developing human infants. Inspection of Fig. 5a and c demonstrate that monkeys have lower fixation percentage than human infants across this early developmental period. This species difference parallels previous cross-species data showing that, when exploring faces, monkeys make less fixations than humans, and spend more time in saccading or scanning (Dahl et al., 2010; Hu et al., 2013). Despite this difference, the developmental trajectory of attention to the eyes in early infancy is remarkably similar for the two species with a first rise in fixation percent towards the eyes for the first 6–8 weeks in monkeys and 6–8 months in humans, followed by a slow decline until 16 weeks for monkeys and 18 months in humans, and then a second rise until 24 weeks for monkeys and 24 months in humans. The parallels in developmental curves that are seen suggest that the attention to the eyes in early infancy is evolutionarily conserved between monkeys and humans. Such degree of similarity suggests that the eyes may provide crucial social information for face processing in both monkeys and humans in early infancy (Nakato et al., 2018).

Regarding the attention to the mouth, however, the infant rhesus macaque pattern of viewing differs from that observed in human infants (see Fig. 5b and c). Although attention to the mouth for monkeys slightly

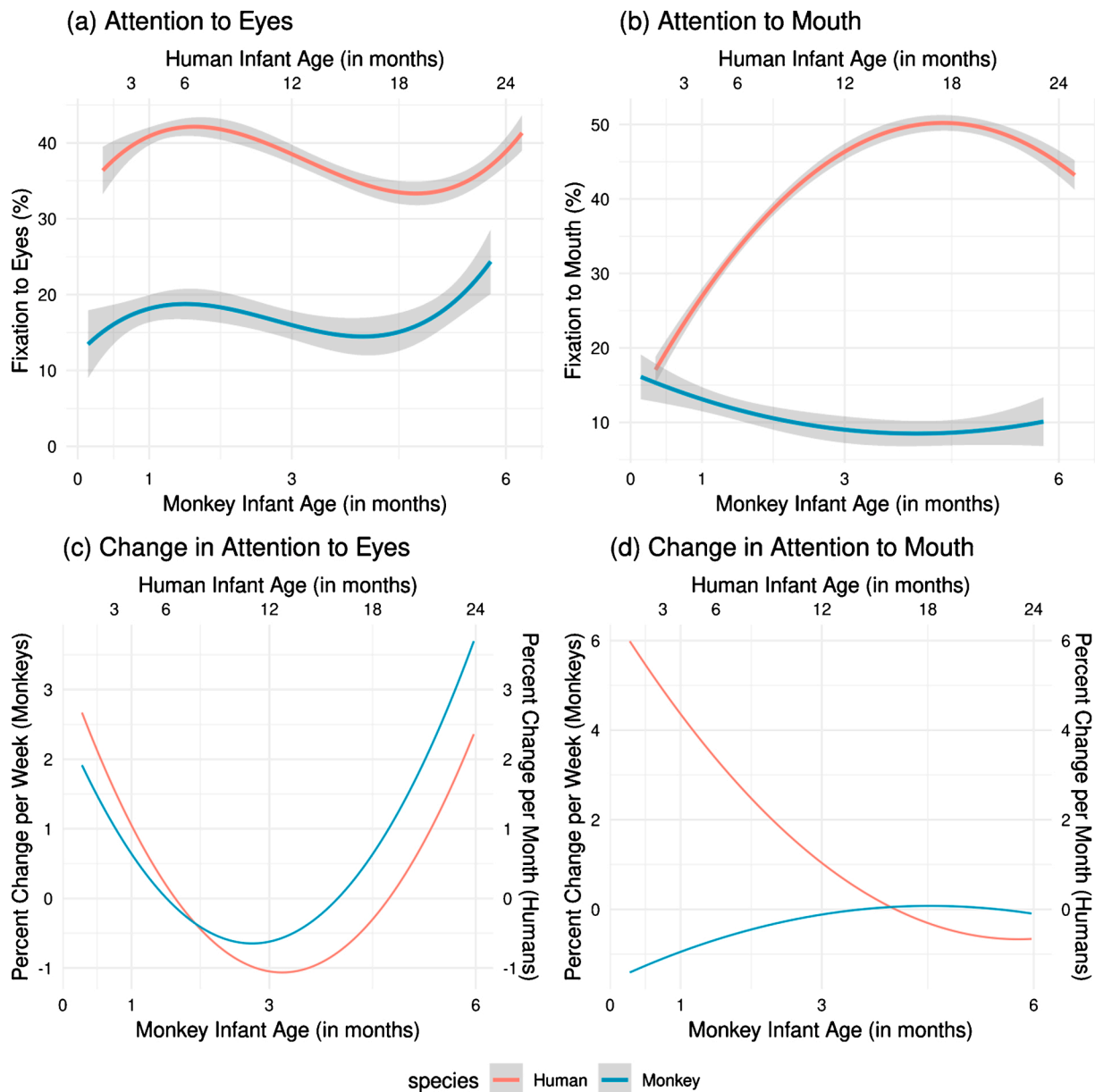


Fig. 5. Comparisons between NHP and human infant trajectory of attention to the eye and mouth regions. **(a)** Both human and NHP infants show parallel trajectories for attention to the eye region, though NHPs have lower fixation percentage overall. **(b)** Although human and NHP infants have similar levels of attention to the mouth region at birth, human infants begin to pay more attention to the mouth throughout development, whereas monkey attention remains relatively stable. **(c)** Taking the central differential of both human and NHP infant trajectories and adjusting for the difference in developmental timescale, both human and NHP infants have similar rates of change in attention to the eyes across development, whereas **(d)** attention to the mouth have vastly different rates of change.

decreases during the first 2 months with a slight rise beginning at 20 weeks of age, attention to the mouth in humans increases sharply and continuously until 14 months. This species difference could highlight an interesting dissimilarity in the ethological relevance of the mouth regions between the two species. The overall increase seen in human infants is likely associated with the beginning of language acquisition during this early period (Klin et al., 2009; Paul et al., 2011; Wyk et al., 2010), whereas mouth movements in rhesus macaque infants are known to be used as social cues to display and indicate either dominant behaviors, such as threat gestures, or submissive behaviors, such as lip-smack cues, that are mainly used during social interactions and could begin to develop at an age (4–6 months) when infant monkeys begin to leave their mother and enter in interactions with peers and other members of the social group. The differences could also be due to methodological differences between the studies. While we aimed to

preserve many of the same aspects of the social stimuli from the human study when preparing clips for this study, our stimuli tended to include more of the body of the stimulus monkeys. The human study utilized close-up videos of caregivers from the shoulder up, thus devoting more of the available visual space to facial features and provided more opportunities to attend to the eyes and mouths. Unfortunately, many of our stimuli presented the full bodies of the stimulus monkeys, thereby limiting the amount of visual space, and therefore limiting the attentional demand, of facial features such as the mouth. Likewise, this difference in stimuli could explain the systematically lower rates of fixation to the eyes in our study compared to the human study, as the eyes took up less area of visual space in our monkey stimuli. While these limitations exist, the parallels that are seen in the overall changes in attention do suggest that there is an evolutionarily conserved mechanism for the development of early social-visual attention.

4.4. Neural basis of attention to facial cues

The specific neural mechanisms that underlie the shifts in visual attention to face cues, particularly fixation to the eyes, in early infancy are still poorly understood and remain speculative. Earlier developmental neuroanatomical and neurophysiological studies in monkeys together with more recent neuroimaging studies in both human infants and infant monkeys have indicated that visual subcortical and cortical regions responding preferentially to faces are present and spatially organized early in infancy, although fully selective face areas emerge much later (Deen et al., 2017; Livingstone et al., 2017; Arcaro et al., 2017; Arcaro and Livingstone, 2017). As reviewed by Johnson (2005) and more recently by (Powell et al., 2018), several converging lines of evidence suggest that a subcortical face-processing route, including the superior colliculi, putamen and amygdala, is present at birth and is responsible for the patterns of face-related stimulus preference that are seen at that age. This subcortical route operates both more rapidly than cortical visual pathways and on low spatial visual information (LeDoux, 1996), and may be functionally more developed for newborn face preference because of the still functionally immature cortical visual areas (Johnson, 2005).

Functional neuroimaging studies in infant rhesus macaques viewing faces have shown a robust early activation of the lateral geniculate nucleus as early as 1 week of age, suggesting an early reliance on subcortical visual processing (Livingstone et al., 2017; Arcaro and Livingstone, 2017; Arcaro et al., 2017). In addition, sharp increase in amygdala volume, most likely resulting from increased interconnectivity of the amygdala with neocortical areas, occurs within the first six weeks of age in monkeys (Payne et al., 2010; Chareyron et al., 2012) and may help tag perceptual face processing with emotional content of a face. In contrast, the ventral temporal visual pathway involved in the perception of facial features and identity, the visual cortical areas located within the superior temporal sulcus important for the detection of facial movements and facial expressions, and the dorsal visual stream in the parietal cortex involved in spatial attentional processes are not fully developed at birth and have a more prolonged development throughout infancy (Webster and Mollon, 1991, 1994; Rodman and Consuelos, 1994; Livingstone et al., 2017; Rodman et al., 1991, 1993; Distler et al., 1996). Additionally, a recent functional MRI study on a subset of infants participating in the current study showed stronger functional connectivity between the most posterior cortical areas of the three visual cortical streams than in the more anterior cortical areas, and functional connectivity between the anterior portion of ventral visual stream and the amygdala increased progressively in the first 12 weeks of age (Kovacs-Balint et al., 2018). Thus, as shown in Fig. 4, we speculate that at birth attention to the eyes may be supported by the early developing subcortical system. The decrease in attention to the eyes from about 6–16 weeks of age followed by the subsequent increase from 16 to 24 weeks may coincide with a decline of more reflexive subcortical processes together with a progressive rise of cortical processing as neonatal looking to faces may become more volitional when infants may choose to look at faces in order to engage in positively valenced and contingent social interactions. By 24 weeks of age, responses to faces in specific regions of extrastriate cortex may be further potentiated by the medial prefrontal cortex regions that respond to prosocial interactions (Johnson, 2005; Powell et al., 2018).

4.5. Summary

Our main findings indicate that infant development of social-visual engagement is conserved in primates. The developmental trajectory for the attention to the eyes in infant rhesus macaques is comparable to that reported in human infants (Jones and Klin, 2013). Both begin with an increase in attention to the eyes that peaks relatively early in development, followed by a prolonged decrease and finally a progressive rise. The similarities in this longitudinal development implies

conserved neural processing between nonhuman primates and humans. Yet, there were also important species differences that are likely guided by ethological constraint. Fixation to the mouth for example has different developmental trajectories for infant monkeys and humans, suggesting the information provided by mouth movements that are related to language acquisition in human infants at this early age but not in infant monkeys. However, these changes could be due to differences that arise when adapting methodologies to a new species. Despite these limitations, rhesus macaques may provide a critically needed nonhuman primate model to further examine the developmental changes in neural systems engaged in social-visual attention. Specifically, a nonhuman primate model is vital for future research in order to assess how genetic variations as well as molecular and/or experimental manipulations of social neural networks alter social development. As recent discoveries in humans point to the importance of early-emerging and highly-conserved social phenotypes, nonhuman primate model could advance understanding of the brain-behavior pathogenesis of ASD as well as help validate efficacy of potential therapeutic treatments for attenuating social deficits in ASD.

Declaration of Competing Interest

All the authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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