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Cami Poole April 1, 2021

Early development of attention networks and their association with social visual attention in infant rhesus macaques: translational potential for autism spectrum disorders

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2021

Abstract

Early development of attention networks and their association with social visual attention in infant rhesus macaques: translational potential for autism spectrum disorders

By Cami Poole

Non-human primates (NHP) are critical translational models for understanding developmental mechanisms of typical and atypical social attention of relevance to neurodevelopmental disorders such as Autism Spectrum Disorder (ASD). The goal of this study was to examine early developmental trajectories of visual attention brain networks that support the maturation of attention to social visual stimuli in infant rhesus macaques.

Longitudinal brain structural MRI scans were acquired at 2, 4, 8, 12, and 24 weeks of age from 31 infant male macaques living with their mothers in social groups and a subset of 21 subjects were also scanned at 16, 20wks. T1- and T2-weighted images were acquired using a 3T scanner to examine volumetric changes in social visual attention networks, which include the primary visual cortex (V1) and extrastriate visual cortex (V3); lateral intraparietal area (LIP) and frontal eye field (FEF) in the dorsal attention network (DAN); temporoparietal junction (TPJ) and ventrolateral prefrontal cortex (vlPFC) in the ventral attention network (VAN); and caudal temporal parietooccipital area (TPOc) and area PG associated region in the superior temporal sulcus (STS). Measures of social development were collected from a smaller subset of subjects (n = 11), using: (1) focal observations and a rhesus ethogram, (2) rating scales of typical and atypical social behaviors (adapted from the Social Responsiveness Scale -SRS- used for ASD diagnosis in humans), (3) visual orientation, following, and attention using a tool adapted from the Infant Neurobehavioral Assessment Scale (INAS), and (4) visual attention to social vs. nonsocial stimuli using eye-tracking methods.

Region-specific developmental changes were identified in these social visual attention brain networks, although rapid growth was shown by most regions between 2 to 8-12 weeks. These changes were paralleled by an increase in social and solitary play, decline in proximity and contact behaviors with the mother by 8 weeks, when infants increase independence-seeking behaviors.

Our findings suggest that during the first 24 weeks of life (equivalent to 2 years in humans), particularly in the first 8-12 postnatal weeks, social visual attention networks undergo robust structural changes that parallel infant maturation to independence and increased attention to salient social visual stimuli and, by extension, social interaction. Understanding typical development of attention relevant to social visual stimuli and the underlying social brain networks in an NHP model can help elucidate the roots of brain-behavior pathogenesis of human social deficits.

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Acknowledgements

First, I would like to thank Dr. Mar Sanchez, who has been an amazing advisor and mentor throughout my last two years in her lab. I have learned so much about research alongside my classes, and this process of completing a thesis has served as a culmination of the knowledge I have gained from her. She has dedicated substantial time in supporting me every step of the way in the development of this thesis. She has always held high expectations for me that led me to feel more confident in my own abilities to research and understand scientific literature, as well as synthesize my own interpretations of findings. I have progressed much further as a scientist with her mentorship than I had ever expected upon entering college; for this, I am incredibly grateful.

I would also like to thank Dr. Jocelyne Bachevalier and Dr. Eladio Abreu for agreeing to serve as committee members for my thesis, providing their time and mentorship throughout this process. Dr. Bachevalier has kindly not only given wonderful feedback but has also assisted in assembling the early pieces of the project, ultimately making this thesis possible. Dr. Abreu— in addition to his feedback and support in developing my thesis— has been an unwavering mentor throughout my undergraduate career from the very beginning, fostering my scientific curiosity. As he has been there to support me since the beginning, I am so contented that he is able to be present for what I hope to be an amazing ending.

Moreover, I want to express my appreciation to Dr. Zsofia Kovacs-Balint who has also been an incredible mentor. She has taught me an unbelievable amount throughout my time in the lab and seemingly had answers for every single one of the multitude of questions I had. Additionally, I wanted to acknowledge that she has shown an astounding ability to continue providing significantly beneficial feedback despite having drastically increased responsibilities throughout this past year.

Thank you to all members of the Sanchez lab who have also been very supportive during my time in the lab. Everyone has always been welcoming and kind, never hesitating to assist if needed.

Thank you to my family and friends who have never stopped believing in me during this process, providing endless love and encouragement that gave me the motivation to continue moving forward, especially during trying moments.

Above all, I admire every one of the aforementioned people and aspire to integrate the skills they have taught me into every aspect of my life, as a student, scientist, and ultimately as a person.

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Introduction

Autism Spectrum Disorder (ASD) is defined by the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) as a neurodevelopmental disorder with deficits in social communication and social interaction as well as restricted, repetitive patterns of behavior (American Psyciatric Association, 2013). Though commonly reported as 4:1, the male-to-female ratio of ASD diagnosis has been recently identified as closer to 3:1, most likely due to a gender-bias in diagnosis (Loomes et al., 2017). Still, this ratio indicates a higher prevalence of ASD among males. Current prevalence rates range between 1/64 and 1/54 for children 4-8 years old (Shaw et al, 2020; Maenner et al, 2020) and studies show an increased prevalence from previous estimates in 2014 likely due to improved identification, while still highlighting the variability in detection of ASD and need for improving early identification (Maenner et al., 2020; Shaw et al., 2020). Symptomatology of ASD is not typically apparent at birth, with detection of atypical development of social communication and interactions beginning between 6-12 months (Ozonoff et al., 2010). Because atypical behavior related to ASD do not become obvious until approximately 2 years of age in most children, diagnosis and intervention early on are challenging (Levy et al., 2009). But they are also critical because symptoms of ASD interfere progressively with learning and social relationships over time, and early identification and intervention significantly improve developmental outcomes (Lai et al., 2014; Volkmar, 2014). Recent evidence by researchers at the Marcus Autism Center (Atlanta, GA) suggests that ASD atypical social visual engagement (eye gaze and eye-looking preferences) is already detectable during infancy, as early as 2 months of age (Jones and Klin, 2013).

Identifying social deficits related to ASD at earlier ages and the underlying neurodevelopmental alterations is, therefore, critical for development of therapies early in life. Based on this, the Yerkes National Primate Research Center (YNPRC) labs of Drs. Sanchez and Bachevalier are collaborating with the Marcus Autism Center as part of an NIH-funded Emory Autism Center of Excellence (ACE) to examine social visual developmental trajectories and their underlying neural correlates in macaque infants, which show high behavioral complexity and similar social and neural developmental trajectories and milestones as human infants (Bauman and Schumann, 2018). Rhesus macaques (*Macaca mulatta*) serve as highly translational nonhuman primate (NHP) model that addresses the limitations of experimental control over environmental and confounding factors in humans (e.g., diet, prenatal exposure to stress/drugs, income level, education), and allows densely sampled data collection in longitudinal studies. In infant macaques, early social development parallels that of human infants but at a maturational rate four times faster (Bauman and Schumann, 2018), with neural regions that regulate complex social behavior showing rapid maturational growth in brain development, which follows the patterns observed in humans (Liu et al., 2015; Malkova et al., 2006; Scott et al., 2016). In macaques, there is rapid growth of grey matter (GM) over the first 3 months of life (approximately equivalent to the first year of life in humans), followed by slower growth up to puberty (3-4 years in macaques), and paralleling the development of humans by reaching a maximum in total brain volume around puberty (Malkova et al., 2006). Importantly, macaques, like humans, live in complex social environments in which social behavior is an important part of integration into the group (Chang et al., 2013), likely supported by homologous underlying neural mechanisms in both species (Rushworth et al., 2013).

Additionally, when attending to social stimuli, macaques exhibit visual attention focusing heavily on the eyes and mouth, much like humans (Machado et al., 2011). Thus, among preclinical studies modeling ASD, a uniquely human disorder, NHP models such as the rhesus macaque are advantageous due to the prominent evolutionary, neural, and behavioral development closeness.

The ACE study addresses the structural and functional neural circuits responsible for emergence of social skills, including the maturation of social visual engagement in a group of typically developing male infant macaques. The three aims of the study are to (1) characterize social visual engagement and neuromotor development, (2) trace the development of social contingency and mother-infant reciprocal behavior, and (3) map the development of neural networks mediating changes in perception and attention to social stimuli. The present thesis will build from the third aim, mapping the development of social visual attention brain networks, and their associations with behavioral measures of visual attention to social stimuli.

ASD phenotypes include atypical attention to social stimuli such as low fixation on eyes in comparison to other facial features, which is widely reported as a diagnostic biomarker of the disorder (Jones et al., 2008; Jones and Klin, 2013; Papagiannopoulou et al., 2014) and was noted in the first description of the disorder (Kanner, 1943). Though it has previously been hypothesized that gaze aversion is present in ASD, it has more recently been suggested that diminished eye-looking may be, instead, consistent with passive insensitivity to the salient social cues of others' eyes (Moriuchi et al., 2017). Importantly, eye looking is a facilitator of social adaptation, which is the ability to function successfully in social interactions with others (Jones and Klin, 2013). These authors found in their eye-tracking study, that contrary to

theories of congenital absence of preferential eye looking, human infants later diagnosed with ASD (at 36 months) actually exhibit increased attention to eyes compared to typically developing (TD) infants at 2 months of age. This suggests that some socially adaptive behaviors may be present initially in infants later diagnosed with ASD (Jones and Klin, 2013). After 2 months, this heightened attention declines to reach a level approximately half that of TD peers by 24 months, while attention to eyes in TD infants increases drastically after 2 months to become the primary fixation point out of a visual scene (subdivided into eye, mouth, body, and object regions) by 8-10 months. Additionally, in infants later diagnosed with ASD, mouth fixation increases from 2 until approximately 18 months. These results indicate developmental differences already present at 2-6 months of age in infants later diagnosed with ASD. The use of eye-tracking in the Jones and Klin (2013) study provides early measures of social visual attention alterations, such as different patterns of social (eye/mouth) and nonsocial (object) fixation, prior to the manifestation of overt social behavioral symptoms seen later in children diagnosed with ASD. Moreover, it has been suggested that the greater the dominance of fixation on areas of the face, body, or objects—rather than eyes—, the greater the likelihood of more severe social disabilities (Jones et al., 2008; Klin et al., 2002). Thus, the decline of eye looking during a specific early period reveals a narrow developmental window in which children's social adaptive behaviors that should guide social development are disrupted and can be targeted by interventions.

Regarding social attention, Kanner (1943) described children he diagnosed with "infantile autism" as showing a pronounced attention to objects in contrast to people, who were often ignored as if they did not even exist. And if a part of another person's body, such as a hand, was

in the way of the children, they regarded it as a detached object rather than belonging to a person. In contrast, TD infants show preferential attention to biological motion within the first days of life, which is highly conserved in NHPs as well (Klin et al., 2009).

Children diagnosed with ASD exhibit early atypical attention to social stimuli (Chawarska et al., 2013; Klin et al., 2009) and atypical visual orienting by 12 months (Zwaigenbaum et al., 2005). Interestingly, atypical visual attention in infants with ASD may not be reliably distinguishable from TD infants at 6 months but becomes increasingly more apparent from 6 to 12 months (Zwaigenbaum et al., 2005), an age period in which differences in social behavior become apparent as well (Ozonoff et al., 2010).

Klin et al. (2003) explained that attention to salient stimuli within the social environment is fundamental to both social adaptation and social cognition. Because social cognition is constructed over time through interactions with others, typical attention to social cues is necessary for gaining an accumulation of experiences in this area. Unfortunately, in ASD, the typical salient dominance of social stimuli appears to be absent and therefore derails the process of gaining social experiences to improve social cognition. Consistent with Kanner's observations (1943), non-social physical stimuli rather than social ones attract the attention of children with ASD, developing further experiences with objects and leading to specialization in objects instead of people (Klin et al., 2003).

Though impairments in social attention across multiple domains appear early and persist throughout life in individuals with ASD, there is a gap in knowledge regarding the alterations in brain networks underlying social attention deficits in ASD (Farrant and Uddin, 2016). This is in

part due to scarce literature addressing the development of social attention systems and changes during early typical development in infants. Thus, further research is needed to understand early neurodevelopmental mechanisms that inform early social attentional deficits for recognition and interventions for ASD (Lai et al., 2014). By studying the early developmental changes in the structure of social attention networks in the macaque infant brain and parallel behavioral changes in the development of social visual attention, the **goal** of this thesis is to elucidate potential neural biomarkers of typical social attentional development and even identify social attentional divergences of relevance to ASD in our macaque breeding colony. This will inform our understanding of the emergence of differences in developmental trajectories and better inform interventions to help redirect these differences to improve social adaptation behaviors.

For this, I will examine the structural development of the primary visual cortex (V1)— because of (1) its involvement in both the dorsal and ventral visual attention networks described below and (2) it is the primary sensory input for visual information— as well as extrastriate visual area V3, which receives input from V1 and projects to both the dorsal and ventral attention networks, which are critical for the deployment of visual attention (see Figure 1A for a diagram of these networks).

I will also examine the structural developmental trajectories of the visual dorsal attention network (DAN), as it is responsible for orienting the subjects' attention to stimuli, such as salient social visual stimuli. The DAN allows the selection of visual stimuli based on internal goals or expectations to elicit overt (voluntary), top-down (goal-driven) attention, producing appropriate motor responses and orientation to these cues (Corbetta et al., 2008). Overt

attention is refers to attention directed by eye movements to attend to a stimulus (Gazzaniga et al., 2018). Within this network, I will study the lateral intraparietal area (LIP) because of its crucial role in visuospatial attention that provides a salience/priority map and representation of saccadic end points in it (Bisley and Goldberg, 2003; Bogadhi et al., 2018; Grefkes and Fink, 2005; Ramezanpour and Thier, 2020; Sapountzis et al., 2018). LIP is located in the intraparietal sulcus (IPS), which has been reported in humans to act as an important region within the DAN because of its top-down influence on the visual attention via broadcasting signals to shift attention to important visual targets (Bisley et al., 2011; Farrant and Uddin, 2016; Grefkes and Fink, 2005; Vossel et al., 2014; Vossel et al., 2012). Area LIP in the macaque is a pretty specialized region that has been identified as a key node of the IPS, and neurons within LIP fire during detection of salient visual stimuli, the delay period when stimulus location has been memorized, and during the saccade to the location (Gnadt and Andersen, 1988). These activations make sense as it has been proposed that the region continuously updates top-down predictions about the validity of spatial cues (Vossel et al., 2012). Ramezanpour and Thier (2020) found that activity of neurons in LIP is related to spatial shifts of attention that are evoked by gaze cues and suggest that this region responds to salience of another's gaze to adjust the salience map to reallocate attention. Due to the LIP's ability to evaluate salience/priority of social visual stimuli based on their features, it potentially acts as a source of feature attention signals projected to the frontal eye field (FEF), which controls the initiation of eye movements (Sapountzis et al., 2018). The FEF will also be studied due to its critical role in the DAN, orientation of visual attention in collaboration with LIP, initiation of eye movements (e.g. voluntary saccades and pursue eye movements) and its implicated role in priority mapping

(Bogadhi et al., 2018; Grefkes and Fink, 2005; Ramezanpour and Thier, 2020; Sapountzis et al., 2018; Vossel et al., 2014).

The present study will also examine the ventral attention network (VAN), which is responsible for covert (involuntary, subconscious), bottom-up (stimulus-driven) attention, reorienting attention toward salient stimuli, such as social visual cues. Covert attention refers to attention directed without changes in eye, head, or body orientation toward a stimulus (Gazzaniga et al., 2018). It allows detection of salient and behaviorally relevant stimuli in the environment, particularly when unattended, and is proposed to act like a "circuit breaker" to interrupt ongoing selection in the DAN to shift attention to a novel stimulus (Corbetta et al., 2008). Within the VAN network, I will study the structural development of the temporoparietal junction (TPJ) because this region, as a whole, has been associated with involvement in bottom-up covert attention and overlaps with the salience network (Corbetta et al., 2000; Corbetta et al., 2008; Mars et al., 2012a). Krall et al. (2015) investigated the functional segregation of the right TPJ (rTPJ), due to various postulated roles such as reorienting of attention and understanding of others' mental state — known as theory of mind (ToM). Their study reported that posterior rTPJ is specifically associated with the social cognition network, while the anterior rTPJ facilitates allocation of attention to behaviorally relevant stimuli, interrupting automated routines necessary for reorientation of attention. Krall et al. (2015) suggest that the rTPJ is involved in both social attention and social interactions and that attention reorientation utilizes the same neural resources as in theory of mind (ToM). This convergence of involvement in social cognition in addition to social attention is consistent with results of other studies (Farrant and Uddin, 2016; Krall et al., 2015; Vossel et al., 2014). Additionally, cortical damage to

the TPJ— such as stroke—, leads to unilateral visual neglect— condition described as a deficit in reorienting attention toward stimuli in the visual field opposite the lesion (contralateral visual field)— despite the absence of a primary visual deficit (Corbetta et al., 2000; Gazzaniga et al., 2018; Halligan and Marshall, 1994). Bisiach and Luzzatti (1978) found that neglect is also present in visual memory, and through their study, they concluded that attention was biased in neglect patients. Visual field testing also supports this theory, as neglect patients may detect stimuli within their contralateral visual field when presented in isolation but cannot perceive the contralateral stimulus when an additional stimulus is presented simultaneously in the ipsilateral visual field, competing for attention (Gazzaniga et al., 2018). To sum up, there is strong evidence that the TPJ is crucial in reorienting attention.

Another area that will be studied as part of the VAN, is the ventrolateral prefrontal cortex (vlPFC), also involved in the control of covert visual attention (Bogadhi et al., 2018; Corbetta et al., 2008), and overlaps with the salience network (Bogadhi et al., 2018; Sliwa and Freiwald, 2017). In the study by Sliwa and Freiwald (2017), the vlPFC was included in an exclusively social interaction network (ESIN), proposed to have a role in evaluating species-specific socioemotional rules of social conduct and inferring others' mental states. In contrast to the mirror neuron system (MNS), which is functionally related to body and object patches, the ESIN is closer to face patches (Sliwa and Freiwald, 2017). Neuroimaging studies in humans have implicated bilateral vlPFC in action observation, execution, and imitation (Levy and Wagner, 2011). Furthermore, the right vlPFC has been suggested as an important region in the MNS, involving mirror neuron cells first observed in primate premotor and parietal cortices that respond to the execution of actions as well as observing another subject performing that same

action (Iacoboni and Dapretto, 2006; Levy and Wagner, 2011; Rizzolatti and Craighero, 2004). Interestingly, it has been suggested that dysfunction of the MNS in humans could be a core deficit in ASD (Iacoboni and Dapretto, 2006). Furthermore, studies of the functional specialization of the right vlPFC report that visuo-spatial stimuli often result in activation within this region, and vlPFC regions involved in orienting are activated when behaviorally relevant stimuli are detected (Levy and Wagner, 2011).

Finally, this study will also include regions within the mid-superior temporal sulcus (STS) because of literature demonstrating significant social visual attention-related activation in these regions, connecting them to control of covert orientation of visual attention to salient social visual stimuli in monkeys (Bogadhi et al., 2018). The STS is responsive to stimuli features relevant to gaze direction (gaze following), such as head orientation and social interactions (Leopold and Krauzlis, 2020; Ramezanpour and Thier, 2020). It also shows increased activation to stimuli during social interactions (Sliwa and Freiwald, 2017), and is implicated in attention to biological motion with information about social cues such as dynamic changes in facial expression, head orientation, and eye gaze (Allison et al., 2000; Freiwald and Tsao, 2010; Grossman et al., 2000; Herrington et al., 2011; Hoffman and Haxby, 2000; Pelphrey and Morris, 2006) ; (Klin et al., 2009). Within the STS, I will focus on the caudal temporal parietooccipital area (TPOc) and the area PG associated region of the STS (PGa). The TPOc is an area recruited for visual attention to faces and is selectively activated during covert attention to peripheral visual stimuli, including visual motion (Bogadhi et al., 2018). In the macaque, area PGa shows significant covert attention-related activation (Bogadhi et al., 2018), and is thought to have a

general role in visual guidance of arm movements in macaques due to reported functional connectivity with premotor areas (Gregoriou et al., 2006).

In sum, the **goal** of this project is to examine early developmental changes in social visual attention brain networks in parallel with social visual attention behaviors of relevance to ASD, which can impact the field by providing early neural biomarkers of social development and dysfunction. To achieve this goal, we followed the social visual neural and behavioral developmental trajectories of 31 male infant rhesus macaques from birth through 6 months of age (equivalent to toddlerhood in humans). Only males were used for this study based on the higher prevalence of ASD in human males than in females. Subjects lived with their mothers and families in socially complex groups. The study utilized two primary approaches: (1) structural Magnetic Resonance Imaging (sMRI) was used to examine structural (volumetric) growth of brain regions of interest (ROIs) related to social visual attention, and map their developmental trajectories in the 31 subjects; (2) measures of social behavior, visual orientation/following/attention and social responsivity were also collected in a subset of these subjects (n=11), as was time looking at eyes during eye-tracking studies in another subset (n=20).

The main **hypothesis** of this study is that brain structures in the attention networks and STS-associated areas involved in social visual attention (regions in the DAN, VAN and STS) will undergo rapid developmental growth during early ages through the beginning of weaning (between birth and 8 weeks of age— equivalent to the first 8 months in human infants—), and these changes will be paralleled by changes in social behavior as the infants start exploring, playing and increasing independence from mom during weaning. We also hypothesized that

periods of high acceleration of specific regional growth within the DAN, VAN networks, or the STS will be predictive of developmental milestones or transitions in specific infant social attention behaviors. Finally, this thesis will establish a framework of how development of social visual attention, specifically within the context of ASD-relevant social behavior, might be driven by early developmental changes within social visual attention networks, as illustrated by a translational rhesus macaque model.

Methods

Subjects and Housing

In this study, 31 male infant rhesus macaques (*Macaca Mulatta*) were examined as part of a larger project studying the development of neural networks mediating changes in social visual perception and attention (e.g., (Kovacs-Balint et al., 2019; Kovacs-Balint et al., 2021; Wang et al., 2020). The subjects were born and reared at the Yerkes National Primate Research Center (YNPRC) Field Station, located in Lawrenceville, GA. They lived in complex social environments with their mothers, families, and other group members in large outdoor/indoor compounds. The study includes mostly offspring of mid-ranking females in order to limit rank effects on early life experience. Their diets consisted of standard high fiber, low fat monkey chow (Purina Mills., Lab Diets, St. Lois, MO), with seasonal fruits and vegetables—in addition to enrichment items— provided twice daily. Water was available *ad libitum*. Behavioral and brain developmental data were collected longitudinally, from 1 week to 6 months of age (equivalent to the first 2 years of life in humans). Infants of primiparous females and/or females with

histories of infant maltreatment (physical abuse, neglect), and infants with low birth weights (<450g)— which would have confounding effects of prematurity on brain development (Scott et al., 2016)— were excluded from the study. All procedures were approved by the Emory University Institutional Animal Care and Use Committee (IACUC), in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services "Guide for the Care and Use of Laboratory Animals." The YNPRC is fully accredited by AAALAC International.

Structural MRI (sMRI) Studies

sMRI Data Acquisition

Structural MRI scans were collected in 31 subjects at 2, 4, 8, 12 and 24 weeks of age. A subgroup of infants (n=21) was scanned at 16 and 20 weeks as well. Infants were transported with their mothers from the YNPRC Field Station to the Main Center on the day before or morning of the scheduled scan for MRI data collection. Scans were acquired with a 3T Siemens Tim Trio MRI scanner (Siemens Med. Sol., Malvern, PA, USA) and an 8-channel phase array knee coil. They included a T1-weighted 3D magnetization prepared rapid gradient echo (3D-MPRAGE) parallel image sequence (TR/TE = 2600/3.46msec, FoV=128mm, voxel size: 0.5mm^3 isotropic, 8 averages, GRAPPA R=2), and a T2-weighted sequence in the same direction as the T1 (TR/TE = 3200/373msec, FoV=128mm, voxel size: 0.5mm^3 isotropic, 3 averages, GRAPPA R=2). T1 and T2 images were collected within the same scanning session, as inclusion of both image types aids with registration to atlas space and to define the contrast more accurately between GM, white matter (WM) and cerebrospinal fluid (CSF) for tissue segmentation, as well

as to delineate anatomical borders of both cortical and subcortical ROIs (Knickmeyer et al., 2010).

Scans were collected under anesthesia with isoflurane (1-1.5%, mean±SEM: 0.912±0.008%, inhalation), following sedation induction with telazol (2.868±0.078mg/kg BW, i.m.) and intubation. The animals' physiological state was closely monitored during the scan with a blood pressure monitor, oximeter, electrocardiograph, and rectal thermometer. Subjects' body temperatures were maintained using an MRI-compatible heating pad, and hydration was maintained through intravenous delivery of dextrose/NaCl (0.45%). To prevent motion artifacts in the scans, a custom-made head restraint with mouthpiece and ear bars was used. A vitamin E capsule was placed over the infants' right temple to identify the right side of the brain. After recovering from anesthesia, each infant was reunited with its mother and the pair returned to their group at the YNPRC Field Station the following day.

sMRI Data Processing

T1- and T2-weighted images were processed using the in-house built pipelines AutoSeg (version 3.0.2) and NeoSeg (version 1.0.7; only necessary for 2 and 4 weeks age points). These pipelines are open-source (Neuro Image Research and Analysis Laboratories— NIRAL—, University of North Carolina) (Wang et al., 2014). Both AutoSeg and NeoSeg are atlas-based automatic segmentation tools for brain tissue, based on probabilistic tissue maps consisting of WM, GM, and CSF). AutoSeg also generates parcellations for cortical and subcortical ROIs.

To create volumetric computations of WM, GM, CSF, and ROIs for each subject, the AutoSeg pipeline follows several steps. The initial step corrects for inhomogeneity in the MRI image's

signal intensity which result from imperfections in coil radiofrequency. Inhomogeneity produces inaccuracies in the tissue segmentation process, and AutoSeg utilizes N4-ITK bias field correction to address this issue (Tustison et al., 2010). AutoSeg next uses a reference space algorithm to align the subject image to a reference atlas space (image registration) based on published protocols (Shi et al., 2017; Styner M et al., 2007; Wang et al., 2014). This linear image registration in AutoSeg is performed with a tool called BRAINSFit— in Slicer image processing software— (Fedorov A et al., 2012; Johnson et al., 2007; Liu et al., 2015; Shi et al., 2017; Styner M et al., 2007). Age-specific T1- and T2-weighted UNC-Emory infant MRI atlases developed by our group (Shi et al., 2017) were used for this step. These are templates of scans acquired longitudinally from 2 weeks to 6 months in 40 infant rhesus macaques from the YNPRC social colony, balanced by sex and social rank. Based on best match of neuroanatomical characteristics, the earliest scan ages (2 and 4 weeks) were registered to the 2-week atlas, the 8-, 12- and 16-week scan ages to the 3-month atlas, and the 20- and 24-week scan ages to the 6-month atlas. Following registration of subject images to their respective atlas, NeoSeg (for 2 and 4 weeks) and AutoSeg (for 8, 12, 16, 20 and 24 weeks) were used for automatic atlas-based classification (ABC), performing segmentation of the image into GM, WM, and CSF tissue classes. The first round of ABC tissue segmentation is run including the skull, but a second round is run after skull-stripping the image (using manually edited whole-brain masks to remove non-brain voxels: skull, muscle, blood vessels outside of the brain (Liu et al., 2015; Tustison and Avants, 2013)). This method improves the quality of registration to the atlas, tissue segmentation and ROI parcellations (Wang et al., 2014). After the second (skull-stripped) ABC round, AutoSeg was used at all ages to generate tissue segmentations (GM, WM, CSF) and

ROI parcellations, which includes computing the ROIs respective volumes. In this study, volumes were calculated by hemisphere (left and right) for all ROIs (Figure 1).

As described in more detail in the Statistical Analyses section, ROI volumes were also corrected by total intracranial volume (ICV: GM + WM + CSF) to account for individual and age differences in whole brain volume by adding ICV as a covariate in the statistical models.

ROIs for this study included visual cortical areas: V1 and the V3 (defined as V3 dorsal (V3d) and V3 ventral (V3v) together, based on Paxinos et al. (2000)). ROIs along the Dorsal Attention Network (DAN): LIP (located in the posterior portion of the intraparietal sulcus (IPS) and defined as internal and external parts of the parietal area POa (Paxinos et al., 2000)) and FEF (defined as ventral and dorsal 8A areas (8Av and 8Ad together)by Petrides and Pandya (1994), corresponding to 8A and 8B Walker areas (Walker, 1940), but excluding BA45). Areas 8Ad and 8Av are posterior dorsolateral areas in the caudal prefrontal cortex, which caudally border the mid-dorsolateral area 9/46 (Petrides, 2005).

ROIs along the VAN: TPJ and vlPFC (area 47/12, lateral portion (Petrides and Pandya, 2002)). Area TPJ included the anterior subregion TPJa as defined by Mars et al. (2012a), which is coupled to the ventral prefrontal cortex (vPFC) in humans, and is defined as anterior fundus of the superior temporal area (aFST)/Intraparietal sulcus associated area in the STS (IPa) within the fundus of the STS in macaques (Bogadhi et al., 2018; Paxinos et al., 2000). The vlPFC definitions were generated from the Paxinos et al. (2000) published parcellations and manually edited based on cytoarchitectural landmarks described in rhesus stereotaxic atlases (Paxinos et al., 2000; Saleem and Logothetis, 2006) and PFC-specific macaque neuroanatomical landmarks

(Petrides and Pandya, 2002). The vlPFC was defined as follows: the most ventral part of the lateral frontal convexity extending on the orbital surface to the lateral orbital sulcus, defined as area 47/12, bordered medially by area 13 (Petrides and Pandya, 2002). Area 47/12 of the monkey can be subdivided into a lateral and orbital portion, and only the lateral portion was delineated for this study.

Other STS ROIs recently reported as activated during social attention tasks, such as TPOc and PGa, were also included. Area TPOc, the caudal subdivision of the TPO, is located within the dorsal bank of the STS. It is anteroventrally bordered by area PGa and the posterior superior boundary defined by the MST (Paxinos et al., 2000). Area PGa is located within the fundus of the STS, caudally bordered by what we defined as FST, and its superior rostral boundary defined by the TPO (Paxinos et al., 2000). The anterior-posterior borders extend approximately the same as FST anterior-posterior extent.

The anatomical ROI delineations were generated from the Paxinos et al. (2000) published parcellations mapped onto the UNC-Emory macaque brain atlases (Shi et al., 2017), and manually edited to ensure accurate anatomical definition following published definitions, guided by expert guidance by Jocelyne Bachevalier and published work by other macaque neuroanatomists (Paxinos et al., 2000; Petrides and Pandya, 2002; Saleem and Logothetis, 2006; Walker, 1940).

Development of Social Visual Behavior

In addition to examining longitudinal development of social brain networks with sMRI, parallel development of infant social visual behaviors was studied using four approaches: (1) infant

focal behavioral observations (OBS) using a well-established macaque ethogram (Altmann, 1962), which is a catalogue of macaque behaviors relevant to the study with their operational definitions; (2) rating scales of typical and atypical social behavior using a tool adapted from humans to adult rhesus monkeys and then validated for juveniles by our lab, the juvenile macaque Social Responsiveness Scale (jmSRS) (Kovacs Balint et al., 2020); (3) visual neuromotor and sensory developmental assessments (visual orientation, following and attention) adapted from the human neonatal Brazelton tests, called the Schneider Neonatal Assessment for Primates (SNAP) (Schneider and Suomi, 1992); and (4) eye-tracking sessions while infants watched video clips to compare percent time fixation on social versus non-social stimuli.

Infant Social Behavioral Observations (OBS)

OBS data were collected longitudinally at 2, 4, 6, 8, 12, and 24 weeks of age for a subset of 11 subjects, which was also tested for jmSRS and SNAP data. This study used a modified version of a well-established macaque ethogram, adapted from Altmann (1962) by our group for studies of infant rhesus social and emotional development and mother-infant interactions (Kovacs Balint et al., 2020; McCormack et al., 2015; McCormack et al., 2009; McCormack et al., 2006; Morin et al., 2019; Raper et al., 2014). For this study, after data processing, quality control and exclusion processes, ten behaviors were included in the statistical analysis, organized into: (1) infant play behaviors; (2) prosocial and affiliative behaviors. The behaviors were calculated as either time proportions (measured in minutes per hour) or frequency rates (measured as behavior counts per hour). Infant play behaviors examined in this study included “Solitary Play”— vigorous play alone — and “Social Play Composite”— engaged in social play with another animal— which were measured as time proportions. The social play composite score was comprised of

combined scores from three species-typical social play behaviors (“Brief Contact Play”, “Chase Play”, and “Rough and Tumble Play”). Infant affiliative behaviors examined in this study were “Proximity”— subject was within arms-reach of another animal—, “Contact”— at least half of the body touching half of another animal’s —, and “Follow”— infant persistently trailing another animal while both in motion —, all measured as time proportions. In contrast, “Leave Beyond”— infant moving beyond arms-reach of its mother or another animal — was coded to measure how much the animal ended “Proximity” or “Contact” with others (measured as a frequency rate). Other infant prosocial behaviors included “Eye Gaze”— initiating direct eye contact with another animal — and “Touch”— infant placing its hand gently on other animal’s body —, both measured as frequency rates.

These data were collected by trained coders (inter-observer reliability: Cohen k>0.8) at the YNPRC Field Station, from observation towers located over the compounds where the subjects lived. Coders used a focal sampling technique, collecting behavioral frequency and duration data from a specific infant during 30-minute observation sessions by recording all behaviors in the ethogram using an in-house program (WinOBS) (Kovacs Balint et al., 2020). The coders performed 4X30 min observations on different days, for a total of 2 hours of observation at each age, between 8am and 12pm, except for rare occasions when observations could not be performed on separate days. In that case, an additional observation was performed in the early afternoon. After OBS data were collected and error-checked, durations and frequencies of each behavior were converted into time proportions and frequency rates. Each behavior’s frequency rates or time proportions were summed across the 4 x 30 min observation sessions at each age for statistical analyses. Low occurrence behaviors (i.e., zero-inflated behaviors) were excluded

from the analyses, following a cutoff rate of 50% (i.e., 50% of the subjects displayed the behavior at most ages).

Juvenile Macaque Social Responsiveness Scale (jmSRS)

The SRS is one of the most widely used screening tools for ASD in children, with 65-items used to rate the individual on both typical and atypical social behaviors that covary with ASD symptom severity (Constantino and Gruber, 2012). The items measure a child's engagement in social reciprocal interactions and in behaviors impairing social interactions and communication in their naturalistic social environment (Constantino et al., 2003). The human SRS has been adapted for translational use with chimpanzees (Marrus et al., 2011) and from chimps to adult rhesus macaques (mSRS; (Feczko et al., 2016). In this study we used the downward extension of the mSRS for juvenile macaques (jmSRS), validated by Kovacs Balint et al. (2020) for macaques of age equivalent to mid-childhood (4-6-year-old children). The tool, which includes 14 items rating typical and atypical macaque social behaviors on a standard 5-point Likert scale (1="never true", 5="always true"), is scored by the same coder who collected the focal behavioral observations (OBS) for each infant. In this study, the jmSRS data were collected at 3 and 6 months of age on a subset of 11 subjects. At each age, each infant was scored 2 to 4 times to examine test-retest/intra-rater reliability.

After the jmSRS ratings were completed, the average score for each item was calculated for each subject. For most items on the jmSRS, a higher average score (closer to 5) is indicative of greater social impairment; however, for 4 items (e.g., "Plays appropriately with peers") a higher score indicates greater social competence/skills. In this study, only three items were analyzed

from the initial pool of 14 items (Table 3): two atypical (item 6: “Avoids eye contact or has unusual eye contact” and item 13: “Stares or gazes off into space”), and one typical (item 7: “Plays appropriately with peers).

Schneider Neonatal Assessment for Primates (SNAP)

Neuromotor and sensory development, as well as temperament data was obtained from a battery of tests modified from the human Infant Neurobehavioral Assessment Scale (INAS) (Brazelton, 1973), and adapted for infant monkeys (SNAP, (Schneider and Suomi, 1992). In the present study, SNAP data was obtained from a subset of 11 subjects, each week during the first month postnatally (ages 1-4 weeks). The data was only collected during the first 4 weeks of life because the measures reach a developmental ceiling at 4 weeks of age (Schneider and Suomi, 1992). Ratings were entered as scores on 4-point Likert scales. The present study focused on data collected to assess developmental maturation in visual orienting, following and attention behavior, particularly with regard to switching from reflexive to voluntary visual motor control in early development. Measuring development of these behaviors will provide a trajectory for social visual attention.

Eye Tracking

A subgroup of 20 infant monkeys in this study participated in 14 eye-tracking sessions at ages 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 weeks. Each session was restricted to 30 minutes, consisting of presentation of multiple high-quality video clips, 10s in length, shown on a screen after infants’ acclimation to a dark chamber (Wang et al., 2020). The stimuli displayed unfamiliar rhesus macaques filmed at the Caribbean Primate Research Center (CPRC) breeding

colony in Cayo Santiago, Puerto Rico. There was balanced representation of female and male, juvenile and adult monkeys across the videos (Wang et al., 2020). Each infant was tested while placed on its anesthetized mother (3-5 mg/kg telazol, i.m.), ventrum to ventrum (Wang et al., 2020). Underneath the monitor displaying videos was an infrared eye-tracking camera mounted on a motorized gimbal, allowing an experimenter to track the location of the infant's eyes (Wang et al., 2020). After testing, the infant-mother pair was placed in a holding cage to allow the mother recover from anesthesia; once the mother recovered, fully alert, the pair was returned to its social group.

After eye-tracking data were collected, MATLAB (MathWorks) was used to analyze eye movements and coding non-fixation (blinks, saccades, and fixations directed away from the screen) and fixation (coded into hand-traced regions of interest with each frame: eyes, mouth, head, and body) (Wang et al., 2020). For the purpose of the present study, we focused on fixation to eyes (social stimuli) and fixation to non-social stimuli ("objects": defined as the background of the video, which was operationalized as total image-monkey body). Percentage of fixation time looking at the eyes ("% Eye Fixation") of other macaques in each video was calculated by dividing the total time spent fixating on the eyes divided by the total number of recorded fixations for the entire (10s) clip multiplied by 100. Percentage of fixation time looking at objects— nonsocial stimuli in the background of videos— ("% Object Fixation") was calculated in a similar way. To conduct statistical analyses, the data were organized at the session level to provide a single timepoint at each age, comprised of data from all clips presented during each session. Sessions determined to be of low-quality were excluded (i.e., scored by coders as having unusable data). Finally, subjects with more than 50% of sessions

missing were also excluded from this study to provide an accurate representation of longitudinal changes.

Statistical Analysis

sMRI

Variables were initially checked for normal distribution using the Shapiro-Wilk test in SPSS (version 27.0), and data was log-transformed if it failed ($p>0.05$). All sMRI data were normally distributed; therefore, Linear Mixed Model (LMM) statistical analysis was used to examine significant developmental volume changes of ICV and brain ROIs in visual attention networks (V1, V3, LIP, FEF, TPJ, vlPFC, TPOc, PGa) across the first 6 months of life, and to determine periods of significant growth acceleration or deceleration. Statistical outliers were identified using SPSS based on criteria of the third quartile plus three times the interquartile range (Q3 + 3xIQR), but they were only excluded from the statistical analysis after Quality Control (QC) procedures verified technical issues with tissue segmentation and/or ROI parcellations. For ICV, LMM was used to examine effects of AGE as fixed factor on total brain volume and entering subject in the model as a random effect. For the initial ROI analyses, AGE (2, 4, 8, 12, 16, 20, 24 weeks) and HEMISPHERE (left, right) were used as fixed factors, with subject entered as a random effect. A secondary analysis was performed adding ICV as a covariate to the statistical model, to control for individual differences in total brain volume. Because AutoSeg does not compute ICV by hemisphere, for this secondary LMM analysis, right and left ROI volumes were summed to yield a total ROI volume. When main AGE, HEMISPHERE or AGE x HEMISPHERE

effects were detected, post-hoc pairwise comparisons of the means were performed using ADJ (Bonferroni) adjustments for multiple comparisons. All analyses were performed using IBM SPSS Statistics version 27, and a significant p-value was set at $p<0.05$ for the sMRI and the behavioral variables listed below.

Infant Social Behavioral Observations (OBS)

The Shapiro-Wilk test was used to check normal distribution of variables at each age. Since all variables were normally distributed (defined as normal distribution for ≥50% ages), LMM was used to examine developmental changes in social behaviors with AGE. Post-hoc pairwise comparisons of the means were performed using ADJ (Bonferroni) adjustments for multiple corrections.

Juvenile Macaque Social Responsiveness Scale (jmSRS)

Before using LMM to examine how scores on the jmSRS changed from 3 to 6 months of age, the Shapiro-Wilk test was used to check normality of variables at the two ages. As none of the variables examined were normally distributed at either age, they were log-transformed. The item “Avoids eye contact or has unusual eye contact” had the same score for all subjects across all ages (i.e., no individual variability), so it was dropped from the statistical analyses. Log-transformation of jmSRS data did not result in normal distributions; therefore, jmSRS scores were analyzed with repeated measures analysis of variance (rmANOVA), using a Greenhouse-Geisser correction. Post-hoc pairwise comparisons of the means were performed with ADJ (Bonferroni) adjustments for multiple comparisons.

Schneider Neonatal Assessment for Primates (SNAP)

Before examining how SNAP scores changed during the first 4 weeks of life, the Shapiro-Wilk test was used to check the normal distribution of variables at the four ages. Because the directionality of the visual orienting behaviors (Visual Orientation: Right-Left, Left-Right; Up-Down, Down-up) had the same scores for each subject at each age timepoint, data was reduced by consolidating it into just one measure (Visual Orientation: RLUD) for statistical analysis. Similarly, scores for visual following behaviors (Visual Follow: Horizontal and Vertical) were averaged and consolidated into one measure (Visual Follow: HV) for consistency in statistical analysis. All variables were non-normally distributed at all or most age timepoints, so they were log-transformed. Because log-transformation did not result in normally distributed data, SNAP scores were analyzed with rmANOVA, using a Greenhouse-Geisser correction. Post-hoc pairwise comparisons of the means were performed with ADJ (Bonferroni) adjustments for multiple comparisons.

Eye Tracking

The Shapiro-Wilk test was used to check normality of variables at each age. Since all variables were normally distributed for ≥50% ages, they were analyzed using LMM. LMM analyses were conducted with consolidated ages (average of weeks 1 and 2), (3 and 4), 5, (7 and 9), (11 and 13), (15 and 17), (19 and 21), and 23 weeks to better correspond with the scanning ages (2, 4, 6, 8, 12, 16, 20, and 24 weeks), respectively. This was done to better align eye-tracking timepoints with those of sMRI scans and other behavioral data, as well as for data reduction to increase

the statistical power of the models. Post-hoc pairwise comparisons of the means were performed with ADJ (Bonferroni) adjustments for multiple comparisons.

Results

sMRI Results

Intracranial (ICV) Volume

Total ICV increased over time, as shown in Figure 2 and demonstrated by a significant effect of AGE ($F_{(6,51.528)}$ =115.745; p=4.0377x10^{-28}). Post-hoc tests in Table 1 revealed significant growth —1.38-fold increase— between 2 and 24 weeks (p=4.5713 x10^{-24}) and 2-12 weeks (2 to 4 weeks: 1.07-fold increase, p=0.002; 4 to 8 weeks: 1.15-fold increase, p=3.4551x10^{-12}; 8 to 12 weeks: 1.05-fold increase, p=0.039) followed by a plateau in growth.

Visual Cortical Area Volumes

Primary Visual Cortex (V1) Volume

Absolute V1 volume increased over time, as shown by the significant effect of AGE ($F_{(6,110.202)}$ =84.421; p=6.7078x10^{-39}), but no HEMISPHERE ($F_{(1,260.453)}$= 0.387; p = 0.535), nor AGE x HEMISPHERE interaction effects ($F_{(6,110.202)}$=0.116; p=0.994) were found (Figure 3). Controlling for subject ICV as a covariate in the LMM model still resulted in significant effect of AGE on V1 volume ($F_{(6,36.591)}$=243.276; p=6.1056x10^{-28}). Post-hoc tests in Table 1 identified significant growth —1.32-fold increase— between 2 and 24 weeks (p=5.9571 x10^{-35}) and between 2 and 12 weeks (2 to 4 weeks: 1.10-fold increase, p=1.7409x10^{-10}; 4 to 8 weeks: 1.20-fold increase,

$p=4.5784x10^{-25}$; 8 to 12 weeks: 1.03-fold increase, $p=2.48x10^{-4}$), followed by a growth plateau from 12 to 20 weeks and a slight, but significant, decrease in volume between 20 and 24 weeks (0.96-fold decrease, p=0.010).

Extrastriate Visual Area (V3) Volume

There was a significant effect of AGE ($F_{(6,95.112)}=195.826$; $p=3.0582x10^{-51}$), no main effect of HEMISPHERE ($F_{(1,248.117)}=0.091$; p=0.763), but an AGE x HEMISPHERE interaction effect ($F_{(6,95.112)}=2.545$; p=0.025) on V3 volumes (Figure 4). The volumetric changes of V3 appeared to be different by hemisphere, with the left hemisphere growing more rapidly than the right between 2 and 24 weeks, particularly from 4 to 8 weeks (Figures 4A, 4B). Adding ICV as a covariate in the LMM model still resulted in significant effect of AGE on V3 volume ($F_{(6,41.187)}=458.702$; $p=4.5778x10^{-36}$). Post-hoc tests in Table 1 detected periods of significant growth— 1.57-fold increase— between 2 and 24 weeks ($p=1.8467 x10^{-49}$), 2 to 12 weeks (2 to 4 weeks: 1.06-fold increase, $p=4.9x10^{-5}$; 4 to 8 weeks: 1.29-fold increase, $p=8.3672x10^{-30}$; 8 to 12 weeks: 1.03-fold increase, $p=1.38x10^{-4}$), and 16 to 20 weeks (1.11-fold increase, $p=6.1258x10^{-13}$), with periods of growth plateaus between 12 to 16 weeks, and 20 to 24 weeks.

Dorsal Attention Network Volumes

Lateral Intraparietal Area (LIP) Volume

There was a significant effect of AGE ($F_{(6,88.210)}=290.734$; $p=7.3172x10^{-56}$), HEMISPHERE ($F_{(1,254.865)}= 39.347$; $p = 1.5116x10^{-9}$), and an AGE x HEMISPHERE interaction effect ($F_{(6,88.210)}=5.613$; $p=5.70x10^{-5}$) on LIP volumes (Figure 5). The volumetric changes of LIP appeared to be different by hemisphere, with the left hemisphere growing more rapidly than

the right between 2 and 24 weeks, particularly from 4 to 8 weeks and 16 to 20 weeks (Figure 5A, 5B). Controlling for subject ICV as a covariate in the LMM model still resulted in significant effect of AGE on LIP volume ($F_{(6,36.759)}$=704.687; p=2.2026x10^{-36}). Post-hoc tests identified significant periods of growth— 1.63-fold increase; Table 1— between 2 and 24 weeks (p=3.9359 x10^{-53}), and between 2 and 20 weeks (2 to 4 weeks: 1.05-fold increase, p=0.038; 4 to 8 weeks: 1.23-fold increase, p=1.4969x10^{-19}; 8 to 12 weeks: 1.05-fold increase, p=1.4603x10^{-10}; 12 to 16 weeks: 1.03-fold increase, p=2.0x10^{-6}; 16 to 20 weeks: 1.17-fold increase, p=2.0738x10^{-17}), followed by a growth plateau from 20 to 24 weeks.

Frontal Eye Field (FEF) Volume

There was a significant effect of AGE ($F_{(6,77.691)}$=65.889; p=1.9238x10^{-28}), HEMISPHERE ($F_{(1,275.061)}$=65.721; p=1.7216x10^{-14}), but no AGE x HEMISPHERE interaction effect ($F_{(6,77.691)}$=0.100; p=0.996) on FEF volumes (Figure 6). Adding ICV as a covariate in the LMM model still resulted in significant effect of AGE ($F_{(6,46.369)}$=227.439; p=1.165x10^{-32}). Post-hoc tests revealed significant growth periods —1.47-fold increase; Table 1— between 2 and 24 weeks (p=1.1436 x10^{-42}), 2 and 8 weeks (2 to 4 weeks: 1.07-fold increase, p=9.3x10^{-5}; 4 to 8 weeks: 1.25-fold increase, p=4.872x10^{-24}), and 16 to 20 weeks (1.08-fold increase, p=1.4808x10^{-8}), with growth plateaus between 8 and 16 weeks and from 20 to 24 weeks.

Ventral Attention Network Volumes

Temporoparietal Junction (TPJ) Volume

There was a significant effect of AGE ($F_{(6,89.654)}$=15.942; p=2.182x10^{-12}), but not a HEMISPHERE ($F_{(1,329.635)}$=0.428; p=0.514) nor an AGE x HEMISPHERE interaction effect ($F_{(6,89.654)}$=1.099;

p=0.369) on TPJ volumes (Figure 7). Adding ICV as a covariate in the LMM model still resulted in significant effect of AGE on TPJ volume ($F_{(6,33.548)}$=56.163; p=4.4356x10^{-16}). Post-hoc tests detected significant periods of growth— 1.24-fold increase; Table 1— between 2 and 24 weeks (p=1.4045 x10^{-20}), 2 to 4 weeks (1.10-fold increase, p=3.0x10^{-6}) and 8 to 12 weeks (1.07-fold increase, p=4.2494x10^{-7}), with growth plateaus between 4 to 8 weeks, and 12 to 24 weeks.

Ventrolateral Prefrontal Cortex (vlPFC) Volume

There was a significant effect of AGE ($F_{(6,84.155)}$=74.080; p=1.7768x10^{-31}), and an effect of HEMISPHERE ($F_{(1,279.158)}$=131.906; p=2.9149x10^{-25}), but no AGE x HEMISPHERE interaction effect ($F_{(6,84.155)}$=0.880; p=0.514) on vlPFC volume (Figure 8). Controlling for subject ICV as a covariate in the LMM model still resulted in significant effect of AGE on vlPFC volume ($F_{(6,43.941)}$=266.219; p=7.461x10^{-33}). Post-hoc tests revealed significant growth periods —1.44-fold increase; Table 1— from 2 to 24 weeks (p=7.1126 x10^{-36}) and between 2 and 8 weeks (2 to 4 weeks: 1.06-fold increase, p=0.004; 4 to 8 weeks: 1.24-fold increase, p=1.873x10^{-21}). There was a period of slight decrease in volume from 8 to 16 weeks (8 to 12 weeks: 0.97-fold decrease, p=0.044; 12 to 16 weeks: 0.95-fold decrease, p=0.013), followed by another period of growth from 16 to 20 weeks: 1.17-fold increase, p=1.4331x10^{-15}), and a growth plateau from 20 to 24 weeks.

Superior Temporal Sulcus Area (STS) Volumes

Temporal Parietooccipital Area (TPOc) Volume

There was a significant effect of AGE ($F_{(6,95.748)}$=116.193; p=1.0568x10^{-41}), but not an effect of HEMISPHERE ($F_{(1,248.834)}$=0.758; p=0.385). However, there was an AGE x HEMISPHERE interaction effect ($F_{(6,95.748)}$=3.850; p=0.002) on TPOc volume (Figure 9). The volumetric changes of TPOc

appeared to be different by hemisphere, with the right hemisphere growing more rapidly than the left from 4 to 8 weeks (Figure 9A, 9B). Controlling for subject ICV as a covariate in the LMM model still resulted in a significant effect of AGE on TPOc volume ($F_{(6,36.623)}$=192.308; $p=3.8048x10^{-26}$). Post-hoc tests showed periods of significant growth —1.74-fold increase; Table 1— from 2 to 24 weeks ($p=2.9943\ x10^{-44}$) and between 4 and 20 weeks (4 to 8 weeks: 1.46-fold increase, $p=1.9325x10^{-28}$; 8 to 12 weeks: 1.03-fold increase, $p=2.92x10^{-4}$; 12 to 16 weeks: 1.01-fold increase, p=0.023; 16 to 20 weeks: 1.08-fold increase, $p=8.9122x10^{-7}$), with growth plateaus between 2 to 4 weeks and 20 to 24 weeks.

Area PG Associated Region of the Superior Temporal Sulcus (PGa) Volume

There was a significant effect of AGE ($F_{(6,105.397)}$=157.552; $p=2.814x10^{-50}$), HEMISPHERE ($F_{(1,261.592)}$=4.773; p=0.030) and an AGE x HEMISPHERE interaction effect ($F_{(6,105.397)}$=3.391; p=0.004) on PGa volumes (Figure 10). The volumetric changes of PGa appeared to be different by hemisphere, with the left hemisphere growing more rapidly than the right from 4 to 8 weeks and decreases more rapidly than the right from 16 to 20 weeks, with both hemispheres close to equal by 24 weeks (Figure 10A, 10B). Adding ICV as a covariate in the LMM model still resulted in significant effect of AGE on PGa volume ($F_{(6,36.623)}$=192.308; $p=3.8048x10^{-26}$). Post-hoc tests identified periods of significant growth— 1.57-fold increase; Table 1) from 2 to 24 weeks ($p=7.485\ x10^{-25}$) and from 4 to 8 weeks (1.56-fold increase, $p=5.3917x10^{-23}$), with growth plateaus from 2 to 4 weeks, 8 to 16 weeks, and 20 to 24 weeks. Interestingly, there was also a significant decrease in volume from 16 to 20 weeks (0.92-fold decrease, $p=7.0x10^{-6}$).

Behavioral Results

Infant Social Behavioral Observations (OBS)

Infant Play Behaviors: Time spent in "Solitary Play" increased with AGE ($F_{(5,25.714)}$=10.792; $p=1.10x10^{-5}$; Figure 11A). Post-hoc tests revealed significant increases in proportion of time spent in "Solitary Play" from 2 to 24 weeks (p=0.002), with the sharpest increases during the first 12 weeks (2 to 12 weeks: p=0.001; 4 to 12 weeks: p=0.032). There was also a significant effect of AGE ($F_{(5,14.695)}$=10.802; $p=1.66x10^{-4}$; Figure 11B) on "Social Play" behavior. Post-hoc tests also revealed significant increases in proportion of time spent in "Social Play Composite" between 2 and 24 weeks (p=0.015), but particularly during the first 12 weeks (2 to 8 weeks: p=0.008; 2 to 12 weeks: p=0.003; 4 to 12 weeks: p=0.015; 6 to 12 weeks: p=0.019).

Infant Affiliative/Prosocial Behaviors: There was no AGE effect ($F_{(5,19.899)}$=1.061; p=0.411; Figure 12A) on the proportion of time an infant spent in "Proximity" to another animal. There was a significant effect of AGE ($F_{(5,18.097)}$=22.438; $p=3.5569x10^{-7}$; Figure 12B) on the time an infant spent in "Contact"; post-hoc tests showed significant decreases in "Contact" frequency from 2 to 6 weeks (p=0.004), 4 to 12 weeks (p=0.004), 6 to 12 weeks (p=0.046), and 8 to 24 weeks (p=0.003). The frequency rate of "Leave Beyond", on the other hand, increased with AGE ($F_{(5,15.337)}$=16.922; $p=9.0x10^{-6}$; Figure 12C). Post-hoc tests revealed significant increases from 2 to 8 weeks ($p=2.3x10^{-4}$), 4 to 8 weeks (p=0.013), and 2 to 12 weeks ($4.0x10^{-5}$). The duration of time spent "Following" other animals also increased with AGE ($F_{(5,16.598)}$=12.047; $p=4.8x10^{-5}$; Figure 12D). Post-hoc tests uncovered a significant increase from 2 to 8 weeks (p=0.008) for this behavior.

Neither the frequency rates of "Eye Gaze" ($F_{(5,22.161)}$=1.296; p=0.301; Figure 13A) nor "Touch" showed significant effects of AGE ($F_{(5,20.060)}$=0.272; p=0.923; Figure 13B).

Juvenile Macaque Social Responsiveness Scale (jmSRS)

There was a significant AGE effect ($F_{(1,9)}$=5.867; p=0.038), with an increase in "Plays appropriately with peers" scores from 12 to 24 weeks of age (see Figure 14A; Table 3). No AGE effect was detected on "Stares or gazes off into space" (F(1,9)=0.000; p=1.000; Figure 14B; Table 3).

Schneider Neonatal Assessment for Primates (SNAP)

Visual Orientation (RLUD): There was no significant effect of AGE ($F_{(2.105,18.948)}$=0.110; p=0.905; Figure 15A).

Visual Follow (HV): There was no change in Visual Follow scores with AGE ($F_{(2.114,14.795)}$=0.544; p=0.601; Figure 15B).

Visual Attention: There was no significant change in visual Attention scores with AGE ($F_{(1.190,5.951)}$=2.455; p=0.169; Figure 15C).

Eye-Tracking

Eye Percent Fixation: There was no significant effect of AGE ($F_{(7,26.108)}$=2.270; p=0.060) on the time an infant spent fixating on eyes.

Object Percent Fixation: There was a significant effect of AGE ($F_{(7,31.951)}$=2.867; p=0.019) on the time infants spent fixating on objects or the background; however, post-hoc tests did not detect any significant changes between ages.

Discussion

The overall goal of this project was to examine early developmental changes in brain social visual attention networks in relation to social visual attention behaviors of relevance for ASD. The findings can lead us to identify early neural markers of atypical social attention in a rhesus macaque model. This study used MRI to map structural neural developmental trajectories of brain ROIs throughout the first 24 weeks of infant macaques' life, which is equivalent to the first 24 months of life in humans. We found significant age-related volumetric growth from 2-24 weeks in social visual attention networks that followed region-specific developmental trajectories. Thus, while the primary (V1) and extrastriate (V3) visual cortical areas showed significant volume increases in the first 12 weeks— though with small fold increases—, regions in the DAN— LIP, in particular—, showed drastic and more continuous growth through 20 weeks; those in the VAN (TPJ, vlPFC) showed more blunted and earlier growth, during the first 4 or 8 postnatal weeks. On the other hand, regions in the STS (TPOc, PGa) showed very fast and drastic volume increases from 4 to 8 weeks, with slow growth afterwards. Using complementary measures of social and visual attention behavioral development in a subgroup of the same subjects, we found increased play and prosocial behaviors in parallel to reduced contact with the mother as the infants matured— particularly in the first 12 weeks—, as well as increased scores from 12-24 weeks in the jmSRS item "Plays appropriately with peers", which

indicates improvement in infants' social competency at the later ages. Although no age effects were detected in the visual orienting/following/attention measures, the animals showed increased fixation toward objects in eye-tracking studies as they got older. Our findings suggest that during the first 24 weeks of life, and particularly during the first 8-12 weeks brain regions associated with social visual attention undergo rapid and robust structural changes that parallel important social behavior milestones (increased play and independence from mom) in infant macaques. The neural changes likely to support the infant's adjustment to independence and refined attention to relevant social visual cues in a naturalistic, highly social environment. Understanding how early social visual attention and underlying brain networks develop in a nonhuman primate model can help map the neural origins of brain-behavior pathogenesis of human neurodevelopmental social divergences, such as those in ASD.

The first goal of this study was to examine longitudinally the development of visual attention brain networks and associated regions in infant rhesus macaques as they mature, with a focus on the development of areas involved in visual attention to social stimuli. Both the dorsal (DAN) and ventral (VAN) attention networks (and the STS) interact with one another and receive sensory information from the visual cortex in the human (Corbetta et al., 2008; Corbetta and Shulman, 2002) and macaque brain (Bogadhi et al., 2018; Ramezanpour and Thier, 2020; Sapountzis et al., 2018), and the macaque ROIs selected in the present study are critical components of these attention networks. Those ROIs included visual cortical areas V1 and V3, DAN areas LIP and FEF, VAN areas TPJ and vlPFC, and STS areas TPOc and PGa. The structural development of these ROIs was also analyzed in relation to the overall brain growth— measured as ICV— which was included as a covariate in the statistical models. Regional brain

growth trajectories are similar across humans and macaques, despite the approximately 4-fold faster maturation of the latter, including timing of ROI cortical volumetric changes (Scott et al., 2016). The similarities in social and brain development across these species is one of the reasons supporting the translational use of a macaque brain model to understand typical and atypical human neurodevelopment.

Neurodevelopmental changes using MRI

This study found rapid ICV growth across the first 12 weeks of life, at which point it begins to level off. In a study by Kovacs-Balint et al. (2021), ICV was shown to significantly increase from 2 to 20 weeks of age, leveling off thereafter, which is consistent with the results of this study with the exception that the plateau begins earlier in this study. These results are also consistent with the findings of other studies that examined early neurodevelopmental trajectories of rhesus macaques, reporting extensive total brain growth early in life with the most rapid growth in total brain volume (TBV; calculated as GM + WM) from 1 week to 1 month of age, followed by a slower significant growth period up to 3 years (Malkova et al., 2006; Scott et al., 2016). An important methodological detail of our study was the use of ICV instead of TBV as a metric of whole brain growth that accounts for CSF in addition to WM and GM. The growth trajectory of ICV observed here, though, was comparable to that of TBV reported in other macaque studies (Malkova et al., 2006; Scott et al., 2016), which is reasonable as ICV and TBV are correlated and both considered appropriate measures of whole brain volume (Mills and Tamnes, 2014). In human infants, there is an early critical period for whole brain growth during the first year of life, which is characterized by rapid cortical GM volume increases (Gilmore et

al., 2012; Knickmeyer et al., 2008). Bigger brain volumes have been well documented in children with ASD in comparison to TD children, with a cortical surface overexpansion from 6 to 12 months of age followed by overall brain overgrowth until 24 months, as well as excessive CSF in the subarachnoid space from 6 to 24 months of age (Cárdenas-de-la-Parra et al., 2021; Courchesne et al., 2003; Hazlett et al., 2017; Shen et al., 2013). The similarities between infant human and macaque brain developmental trajectories highlight the translational value of the NHP primate model. However, an important distinction between human and macaque infant brains, is the faster rate of human brain volume increases (approximately 100% growth over the first year of life) than in macaques (50% growth in an equivalent age span: during the first 3 months of life; Scott et al. (2016)). There are additionally many early developmental changes occurring in gray matter.

GM developmental changes are thought to be due to changes in dendrites, axons and synapses between them (Lewis, 2000). Synaptogenesis— or new synapse formation— occurs in abundance very early in infancy concurrently with dendritic and axonal growth, with high levels of synaptic density followed by a phase of net synapse elimination— or developmental pruning— occurring during childhood in both humans and macaques (Huttenlocher and Dabholkar, 1997; Rakic et al., 1986). Similar to synaptic pruning, both dendritic and axonal pruning facilitate removal of supernumerary neuronal connections during neural remodeling in early development (Riccomagno and Kolodkin, 2015), and neuronal cell death also contributes to this remodeling (Dekkers et al., 2013; Hutchins and Barger, 1998; Oppenheim, 1991). Cortical dendritic spine density in humans has been shown to be much more abundant in early childhood compared to adulthood, with elimination of exuberant spines not functionally

connected with other neurons around the same time as synaptic pruning via mechanisms likely relying on an interaction between learning-based environmental input and behavioral output (Gipson and Olive, 2017). In addition, axonal pruning is tightly associated with synapse elimination (Riccomagno and Kolodkin, 2015), and it has been suggested to have an important role in creating connectional diversity and specificity (O'Leary, 1992). Early exuberance is followed by retraction of axonal connections to develop precise functional connectivity observed in adulthood (Luo and O'Leary, 2005). Similarly, there is originally an overabundance of neurons generated, and during early development cellular death occurs to eliminate excess neurons; the initial overabundance of neurons is likely due to a mechanism ensuring distal targets will be adequately innervated during development (Dekkers et al., 2013; Oppenheim, 1991). Synaptogenesis and dendritic and axonal growth contribute to the increasing GM volume, while synaptic pruning, axon retraction and cellular death contribute to decrease in GM volume.

Both visual cortical areas V1 and V3 showed age-related volumetric growth from 2-24 weeks, particularly in the first 12 weeks. In V1 the most rapid growth took place from 4 to 8 weeks (1.20-fold increase), peaking at 12 weeks, followed by a plateau until 20 weeks and then declining from 20 to 24 weeks. We found an overall 1.32-fold increase in volume from 2 to 24 weeks, which is one of the smallest overall volumetric increases of all ROIs. This is consistent with results from another macaque MRI study reporting a rapid growth in the occipital lobe until 13 weeks of age, at which point it had reached its maximal volume, and this peak was followed by a continuous decline in volume through 5 years of age (Scott et al., 2016). Scott et al. (2016) reported that the occipital lobe was closer to its maximal volume at birth than any

other neocortical area in their study. Kovacs-Balint et al. (2021) also reported the smallest volumetric growth of all cortical lobes during the first 24 postnatal weeks in occipital cortex, with a 1.2-fold increases in the first 12 weeks , followed by a plateau until 16 weeks and a small volumetric decrease from 16 to 24 weeks (0.97-fold change), consistent with the developmental trajectory of V1 in our study. Postnatal synaptic density undergoes dynamic changes in the macaque primary visual cortex with rapid synaptogenesis increases through 2 months of age in the macaque, followed by a pronounced decline in synaptic density (e.g., via pruning) through 2 years, which likely contribute to these observed volumetric changes (Bourgeois and Rakic, 1993; Scott et al., 2016). It has also been reported that development of V1 in macaques is minimal after 8 weeks of age, as the maturation of the region is near adult-like by this age, suggesting that influences on visual development lie downstream from V1— such as in V3— (Kiorpes, 2015). V1 functional differentiation emerges early: in a multichannel near-infrared spectroscopy (NIRS) study measuring brain activation Watanabe et al. (2010) examined the functional development of the human cortex with regard to visual perception; their findings suggest that broad regions across cortical lobes are activated during visual perception in 2 month-old infants (equivalent to 2 weeks in macaques), followed by a functional differentiation of sensory cortical regions (including V1) emerging between 2-3 months. The V1 is the first cortical structure in the visual stream, integrating information from the eyes at the earliest stage of cortical vision (Samonds and Priebe, 2020). The developmental trajectory we describe in this study may be functionally relevant for explaining the maturation of the visual cortex responsible for the earliest stage of cortical vision. The rapid growth from 2 to 12 weeks followed by stagnation and a slight decline around 6 months suggests that this

region undergoes early and rapid maturation to promote early development of visual skills, such as visual object discrimination which emerges around 2 months of age in macaques (Goldman-Rakic, 1987; Rakic et al., 1986).

In another occipital region, V3, we found an overall 1.57-fold increase in volume from 2 to 24 weeks, which was greater than in V1 (1.32-fold increase). The most rapid growth was detected from 4 to 8 weeks (1.29-fold increase), peaking at 12 weeks, followed by a volume plateau from 12 to 16 weeks, another volumetric increase (1.11-fold) until 20 weeks and finally another plateau from 20-24 weeks. These findings are consistent with other reports of infant macaque occipital lobe growth (Scott et al., 2016); Kovacs-Balint et al. (2021)) with the exception of some differences between 16 to 24 weeks. It was also reported in a resting state fMRI study— that there is strong functional connectivity (FC) between visual areas V1 and V3 present early after birth (at 2 weeks of age), followed by a slight increase after 8 weeks of age (Kovacs-Balint et al., 2019). There was also lateralized hemispheric growth observed in V3, with the left hemisphere growing more rapidly than the right, particularly from 4 to 8 weeks. It has been reported in humans that the left occipital lobe extends farther back, compared to the right, reflecting greater volume in the left occipital lobe (Balzeau et al., 2012; Neubauer et al., 2020), and men on average have a more structurally and functionally lateralized brain than women (Shaywitz et al., 1995; Toga and Thompson, 2003). Interestingly, there is evidence of decreased lateralization in ASD (Postema et al., 2019). Lateralization is important to investigate as functional inferences can be made from morphological variations, with demonstration that there is a variable relationship between sulcal organization and cytoarchitectural boundaries(Fischl et al., 2008; Gómez-Robles et al., 2013); brain asymmetries are not

necessarily genetically determined and could additionally be resultant of lateralized sensory stimulation (Barnéoud and Van der Loos, 1993; Toga and Thompson, 2003), indicating that early experiences may influence laterality. The observed V3 cortical lateralization may indicate underlying functional laterality as certain higher cortical abilities are known to be unequally distributed between hemispheres with the specific processing localized to one hemisphere (Pulvermüller and Mohr, 1996), so more complex visual processing may be somewhat lateralized to the left. The developmental trajectory of V3 seems to parallel the continual increase of occipital lobe volume observed in Kovacs-Balint et al. (2021), as well as the continued increase in V3 volume in our study. Area V1 projects to V3 (Van Essen et al., 1986) and maturation of this pathway occurs early to support local feature detection. Area V3 is necessary for visual perception in general, as well as visual consciousness (Salminen-Vaparanta et al., 2019). The volumetric developmental trajectory we describe in this study may be functionally relevant for both visual processing and visual consciousness involved in social visual attention. Area V3 shows a rapid growth that coincides with development in V1, though V3 undergoes continuous development through 24 weeks while V1 appears to stagnate in growth earlier. These findings are consistent with reports that metabolic activity in area V1 reaches adult levels by 3 months of age whereas that of area V3 did not reach adult even by 6 months of age (Distler et al., 1996). Postnatal development of metabolic activity support neural physiological processes, and metabolism is reflective of neuronal activity, thereby providing a connection between brain structure and function (Distler et al., 1996; Watts et al., 2018). The slower increase in metabolic activity in V3 compared to V1 provides supportation of a slower functional development of the higher order visual cortical area. The more prolonged

development of V3 as compared to V1 is likely because V3 is not as involved in the initial stage of visual processing and continues to develop throughout infancy to support more complex visual processes.

Overt (goal-driven) attention is supported by the DAN, which includes the LIP and FEF (Corbetta et al., 2008; Farrant and Uddin, 2016) studied here. Regions in the DAN— LIP, in particular—, showed drastic and more continuous growth through 20 weeks than V1 or V3. LIP volume had an overall 1.63-fold increase in size from 2 to 24 weeks. Volume increased continuously until 20 weeks of age, and the growth plateaued from 20 to 24 weeks. The most rapid growth occurred between 4 and 8 weeks (1.23-fold increase). Scott et al. (2016) found that the parietal lobe increased until 9-10 months of age in the macaque, followed by little to no increase after; Kovacs-Balint et al. (2021) found that the peak of volumetric increase to be earlier, at 16 weeks, at which point the growth leveled off. The results of this study more closely follow those of Kovacs-Balint et al. (2021), only with a later peak in volume at 20 weeks instead of 16. There was also lateralized hemispheric growth observed in LIP, with the left hemisphere growing more rapidly than the right during the first 6 months of life, particularly from 4 to 8 weeks and again from 16 to 20 weeks. The parietal cortex has lateralized function, with the right hemisphere implicated in visuospatial attention redirection and the left in motor attention redirection and temporal orienting (Corbetta and Shulman, 2002; Davranche et al., 2011; Rushworth et al., 2003), so the observed leftward structural lateralization may be supportive of developing motor attention redirection and temporal orienting. To further investigate the function of LIP in reference to its association with other regions, Kovacs-Balint et al. (2019) reported that FC between V3 and LIP progressively decreased between 4 and 12 weeks of age,

reaching FC levels observed in adults by 3 months of age; this finding suggests maturation of visuospatial abilities in monkeys is slow, taking place around 10-12 months in humans (Braddick and Atkinson, 2011). Metabolic activity in LIP increases until 3-6 months of age (Distler et al., 1996). This indicates that LIP is still functionally maturing during that period, consistent with the developmental trajectory observed in a previous FC connectivity study (Kovacs-Balint et al., 2019) and the current structural study. Macaque LIP is homologous to human LIP (hLIP), which controls spatial attention (Corbetta and Shulman, 2002). Studies on macaque LIP suggest that the area has a role in a saliency map, which may be modulated by bottom-up cues (Bisley and Goldberg, 2010; Kraemer et al., 2020); bottom-up cues rely on local level features such as contrast, color, motion, orientation (Itti et al., 1998; Patel et al., 2014; Rosenholtz, 1999) as opposed to top-down cues that rely on global features such as the contextual information of an object or scene, which can be defined by statistical probability distribution of it (Blaser et al., 1999; Frintrop et al., 2005; Navalpakkam and Itti, 2005; Oliva and Torralba, 2007; Patel et al., 2014). Ramezanpour and Their (2020) have found that LIP neurons show activity related to spatial shifts of attention induced by gaze cues, suggesting that LIP may draw on input from the "gaze-following patch" (GFP)— located in the immediate locality of the face patch system in both macaques and humans (Marciniak et al., 2014; Marquardt et al., 2017)— providing information on spatial choices to inform the spatial saliency map and reallocate spatial attention. Human GFP activity has been linked to processing gaze direction in others using fMRI in joint attention tasks (Kraemer et al., 2020). Activity in hLIP reflected processing of total information from a scene in a contextual gaze following task, to pinpoint and shift the observer's attention to the target objects based on integration of another's gaze direction. The

hLIP integrates streams of information from the GFP (directional information) and the inferior frontal junction (IFJ; further analysis of scene details when gaze direction is insufficient information) to shift attention to distinct spatial locations (Kraemer et al., 2020). Area LIP is crucial for visual searching (Liu et al., 2010; Wardak et al., 2002) and also has roles in visual-motor transformation (Bisley and Goldberg, 2010), with LIP proposed to provide a salience map that is interpreted by the oculomotor system as a saccade goal, when appropriate, and providing the visual system with a locus of attention (Bisley and Goldberg, 2003; Goldberg et al., 2006). The volumetric developmental trajectory we describe in this study may be functionally relevant for maturation of salience mapping and shifting attention to salient social visual cues throughout early infancy. The developmental trajectory of LIP seems to parallel that of V3, from which LIP receives direct projections; area LIP may develop alongside V3 as it develops to support more complex visual processes and salience mapping to better inform attention to salient social visual stimuli.

FEF volume showed a big increase (1.47-fold) from 2 to 24 weeks. Growth was significant from 2 to 12 weeks, with the most rapid volumetric increase occurring between 2 and 8 weeks—from 2 to 4 weeks (1.07-fold increase) and 4 to 8 weeks (1.25-fold increase)—, followed by a plateau from 12 to 16 weeks, a further increase from 16 to 20 weeks (1.08-fold increase), and another plateau from 20 to 24 weeks. Scott et al. (2016) found that enlargement trajectory in the macaque brain differed across cortical regions, with the frontal lobe— containing the FEF—showing one of the greatest and most protracted growth of all cortical regions. The frontal lobe had rapid growth in the first 3 months of life, slowing until reaching its peak by 3 years and slightly decreasing in size by 5 years (Scott et al., 2016). In a recent study, Kovacs-Balint et al.

(2021) also showed that the frontal cortex had a large increase (1.36-fold) from 2 to 24 weeks, with the most rapid volumetric increases between 2 and 8 weeks— from 2 to 4 weeks (1.1-fold increase) and 4 to 8 weeks (1.1-fold increase)— which is consistent with our study. The FEF is responsible for controlling saccadic eye movement (Petrides and Pandya, 1994; Sapountzis et al., 2018), and shows a strong functional association with covert spatial attention, suggesting that FEF spatial signals directly influence visual processing during identification of stimuli by the visual system (Monosov and Thompson, 2009). Additionally, the FEF is connected with the PFC— including the vlPFC— in macaques (Petrides and Pandya, 2007; Yeterian et al., 2012), which is not only involved in attention but also associated with motivation circuits in humans (Cardinal et al., 2002); the PFC may provide signaling to the FEF to attend to important social visual cues— via signals from the vlPFC— and project signals from the motivation circuits for movement of the eyes (Syal and Finlay, 2011). In humans, infants begin to fixate and follow objects in their visual field around 3 months of age— approximately equivalent to 3 weeks in macaques— (Nye, 2014), and visual following and orientation behaviors in macaques has been reported to emerge and rapidly increase across the first month of life (Schneider and Suomi, 1992). These results indicate that rapid growth of the FEF in the first 8 weeks of life is during a critical period for refinement of social skills supporting social visual attention and visual searching for salient stimuli, through saccades, that are early emerging in both humans and macaques (Amso and Johnson, 2008; Frank et al., 2014; Kwon et al., 2016; Wang et al., 2020)

Covert, or stimulus-driven attention, is supported by the VAN, which includes the TPJ and vlPFC (Corbetta et al., 2008; Farrant and Uddin, 2016). TPJ volume had an overall 1.24-fold increase from 2 to 24 weeks, with the most rapid growth occurring between 2 and 4 weeks (1.10-fold

increase), followed by a plateau from 4-8 weeks, another period of growth from 8-12 weeks and growth stagnation thereafter. The TPJ volumetric changes were blunted (small fold increases) in comparison to other ROIs, but there were still significant periods of growth. Scott et al. (2016) reported that the temporal lobe (in addition to frontal lobe) showed the greatest and most protracted growth of cortical regions, though temporal lobes were analyzed as a consolidation of all subregions, and the TPJ is a small region within the lobe. The temporal lobe had a rapid increase in volume during the first 3 months, followed by a slower pace until near maximal volume was achieved by 39 weeks. Kovacs-Balint et al. (2021) reported continuous growth in temporal visual cortex volume from 2 to 16 weeks, followed by a plateau until 20 weeks when growth resumed. The volumetric changes of TPJ reported here are consistent with the earlier trajectory of the temporal visual cortex (during the first 12 weeks), but the plateau in growth began earlier and was sustained throughout 24 weeks of age; the overall growth in the TPJ was also blunted in comparison to growth in the entire temporal visual cortex. Again, the TPJ is a small region in the temporal lobe located in the fundus of the STS in macaques, which may contribute to some of the differences with previous reports. The developmental trajectory of the TPJ is consistent with reports of synaptic proliferation and dendritic spine increase during the first 12 weeks of life (Rakic et al., 1986). The macaque homolog of human TPJ in this study was functionally defined as in Bogadhi et al. (2018), including the TPJa area by Mars et al. (2012a) plus the anterior FST(aFST)/IPa defined by Paxinos et al. (2000), which are regions in the fundus of the STS. In humans, the TPJ is anatomically defined as the cortex at the intersection of the posterior end of the STS, inferior parietal lobule and lateral occipital cortex— the “temporoparietal junction” (Corbetta et al., 2008); and is important in retrieving

behaviorally relevant information about stimuli, such as visual salience, to reorient the focus of attention— particularly toward unexpected stimuli appearing at unattended locations outside the current focus of attention (Corbetta et al., 2000; Gazzaniga et al., 2018). The TPJ may also receive information about visual salience from salience maps provided by the DAN (Corbetta et al., 2000). There also appears to be a lateralized function in which the right TPJ (rTPJ) is implicated in theory of mind (ToM), in addition to reorienting attention (Corbetta et al., 2008; Mars et al., 2012b). The TPJ is activated when a behaviorally relevant stimulus is presented, and deactivated during activation of the dorsal network to suppress orienting of attention to potentially distracting stimuli (Corbetta et al., 2008). Additionally, damage to the TPJ in humans decreases the ability to detect and orient attention to novel stimuli, which is known as visuospatial neglect (Bartolomeo, 2013), showing that this region is necessary for detecting and orienting toward unattended stimuli in the environment. Similarly, Bogadhi et al. (2019) recently reported in macaques that reversible inactivation of the area they have previously described as homologous to human TPJ, aFST/IPa (Bogadhi et al., 2018), produced selective contralateral visual inattention as is seen in human neglect patients with TPJ damage, further supporting that this region in macaques has the same important role in deploying visuospatial attention to unattended stimuli. The volumetric developmental trajectory we describe in this study may be functionally relevant for assessing relevance of social visual stimuli unattended within a complex social environment early in life. The early rapid development and continued blunted growth of this area suggests that TPJ develops early in the infant macaque for detection of important social cues peripheral to their focus of attention, and important adaptive behavior.

The vlPFC had an overall 1.44-fold increase in volume from 2 to 24 weeks. Volume increased from 2 to 8 weeks— with the most rapid growth occurring between 4 and 8 weeks (1.24-fold increase—, followed by a period of slightly decreasing volume from 8 to 16 weeks, a significant growth period from 16 to 20 weeks, and a growth plateau from 20 to 24 weeks. As mentioned previously, frontal lobe has rapid growth in the first 3 months of life, slowing until reaching its peak by 3 years and slightly decreased in size by 5 years (Scott et al., 2016); Kovacs-Balint et al. (2021) also showed that the PFC continuously increased in volume across the first 24 weeks of life (1.32-fold increase), with the most rapid volumetric growth from 4 to 8 weeks (1.13-fold increase), which is consistent with what was observed in this study. Maturation of the PFC in humans is delayed, with a slower PFC growth during the first year of life (equivalent to the first 12 weeks in macaques), followed by a period of faster growth after 2 years of age (equivalent to 24 weeks in macaques), a growth spurt around 8 years of age, and continuous growth throughout adolescence (Gilmore et al., 2012; Kanemura et al., 2003). The PFC, overall, undergoes rapid synaptogenesis through the first 2 months of age— which may contribute to volumetric changes— and does not show net elimination of synapses until 3 years of age in the macaque (Bourgeois and Rakic, 1993). In humans, rapid synaptogenesis occurs during the first 2 postnatal years, and the first net synapse elimination does not occur until puberty, ending in mid-adolescence (Huttenlocher and Dabholkar, 1997). The difference between macaque and human developmental timelines may be due to differences between species milestones: macaques begin exploring their environment during weaning (2-3 months old; equivalent to 1 year in humans) (Hinde and Spencer-Booth, 1967), while humans do not become socially independent until preschool age (around 4 years). Therefore, earlier rapid growth in the

macaque PFC may play a role in their earlier transition to a complex social environment. The PFC is important for cognitive control, and it monitors the activities in other cortical and subcortical structures and coordinates the operations of multiple neural systems through top-down signaling (Funahashi and Andreau, 2013; Miller and Cohen, 2001). The vlPFC was investigated in this study because of its important role in both humans and macaques, involved in covert attention and associated with executive control, including response inhibition, selection of goal-appropriate responses, and social interaction analysis (Aron et al., 2004; Bogadhi et al., 2018; Corbetta et al., 2008; Sliwa and Freiwald, 2017). The results reported in this study indicate that the early rapid growth of vlPFC in the first 8 weeks allow rapid maturation of covert attention and executive functioning, which may allow development of typical social milestones around this time.

Areas within the STS that have been found to coactivate with attentional network areas during attention tasks and have important social roles include the TPOc and PGa (Bogadhi et al., 2018); both TPOc and PGa have also been suggested to represent “polymodal” zones within the STS (Seltzer and Pandya, 1989). There were also hemispheric differences observed in the development of both STS ROIs. It has been observed that macaques show a rightward asymmetry in the STS, with in the surface area greater in the right hemisphere (Bogart et al., 2012), and a human infant study found significant rightward asymmetry in one section of the STS (Glasel et al., 2011). The mechanisms underlying the asymmetry are unclear, but it is possible that selection for cognitive and motor functions associated with tool manufacturing and usage— as well as language— resulted in anatomical and functional asymmetry in the macaque, and the asymmetry in STS surface area may have developed as a consequence of

stronger lateralization in connectivity to cortical regions in one hemisphere over another (Bogart et al., 2012).

TPOc volume had a 1.74-fold increase from 2 to 24 weeks, which was one of the greatest volumetric increases (fold increases) in comparison to other ROIs during the first 6 months of age. Volume increased rapidly from 4 to 20 weeks of age, with the most rapid growth occurring from 4 to 8 weeks (1.46-fold increase), followed by a growth plateau through 24 weeks. There was also lateralized hemispheric growth observed in TPOc, with the right hemisphere growing more rapidly than the left from 4 to 8 weeks. The STS shows rightward activation in tasks investigating the MNS (Aziz-Zadeh et al., 2006) and observing dynamic face stimuli (De Winter et al., 2015). Thus, the observed rightward structural lateralization of TPOc in this study may be supportive of covert recognition of faces and appropriate attention to facial cues for important social skills such as imitation and acquiring theory of mind during early development. The temporal lobe has been reported (in addition to frontal lobes) to have the greatest and most protracted growth of cortical regions, with rapid increase in volume during the first 3 months followed by a slower pace until near maximal volume by 39 weeks in the males (Scott et al., 2016). The developmental trajectory of TPOc was consistent with the temporal lobe growth reported by Kovacs-Balint et al. (2021) as continuous volumetric increase from 2 to 16 weeks, followed by a plateau until 20 weeks, when growth resumed. In humans, the TPOc is a mid-STS area responsible for facial recognition and is implicated in covert visual attention in the macaque (Bogadhi et al., 2018). The macaque TPOc has connections with the FEF (Cusick et al., 1995; Schall et al., 1995), which may support visual guidance of saccades by providing information about stimuli features— such as faces. The results reported in this study indicate

that early rapid growth, including a robust increase in volume from 4 to 8 weeks, supports early emerging attention to important features of social visual stimuli— such as faces— present throughout the infant's complex social environment.

The PGa is another mid-STS area located in the fundus adjacent to the TPO and expands to the upper bank of the sulcus (Seltzer and Pandya, 1978). This region has been implicated in covert visual attention in the macaque (Bogadhi et al., 2018). PGa volume increased 1.57-fold from 2 to 24 weeks. There was a very rapid growth period between 2 and 8 weeks (1.70-fold increase)— with a 1.56-fold increase from 4 to 8 weeks of age— followed by a growth plateau until 16 weeks. Interestingly, a significant 0.93-fold decrease in volume was observed between 16 and 20 weeks, followed by a plateau from 20 to 24 weeks. There was also lateralized hemispheric growth observed in PGa, with the right hemisphere growing more rapidly than the left from 4 to 8 weeks. Like the other STS area, the rightward lateralization may be supportive of covert attention to social visual stimuli processes lateralized in the right hemisphere. The developmental trajectory of the PGa was not consistent with reports in the macaque temporal lobe by Scott et al. (2016) or Kovacs-Balint et al. (2021). The volumetric decrease in the PGa from 16 to 20 weeks could be reflective of mechanisms such as neuronal cell death and rapid synaptic pruning with retraction of nonfunctional connections with other structures (Dekkers et al., 2013; Hutchins and Barger, 1998; Huttenlocher and Dabholkar, 1997; Luo and O'Leary, 2005; O'Leary, 1992; Rakic et al., 1986; Riccomagno and Kolodkin, 2015). Reorganization of synaptic circuits has been proposed underlie functional specialization of brain regions (Silbereis et al., 2016). The rapid growth of PGa from 4 to 8 weeks reported here could be important for early emerging social visual attention, coinciding with early developmental trajectories of other

ROIs associated with covert attention. These findings are also consistent with human studies in which covert attentional shifts have been proposed to occur around 4 months of age (Colombo, 2001; Richards, 2001; Richards, 2000), which corresponds to approximately 4 weeks in the macaque. Additionally, the decrease in volume from 16 to 20 weeks may be due to synaptic, dendritic, and axonal pruning producing further functional specialization of the PGa in supporting covert attention in an older infant that spends increasingly more time exploring the environment and is exposed to a greater amount of complex social visual stimuli and distractors.

All ROIs within the attention networks and associated areas demonstrated unique patterns of growth in comparison to one another (Table 2). All ROIs appeared to follow a pattern of exhibiting a period of rapid growth from 2 to 8-12 weeks, followed by either continued growth, a plateau, or a decrease in volume. These regions experience early growth spurts independent of the rest of the brain's growth during this time since the effect of ICV was controlled for by adding it as a covariate in the statistical models. One explanation for these periods of growth is that the attention network areas are growing rapidly at these timepoints to support species-typical social milestones. As these results are only reflective of GM increases, the proliferation of GM during early development should be considered. The GM consists of neuronal cell bodies, axon tracts, capillaries, and neuropil (Sigaard et al., 2016). Most neurogenesis is complete by birth, though continued postnatal synaptogenesis contributes greatly to increases in GM during early development (Budday et al., 2015). An overproduction of synapses and overall increase in dendritic arborization occurs in both macaque and human infants, which can explain rapid periods of GM growth, as previously mentioned. Similarly, later synaptic pruning

can lead to decrease in GM volume (Huttenlocher and Dabholkar, 1997). GM increases in volume during primate development, reaching a peak around puberty and experiencing a subsequent decline in volume due to synaptic pruning (Gogtay and Thompson, 2010). However, in our study, GM appears to peak by 24 weeks of age (equivalent to 2 years in humans), or even earlier than that. There may simply be a plateau in growth after the 24 weeks age point that is followed by more GM growth later— a trend which would more accurately reflect the growth trajectory observed in humans. There were also laterality effects in development of four ROIs (V3, LIP, TPOc, and PGa), which were the areas with the most robust growth across the first 6 months of age.

Development of Infant's Social Visual Behaviors

The second goal of this study was to examine developmental trajectories of social visual attention behaviors in infant macaques that are of relevance for human infants with ASD using multiple behavioral measures, while also identifying individual differences during the infant period up to 6 months of age. For this, we collected measures of: (1) infant social development based on focal observations of its interactions with the mother and other animals in the social group; (2) typical and atypical social responsiveness using the jmSRS— a translational rating scale widely used for ASD diagnosis in children-; (3) visual orientation, following and attention using the macaque SNAP – with rating scores of early neuromotor and sensory maturation-; and (4) visual attention to social vs nonsocial stimuli using eye-tracking methods.

"Solitary Play" increased with age, with the sharpest increase in the first 12 weeks. The "Social Play Composite" behaviors also increased with age, with sharp increases at 8 and again at 12

weeks of age and continuing to increase through 24 weeks. The latter findings are consistent with reports that social play (defined as “rough and tumble” and “approach-withdrawal” play behaviors) emerges between 7 and 12 weeks, and continues to increase until 6 months to peak at the end of the first year of life (Hinde and Spencer-Booth, 1967). Play behavior is conserved across human and NHPs and is crucial in the social development for both species. In macaques, nonsocial/solitary play emerges first (between 4-6 weeks in this study) and provides with the necessary exploration of the environment and practicing of motor skills for latter functions, while social play follows shortly after and helps facilitate social communication, group cohesion, dominance/submission interactions, and independence from the mother (Smith, 2012). Similarly to macaques, solitary play emerges first in humans, before or around 2 years of age (Naber et al., 2008; Parten, 1932; Yogman et al., 2018). Following solitary play, infants’ experiences continue to assist in development of social skills, beginning to notice others playing and play alongside them (parallel play) until transitioning to social play (associative play) around 3 to 4 years (Naber et al., 2008; Parten, 1932; Yogman et al., 2018). Our findings are consistent with those reports, with solitary play emerging earlier than social play. Play is very important in children for facilitation of strong parent-child and peer-peer bonding, social communication skills, and general social competence (Ginsburg, 2007; Gray, 2011; Nijhof et al., 2018). In ASD, common features of play behavior are much different than those of TD children, with a delayed emergence of play behavior, atypical social play, and preference of solitary play (Black et al., 1975; Naber et al., 2008; Ungerer and Sigman, 1981).

“Proximity” behavior (infant is within arm’s reach of another animal) did not change over time, which can be explained because while infants do spend increasingly less time in proximity with

their mother, they spend more time playing with peers, therefore in proximity to them, or with other monkeys in their family (Hinde and Spencer-Booth, 1967). “Contact” decreased with age, with sharp decreases from 2 to 6 weeks and again from 8 through 24 weeks. The decrease in “Contact” over time can also be explained because: 1) increasing independence from their mothers implies decreased body contact with them, and 2) salient social play behaviors that emerge around 8 weeks were not coded as “Contact”, despite some intense body-to-body contact. Consistent with the decrease in “Contact”, mainly driven by increased independence from the mother, exploration and play, there was an increase in “Leave Beyond” behavior over the first 6 months of age, which refers to moving further than arms-reach from its mother or another animal. Similarly, there was an increase in “Follow” behavior as infants gain independence and curiosity about their environment, with the behavior identified by the infant’s motion, attention, and gaze to another animal that they are trailing behind. “Eye Gaze” was an important behavior for our study and in the literature in relation to mother-infant macaques bonding, peaking around 4 weeks of age (Ferrari et al., 2009). It is an early-emerging behavior in human infants (Muschinski et al., 2016) that is impaired in ASD infants, showing low fixation to the eyes as compared to other regions of the face (Jones et al., 2008; Jones and Klin, 2013; Papagiannopoulou et al., 2014); the low fixation to eyes has been suggested to reflect insensitivity to the social salience of eyes and diminished social visual attention to this important social cue (Moriuchi et al., 2017). Although we did not detect changes in “Eye Gaze” with age, this could be explained because 1) the behavior remains consistent across early development as it decreases with the mother but increases with peers and juveniles, and 2) this behavior was difficult to code from the distance by coders. Similarly, “Touch” did not change

with age. “Touch” requires less of the body to contact another animal (such as laying their hand on another’s back) rather than in “Social Play Composite” and “Contact”, where the infant has a much larger portion of its body touching another animal.

The jmSRS was the second method used to study social visual attention development in this project, looking at three specific items. The SRS is a screening tool for ASD in children, assessing typical and atypical social behaviors that covary with ASD symptom severity (Constantino et al., 2003; Constantino and Gruber, 2012). The SRS was adapted for use in chimpanzees (Marrus et al., 2011), which was further adapted for use in adult macaques (Feczko et al., 2016) to finally be adapted and validated for juvenile macaques by our group (Kovacs Balint et al., 2020). The jmSRS Results indicated that only “Plays Appropriately with Peers” changed over time, with scores significantly higher at the 6 months age than 3 months, indicating improvement of social play skills during early development and suggesting that our subjects, selected from a healthy population, displayed typical social interactions and responsiveness during early development. These results are consistent with reports that social play emerges and continues to increase between 7 and 12 weeks until 6 months, peaking at the end of the first year of life (Hinde and Spencer-Booth, 1967). Playing appropriately with peers is critical for proper social development, as it has been characterized as the most sophisticated manifestation of communication (Bekoff and Allen, 2011; Burghardt, 2005) , preparing juvenile macaques for future social experiences (Burghardt, 2005). In rhesus macaques, low-social (LS) animals, exhibit lower social motivation and poorer social skills than highly social (HS) macaques, and also show differential processing of social information (Sclafani et al., 2016). The authors found that LS monkeys lacked the ability to recognize novel (unfamiliar) conspecific facial stimuli from

familiar in a visual paired-comparison habituation paradigm relying on differential visual attention. Because selective attention to novel stimuli requires accurate processing of salient information, atypical visual attention could lead to the inability to recognize novel from familiar stimuli, as variation in face recognition is associated with variation in attentional bias. These findings are similar to reports of impaired face recognition skills in children with ASD, and it is likely this impairment in LS monkeys originates from a failure in attending to face stimuli, which are highly salient social visual stimuli; atypical social information processing could be detected within the first months of life, with differential patterns of social behavior between LS and HS macaques evident by 3 to 4 months of age (Sclafani et al., 2016). The study found that important early social visual information processing abilities were strongly predictive of subsequent classification as LS or HS, suggesting these abilities are requirements for optimal social development and functioning (Sclafani et al., 2016). Typical development of social play with peers is reliant on typical development of social visual attention which provides efficient attention to social visual cues. The other atypical social visual behavior analyzed here— "Stares or gazes off into space"— did not show changes with age. The lack of developmental changes in this atypical behavior seems to be related to the low scores of our animals, which were selected from typically developing populations, more likely to exhibit typical social functioning and would not be expected to change scores with age. Lastly, the original mSRS (Feczko et al., 2016) found differences in scores influenced by social dominance of the monkeys. Our study consisted mainly of mid-ranking infants, with a very small subset of unequally distributed low- and high-ranking infants; so, there was not a large enough sample size to include social rank in the statistical analyses.

The SNAP was another method used to examine the infants' maturation in visual orienting, following and attention span during the first 4 weeks of life. The SNAP was developed by Schneider and Suomi (1992), adapted from the INAS (Brazelton, 1973), to investigate maturation in neuromotor and sensory functions in macaques. They found that infants began to visually orient and follow by 2 weeks of age, increasing across the first month of life; attention span was also found to increase with age across the first month (Schneider and Suomi, 1992). Their findings are not surprising with visual skills and attention increasing with age, as the neural structures supporting these behaviors are rapidly developing during this time period. Though no significant age effects were found in our study for these measures ("Visual Orientation: Right, Left, Up, Down", "Visual Follow", and "Attention Span"), the high inter-individual variability in this small sample could have contributed to the negative findings of developmental changes on these measures. Repeating these measures with a larger sample size could help to establish the developmental trajectory.

Eye-tracking, the fourth method used to study social visual attention, evaluated fixation times to social stimuli (eyes) and non-social stimuli (objects) in short video clips featuring conspecifics. Surprisingly, there were no significant age effects found for fixation percentages to eyes (% Eye Fixation). In another study drawing from the same dataset but using a longitudinal functional analysis of the developmental trajectories, which is a non-parametric data-driven approach, it was found that fixation to the eye region increases from 2 to about 6 weeks of age, followed by a decrease around 15 weeks, and increasing again until 22 weeks (Wang et al., 2020). These results were similar to those found in TD human infants from 2 to 6 months of age (Jones and Klin, 2013; Wang et al., 2020). The different results in our study are

likely explained by the failure of LMM to capture the non-linear developmental trajectory of this behavior. The developmental trajectory was likely cubic, not linear, based on the developmental trajectory of eye fixations in Wang et al. (2020). In contrast, fixation percentages to non-social stimuli (% Object Fixation on objects) showed a significant increase with age, though appearing to have a non-linear shape as well. No significant changes were found between specific ages, though.

This study provides a unique analysis of early development in social visual attention networks, including two areas not typically associated with attention in the STS. The significant age-related volumetric growth we found from 2-24 weeks in social visual attention networks followed region-specific developmental trajectories. Structural development during similar periods of social development indicates that early developmental changes in these brain regions in macaques may play a role in changes in social visual attention to socially appropriate peers. The contribution of our findings to the field resides on investigation of developmental trajectories of regions of the brain associated with social visual attention and changes in behavioral measures of social visual attention during early development. These finding help provide an understanding of neurodevelopmental processes that mediate attention to salient social visual stimuli in NHPs and further contribute to development of a NHP model of ASD and other neurodevelopmental disorders.

To be thorough in this investigation, it is necessary to discuss limitations of this study as well. First, to fully understand the relationships between the development in ROI GM and social behavior, further multiple regression analyses are needed; although an inherent limitation of

such regression approaches is that it does not prove causality, it is a better statistical approach to correlations because it tests the percent of the variance of the outcome measure (in this case, behavior) explained by each of the potential predictor variables (ROIs growth). In investigating ROI volumetric development using sMRI, we included ICV as a covariate to control for individual differences in ROI development due to brain size. However, we did not include any negative control ROI to demonstrate the specificity of the developmental effects on social visual attention networks. Inclusion of a region not directly associated with attention, such as the motor cortex, would have helped address this specificity issue. All subjects studied were male— which is supported by the greater prevalence of males than females diagnosed with ASD –, though this eliminates evaluation of any potential sex differences and does not address the heavily present male bias in ASD research. Finally, the study's small sample size for the behavioral studies is a strong limitation, as a larger size would increase statistical power to examine developmental changes more closely in behavior. Future iterations of this project plan to increase the sample size in the MRI data, as well as OBS, jmSRS, SNAP and eye-tracking.

Despite these limitations, the findings presented in this study and their implications are still important. The methodology of the study is unique in the longitudinal sMRI analysis, as well as the behavioral data assessment. There are no previous studies in which social visual attention brain structural and behavioral development is measured concurrently with this highly dense data collection at multiple age points throughout the first weeks of life. This multitude of age points allowed identification of specific weeks, as opposed to months, during early infant macaque development when milestones occur. Additionally, the behavioral data collected from socially housed macaques provides a naturalistic representation of the healthy early social

development in one of our closest relatives. Macaques provide a strong model for studying neural development and socially relevant behaviors due to their similarities with both human brain and behavior. Usage of this macaque model also provides intensive investigation into very early developmental ages and allows future experiments that would be very difficult to conduct in human infants and without our high experimental control. We hope these findings serve to map the typical development of social visual skills and the underlying neural networks in macaques, as a baseline for future investigations of social visual attentional deficits of relevance for ASD. In the future, our group plans to investigate the difference in jmSRS scores from 6 months to 1 year of age, extending from this study's investigation of the first 24 weeks of age; we also plan to further investigate effects of dominance rank on jmSRS scores, as well as neural and behavioral development once sample size is increased. It would be important to determine the associations between neural and behavioral development measures during infancy to identify neural biomarkers predictive of social maturation during the first 6 months of life, and it is pending for the future.

Finally, these findings provide a basis to understand how attention (specifically to social visual stimuli) develops in the TD infant macaque. By understanding typical development, we can transition to study social impairments. In conclusion, establishing an understanding of normative development of social visual attention brain networks and the attentional behaviors they mediate within a NHP model will further clarify the origins of brain-behavior pathogenesis of attentional differences observed in ASD. This understanding will greatly improve early interventions that will be beneficial for developing and strengthening social adaptive skills in children who have been diagnosed with ASD, providing the tools they may use to optimize their

outcomes. Hopefully, this will conversely allow TD individuals (such as family members, educators, and healthcare professionals) to have a better understanding of the social attention struggles autistic individuals may face to better accommodate their individual needs.

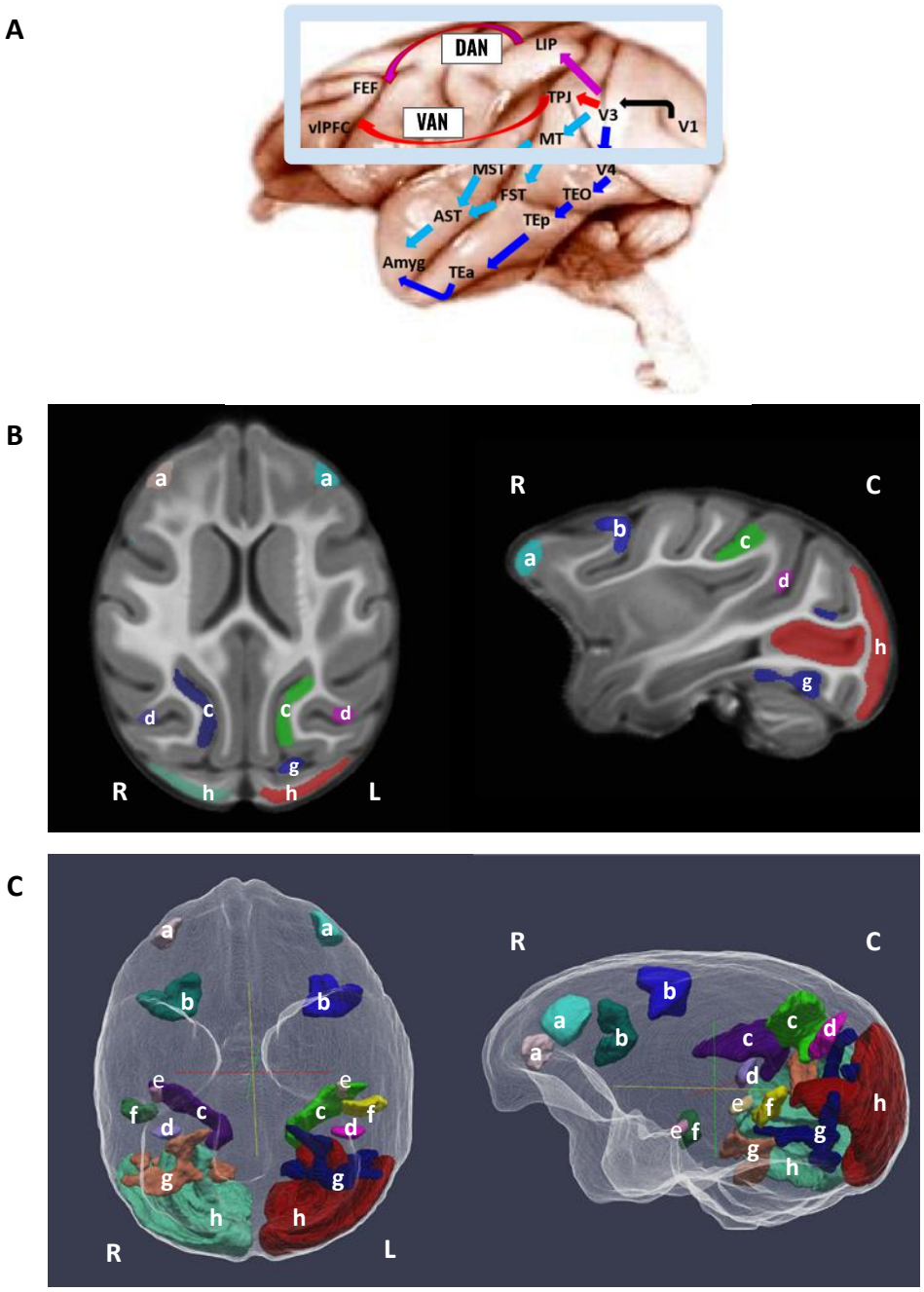

Figure 1: Attention Networks and Associated Areas. (**A**) Attention networks include the primary visual cortex (V1), extrastriate visual area (V3), Dorsal attention network (DAN: lateral intraparietal area (LIP) and frontal eye field (FEF)), Ventral attention network (VAN: temporoparietal junction (TPJ) and ventrolateral prefrontal cortex (vlPFC)). (**B**) Example of ROIs parcellations displayed on the 6-month atlas. Left: axial view (R: right hemisphere, L: left hemisphere), right: sagittal view (R: rostral, C: caudal). Example of ROIs displayed include the vlPFC (a), FEF (b), LIP (c), TPOc (d), V3 (g), and V1 (h); ROIs that could not be displayed: PGa (e) and TPJ (f). (**C**) A 3D rendering of all ROIs generated in one subject at 24 weeks of age, with a wireframe representation of the subject's whole brain.

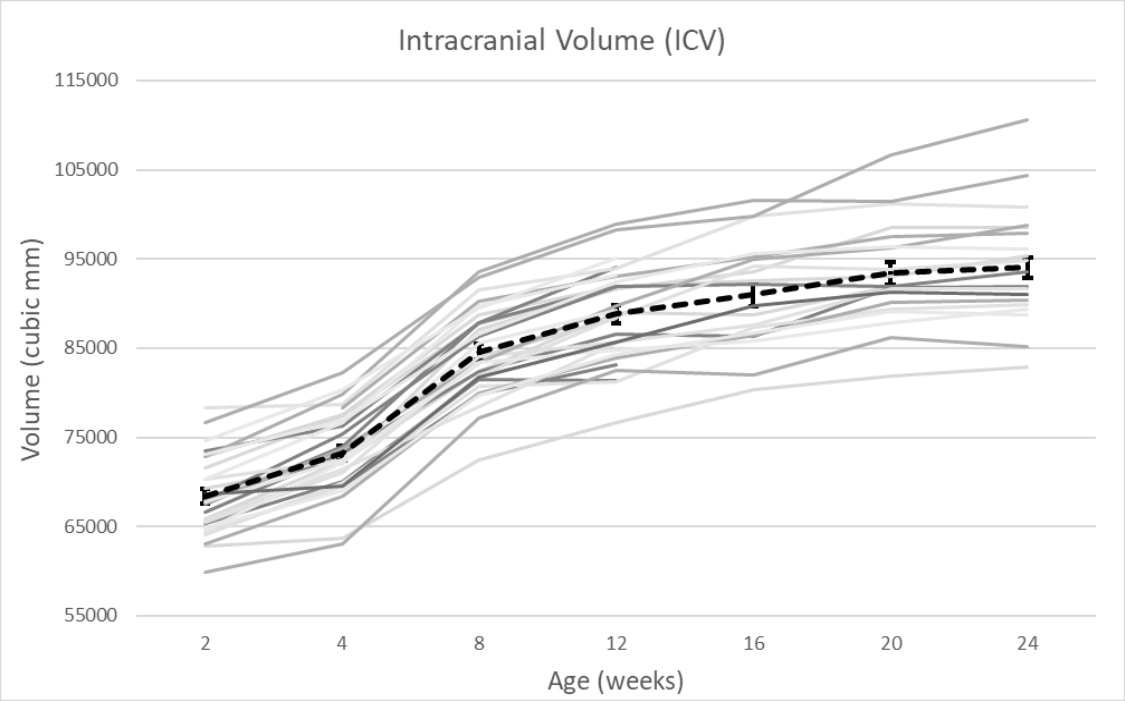

Figure 2: Total ICV changed over time. There was a significant effect of AGE on ICV ($F_{(6,51.528)}$=115.745; p= 4.0377 x10^{-28}). Post-hoc tests revealed periods of significant growth between 2 and 12 weeks (2 to 4 weeks: p=0.002; 4 to 8: p=3.4551x10^{-12}; 8 to 12: p=0.039) followed by a plateau in growth. Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

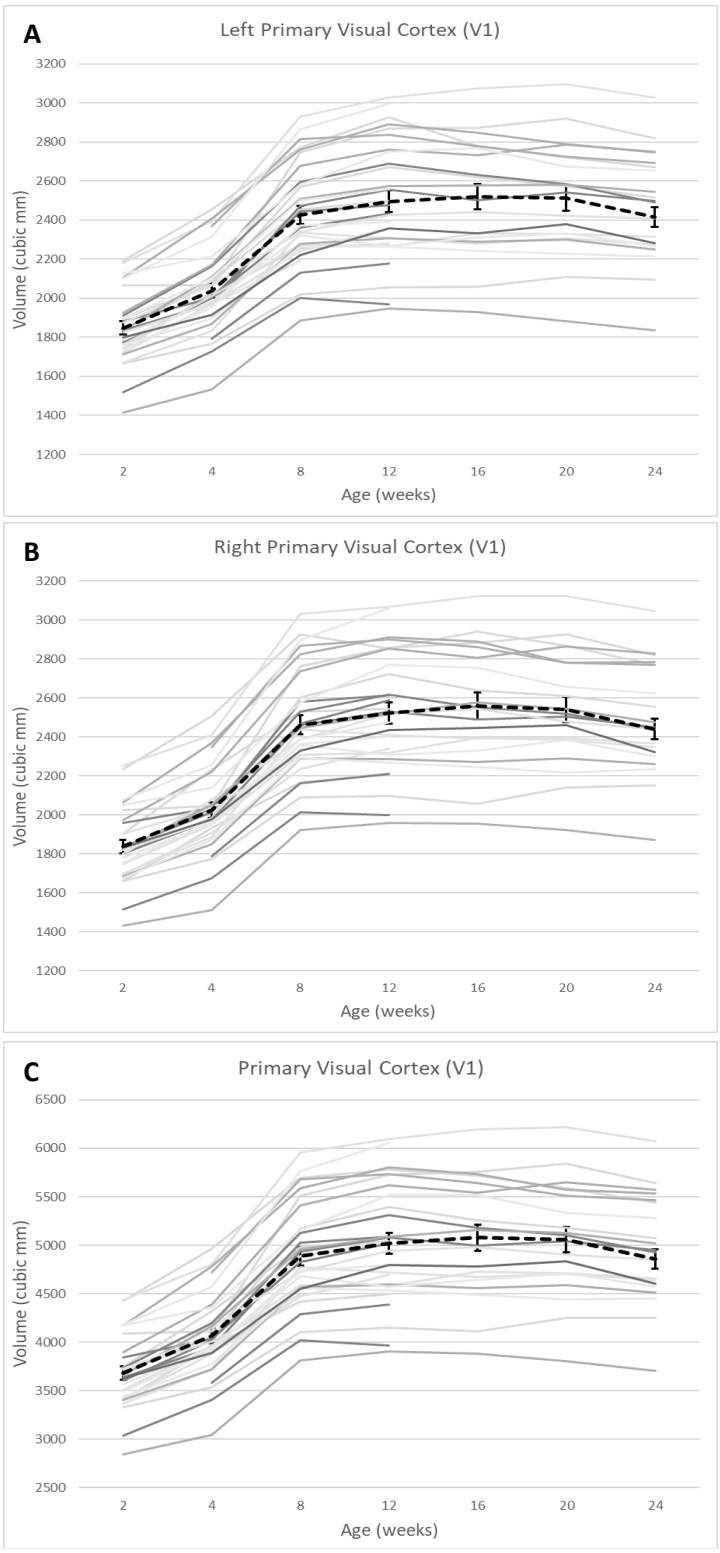

Figure 3: V1 volume changed over time. (**A,B**) There was a significant effect of AGE ($F_{(6,110.202)}$ =84.421; p=6.7078x10^{-39}) on V1 volume. (**C**) Total V1 volume (bilateral: right + left) still shows significant increases with AGE when adding subject ICV as covariate ($F_{(6,36.591)}$=243.276; p=6.1056x10^{-28}); post-hoc tests identified periods of significant bilateral growth between 2 and 12 weeks (2 to 4 weeks: p=1.7409x10^{-10}; 4 to 8 weeks: p=4.5784x10^{-25}; 8 to 12 weeks: p=2.48x10^{-4}) and between 20 and 24 weeks (p=0.010). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

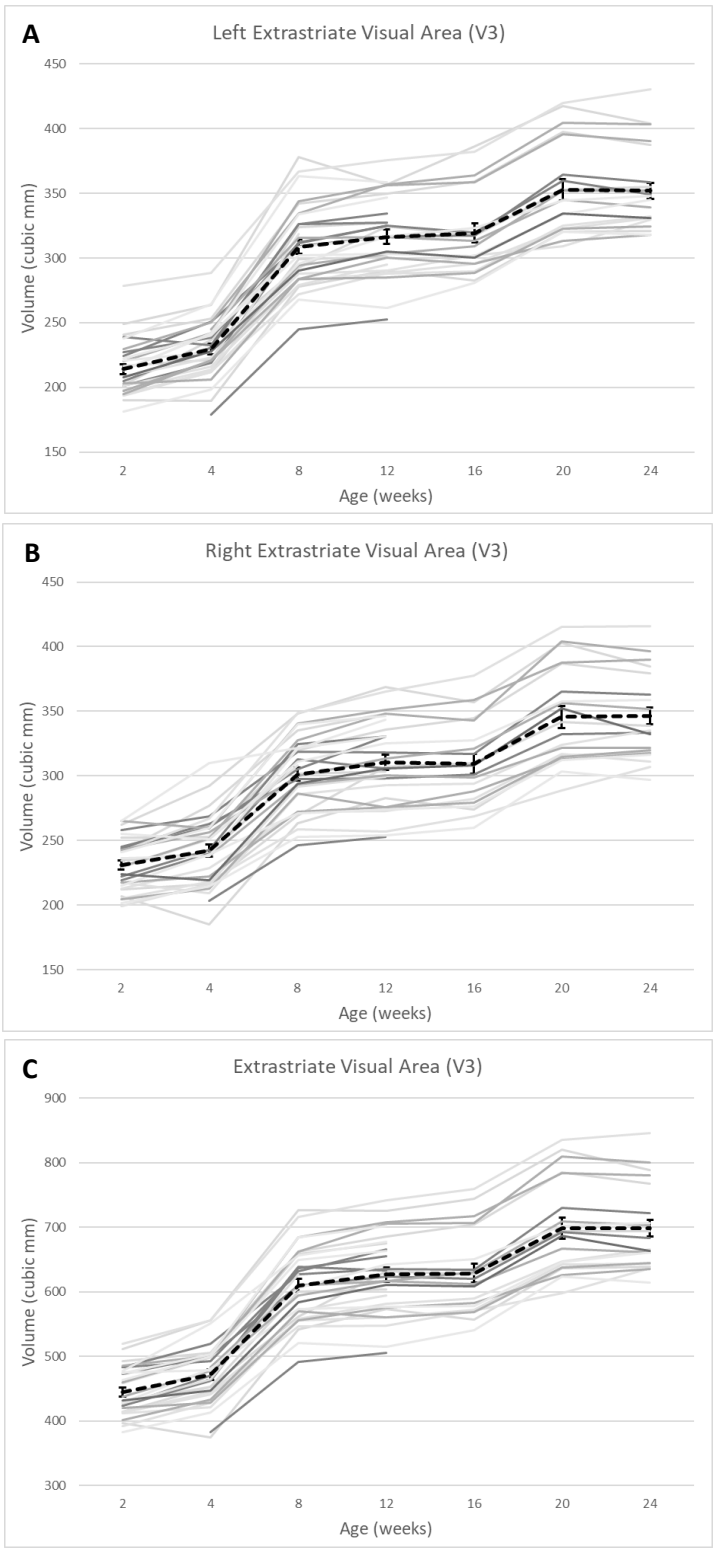

Figure 4: V3 volume changed over time. (**A,B**) There was a significant effect of AGE ($F_{(6,95.112)}$=195.826; p=3.0582x10^{-51}), and an AGE x HEMISPHERE interaction effect ($F_{(6,95.112)}$=2.545; p=0.025). (**C**) Analyses of V3 (bilateral: right + left) volume changes over time when adding ICV as covariate still resulted in significant effect of AGE ($F_{(6,41.187)}$=458.702; p=4.5778x10^{-36}); post-hoc tests detected periods of significant bilateral growth from 2 to 12 weeks (2 to 4 weeks: p=4.9x10^{-5}; 4 to 8 weeks: p=8.3672x10^{-30}; 8 to 12 weeks: p=1.38x10^{-4}) and 16 to 20 weeks (p=6.1258x10^{-13}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

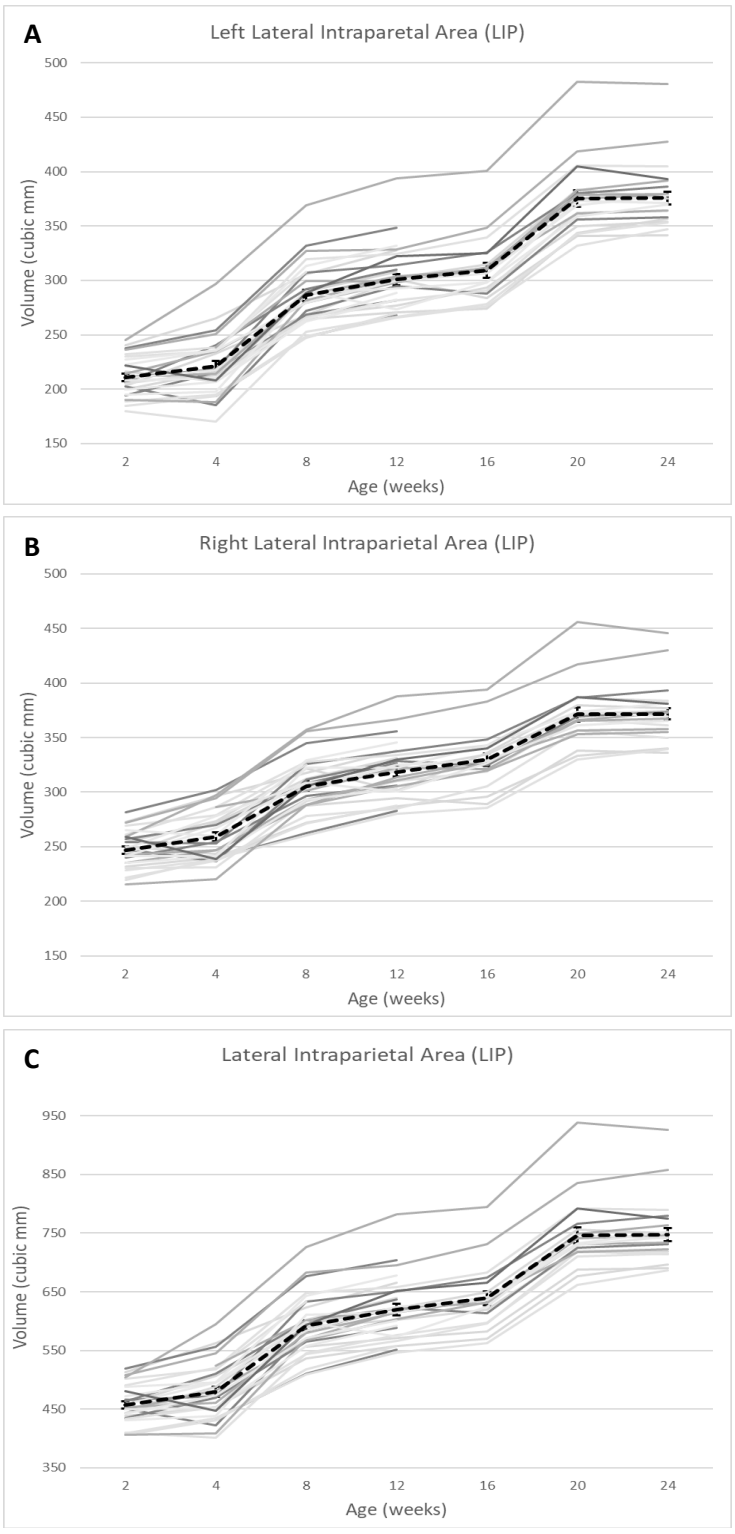

Figure 5: LIP volume changed over time. (**A**,**B**) There was a significant effect of AGE ($F_{(6,88.210)}$ =290.734; p=7.3172x10^{-56}), HEMISPHERE ($F_{(1,254.865)}$= 39.347; p = 1.5116x10^{-9}), and an AGE x HEMISPHERE interaction effect ($F_{(6,88.210)}$=5.613; p=5.70x10^{-5}). (**C**) Analyses of LIP (bilateral: right + left) volume changes over time when controlling for ICV still resulted in significant effect of AGE ($F_{(6,36.759)}$=704.687; p=2.2026x10^{-36}); post-hoc tests identified a significant bilateral growth between 2 and 20 weeks (2 to 4 weeks: p=0.038; 4 to 8 weeks: p=1.4969x10^{-19}; 8 to 12 weeks: p=1.4603x10^{-10}; 12 to 16 weeks: p=2.0x10^{-6}; 16 to 20 weeks: p=2.0738x10^{-17}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

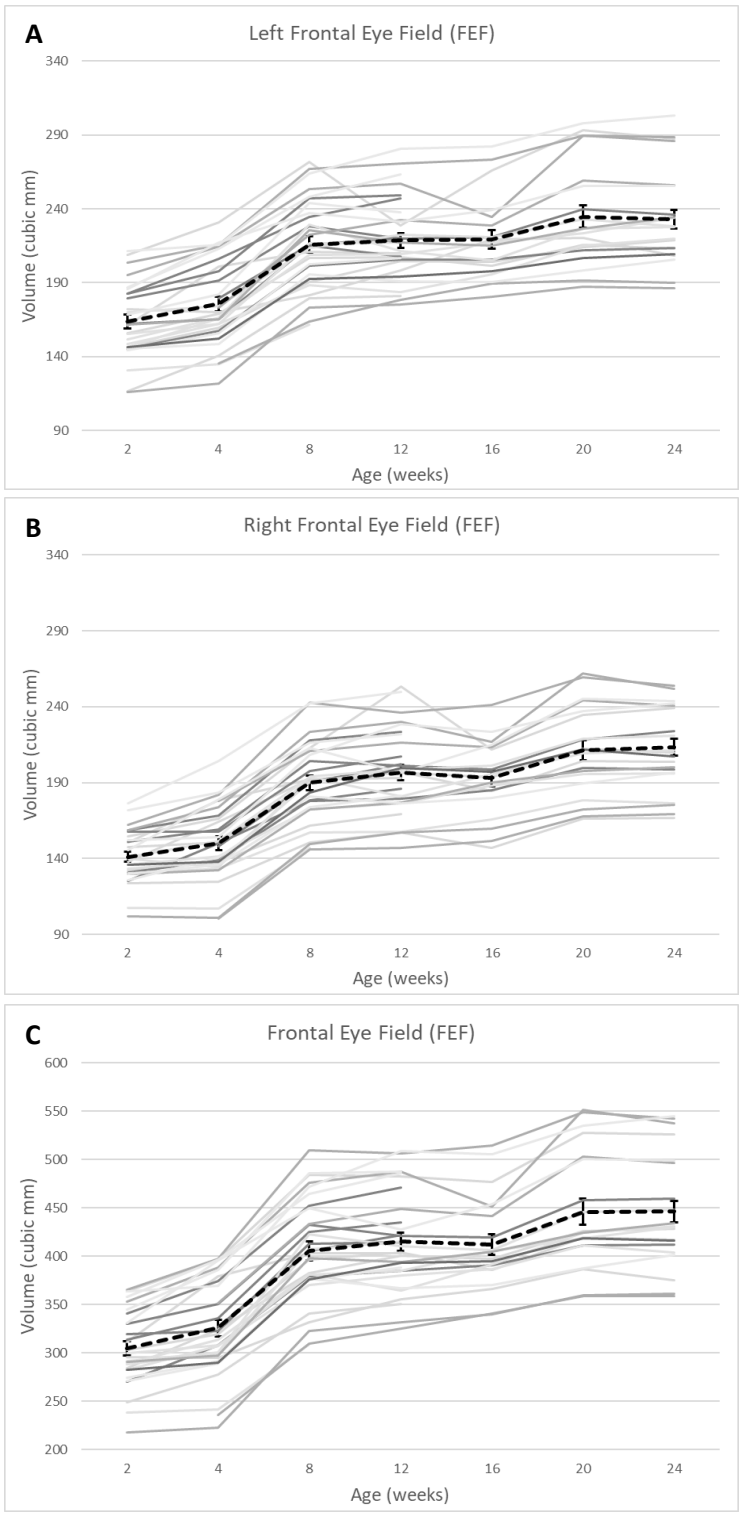

Figure 6: FEF volume changed over time. (**A**,**B**) There was a significant effect of AGE ($F_{(6,77.691)}$=65.889; p=1.9238x10^{-28}) and HEMISPHERE ($F_{(1,275.061)}$=65.721; p=1.7216x10^{-14}). (**C**) Analyses of FEF (bilateral: right + left) volume changes over time when controlling for subject ICV still resulted in significant effect of AGE ($F_{(6,46.369)}$=227.439; p=1.165x10^{-32}); post-hoc tests revealed a significant bilateral growth period between 2 and 8 weeks (2 to 4 weeks: p=9.3x10^{-5}; 4 to 8 weeks: p=4.872x10^{-24}) and 16 to 20 weeks (p=1.4808x10^{-8}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

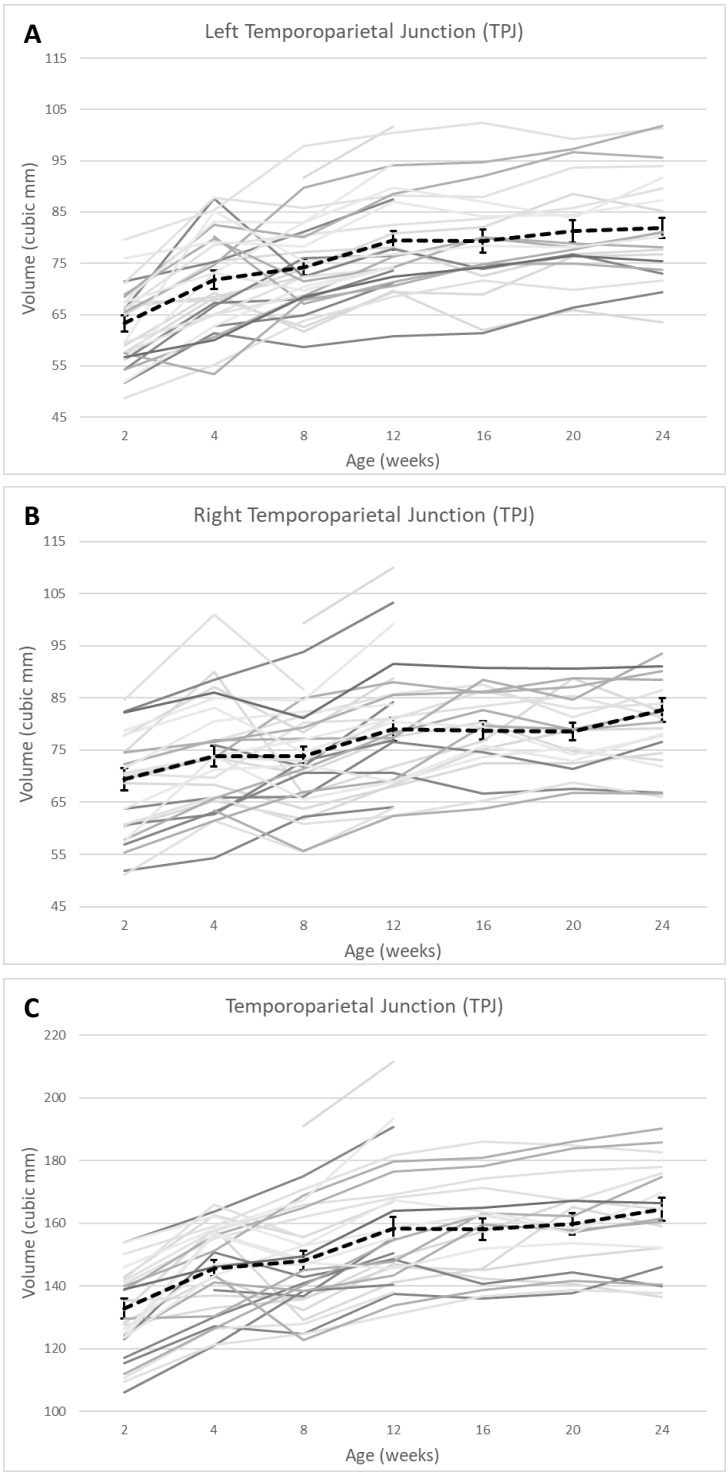

Figure 7: TPJ volume changed over time. (**A**,**B**) There was a significant effect of AGE ($F_{(6,89.654)}$=15.942; p=2.182x10^{-12}). (**C**) Analyses of TPJ (bilateral: right + left) volume changes over time when controlling for subject ICV still resulted in significant effect of AGE ($F_{(6,33.548)}$=56.163; p=4.4356x10^{-16}); post-hoc tests detected significant periods of bilateral growth from 2 to 4 weeks (p=3.0x10^{-6}) and 8 to 12 weeks (p=4.2494x10^{-7}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

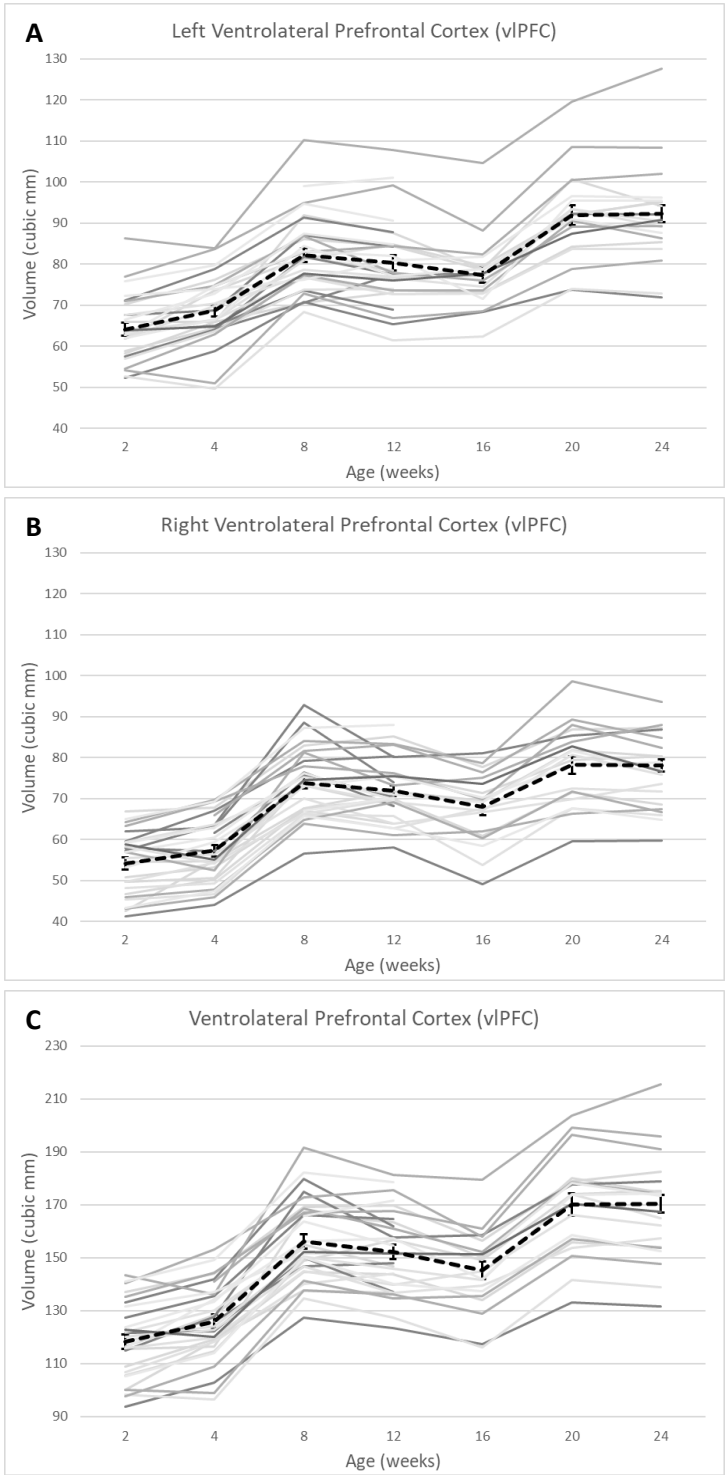

Figure 8: vlPFC volume changed over time. (**A**,**B**) There was a significant effect of AGE ($F_{(6,84.155)}$=74.080; p=1.7768x10^{-31}), and HEMISPHERE ($F_{(1,279.158)}$=131.906; p=2.9149x10^{-25}). (**C**) Analyses of vlPFC (bilateral: right + left) volume changes over time when adding ICV as covariate still resulted in significant effect of AGE ($F_{(6,43.941)}$=266.219; p=7.461x10^{-33}); post-hoc tests revealed a significant bilateral growth period between 2 and 20 weeks (2 to 4 weeks: p=0.004; 4 to 8 weeks: p=1.873x10^{-21}; 8 to 12 weeks: p=0.044; 12 to 16 weeks: p=0.013; 16 to 20 weeks: p=1.4331x10^{-15}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

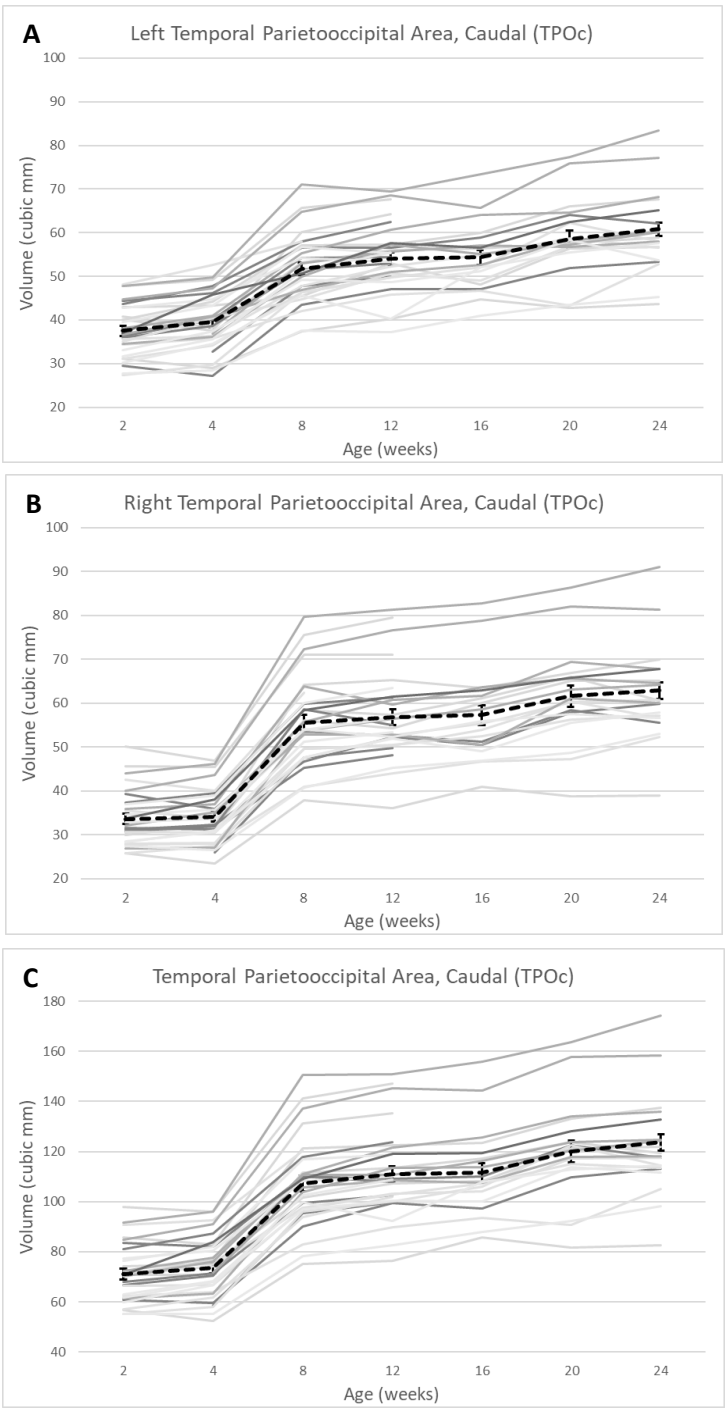

Figure 9: TPOc volume changed over time. (**A**,**B**) There was a significant effect of AGE ($F_{(6,95.748)}$=116.193; p=1.0568x10^{-41}) and an AGE x HEMISPHERE interaction effect ($F_{(6,95.748)}$=3.850; p=0.002). (**C**) Analyses of TPOc (bilateral: right + left) volume changes over time when controlling for subject ICV still resulted in significant effect of AGE ($F_{(6,36.623)}$=192.308; p=3.8048x10^{-26}); post-hoc tests showed a period of significant bilateral growth from 4 to 20 weeks (4 to 8 weeks: p=1.9325x10^{-28}; 8 to 12 weeks: p=2.92x10^{-4}; 12 to 16 weeks: p=0.023; 16 to 20 weeks: p=8.9122x10^{-7}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

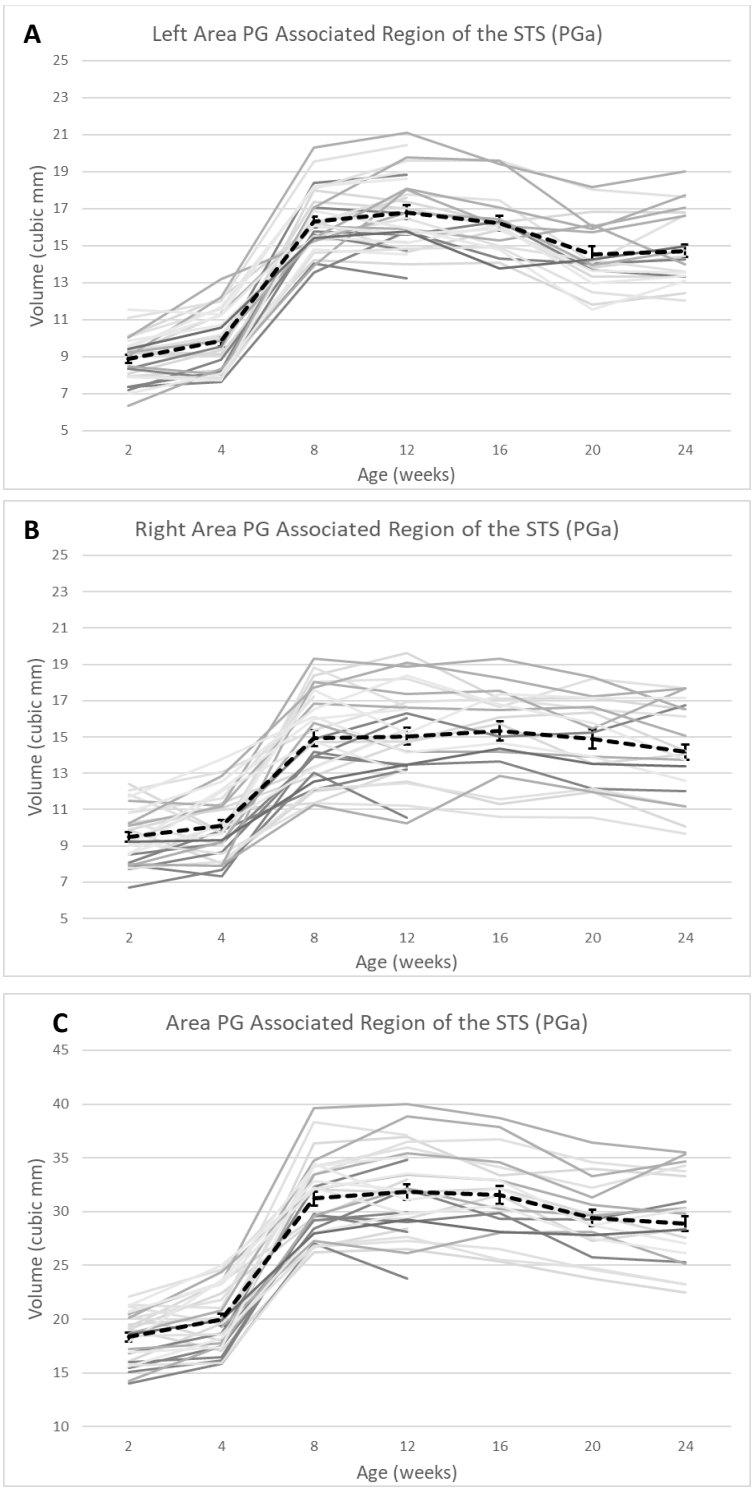

Figure 10: PGa volume changed over time.
(**A**,**B**) There was a significant effect of AGE ($F_{(6,105.397)}$=157.552; p=2.814x10^{-50}), HEMISPHERE ($F_{(1,261.592)}$=4.773; p=0.030) and an AGE x HEMISPHERE interaction effect ($F_{(6,105.397)}$=3.391; p=0.004). (**C**) Analyses of PGa (bilateral: right + left) volume when controlling for subject ICV still resulted in significant effect of AGE ($F_{(6,36.623)}$=192.308; p=3.8048x10^{-26}); post-hoc tests identified a period of significant bilateral growth from 4 to 8 weeks (p=5.3917x10^{-23}), and a significant decrease in volume was found from 16 to 20 weeks (p=7.0x10^{-6}). Gray lines represent individual growth trajectory for each subject; black dashed line is the group average, with error bars (± SEM).

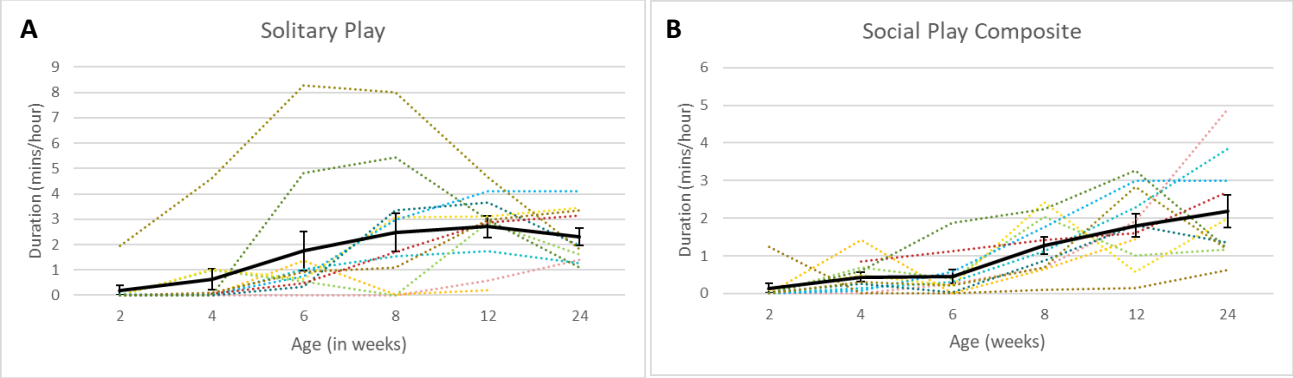

Figure 11: Infant play behaviors over time. Average rate (min/hr) of play behaviors. (**A**) "Solitary Play" durations showed a significant increase with AGE ($F_{(5,25.714)}$=10.792; p=1.10x10^{-5}). (**B**) "Social Play Composite" durations also showed a significant increase with AGE ($F_{(5,14.695)}$=10.802; p=1.66x10^{-4}). Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

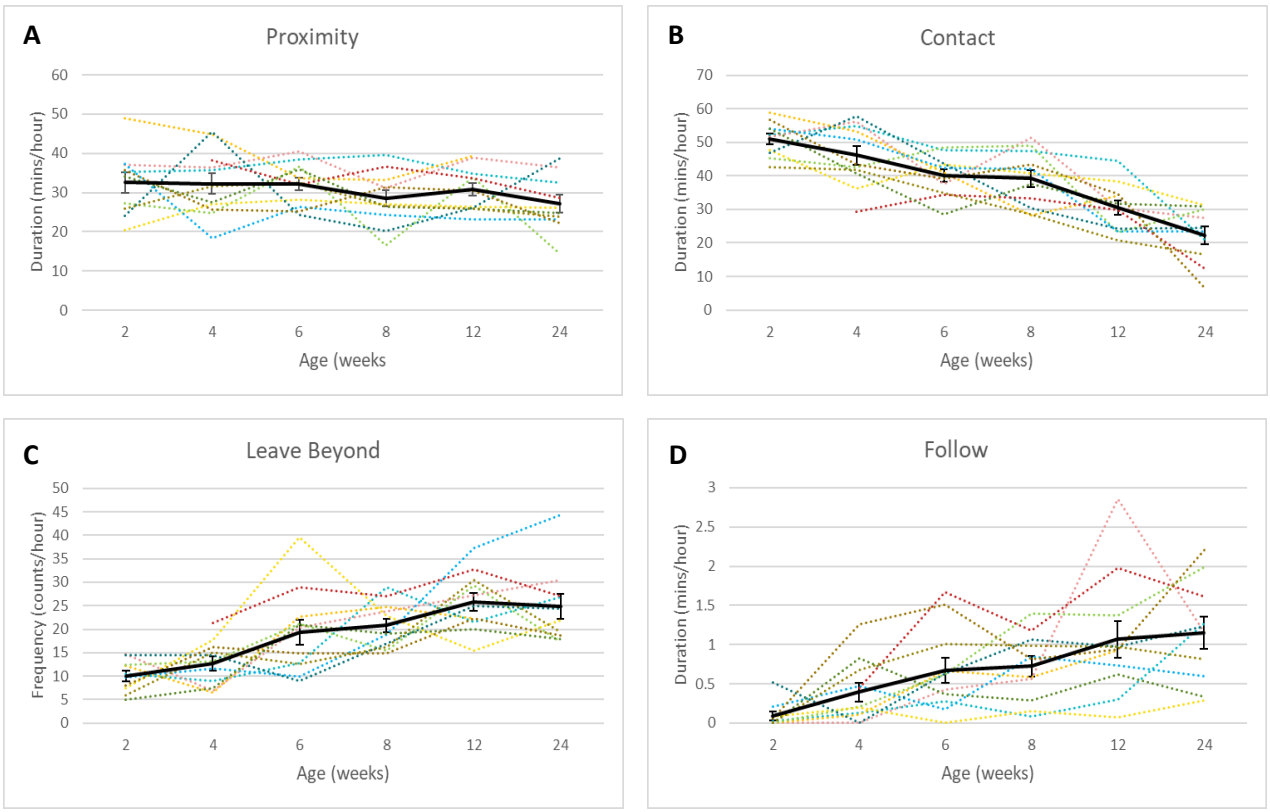

Figure 12: Infant affiliative/prosocial behaviors over time. Average rate (min/hr or counts/hr) of affiliative behaviors. (**A**) There was no significant effect of AGE on "Proximity" duration. (**B**) There was no significant effect of AGE on "Contact" duration, either. (**C**) There was a significant effect of AGE ($F_{(5,15.337)}$=16.922; p=9.0x10^{-6}) on "Leave Beyond" frequency. (**D**) The was a significant effect of AGE ($F_{(5,16.598)}$=12.047; p=4.8x10^{-5}) on "Follow" duration. Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

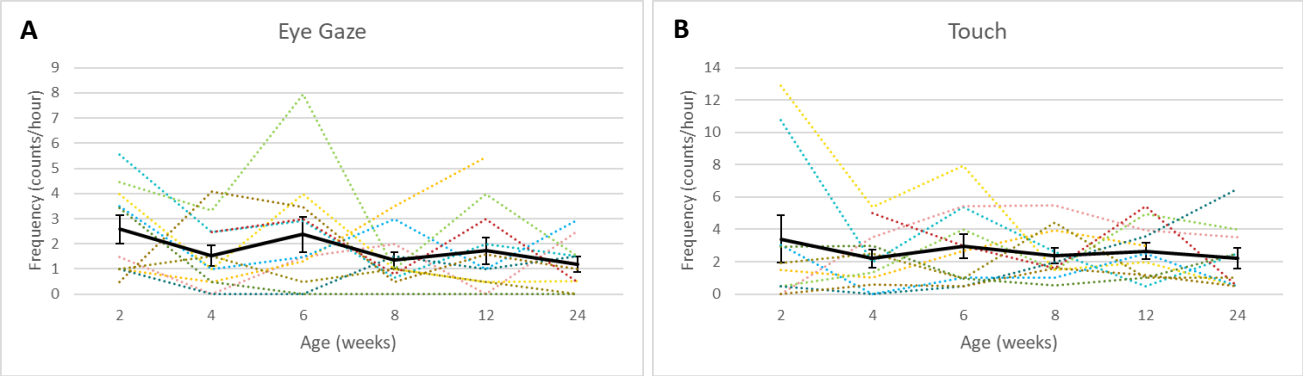

Figure 13: Other infant prosocial behaviors over time. Average rate (counts/hr) of prosocial behaviors. (**A**) There was no significant effect of AGE on "Touch" frequency. (**B**) "Eye Gaze" frequency did not show a significant effect of AGE, either. Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

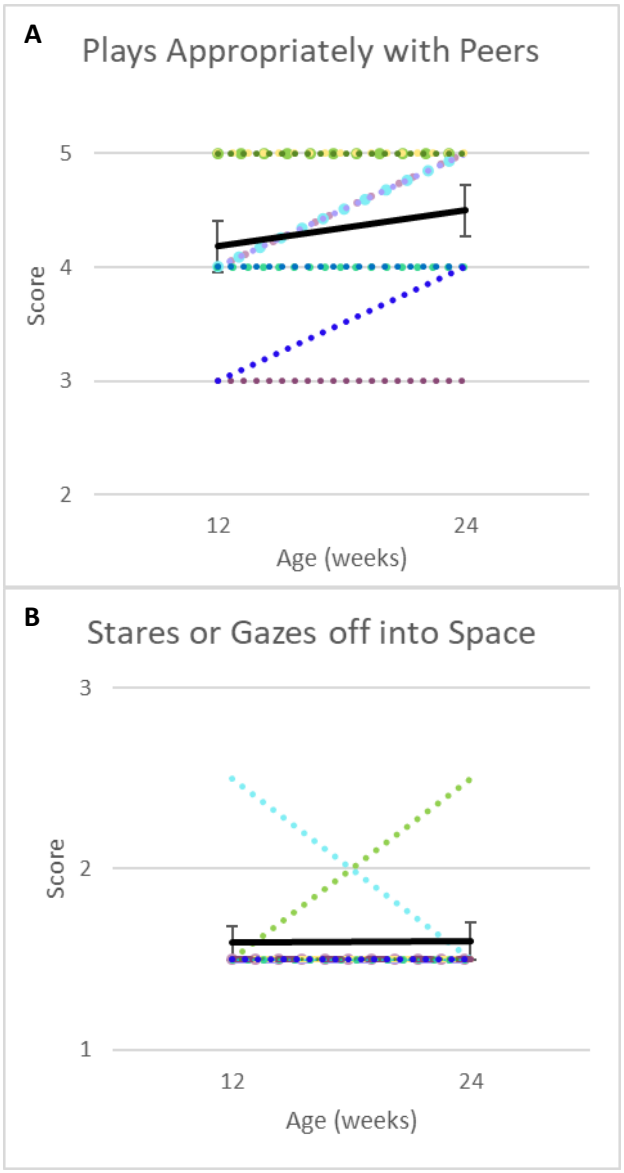

Figure 14: jmSRS scores over time. (**A**) "Plays appropriately with peers" scores increased significantly from 12 to 24 weeks of age ($F_{(1.000,9.000)}$=5.867; p=0.038). (**B**) "Stares or gazes off into space" scores were low and did not change significantly from 12 to 24 weeks of age. Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

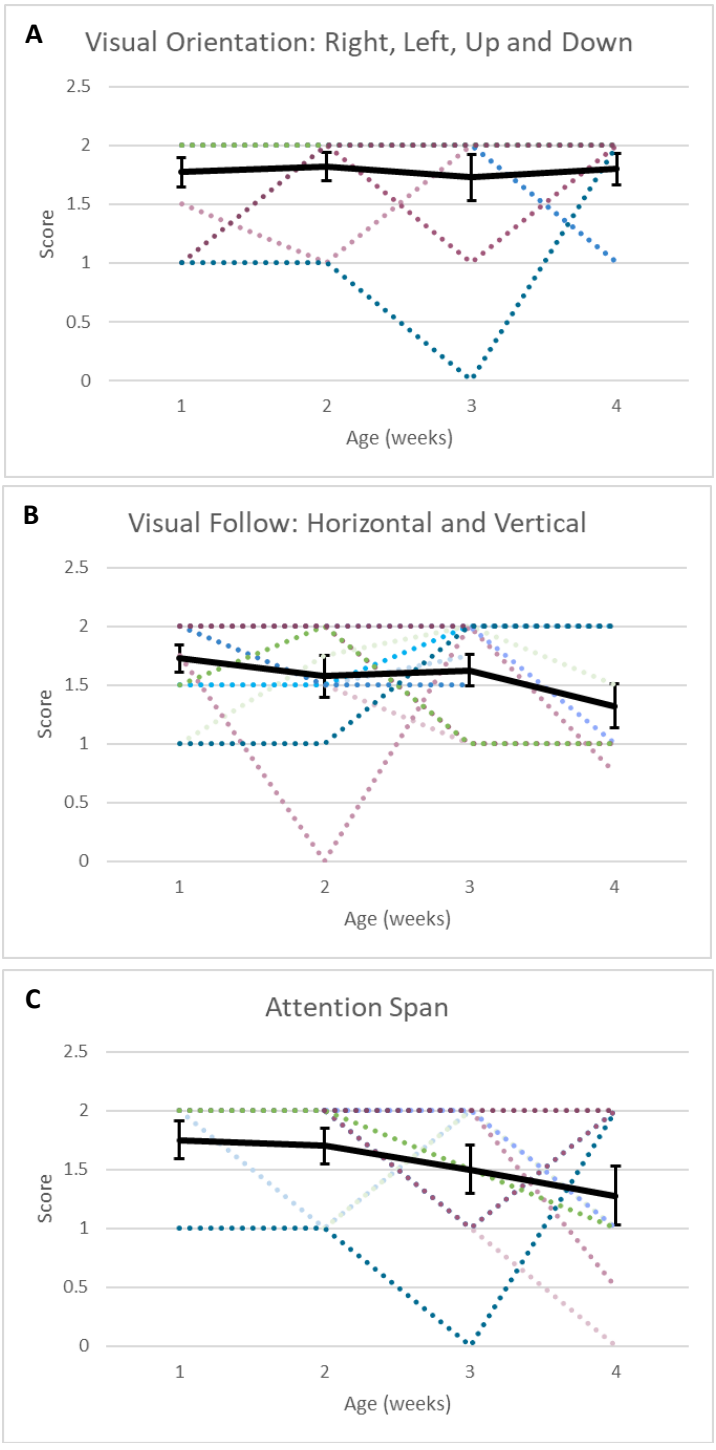

Figure 15: SNAP scores over time. Figure 14: SNAP scores over time. Neither Visual Orientation scores (**A**), Visual Follow scores (**B**), nor Visual attention scores (**C**) showed significant changes over time. Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

Figure 16: Percentage of fixation time spent on eyes and objects over time. (**A**) Plot of eye fixation percentages at all recorded ages. (**B**) Plot of eye fixation percentages at consolidated ages, which were used in analyses to find that there was not a significant effect of AGE. (**C**) Plot of object fixation percentages at all recorded ages. (**D**) Plot of object fixation percentages at consolidated ages, which were used in analyses to find there was a significant effect of AGE ($F(7,31.951)=2.867$; $p=0.019$).

Colored lines represent individual subjects; black line is the group average, with error bars (± SEM).

Table 1: Volumetric fold-increase matrices.

Matrices showing age-by-age volumetric increases of ICV and ROI. The number in each cell shows the fold increase in volume between 2 ages; the darker the color, the greater the volume increase).

*: $10^{-5} \leq p < 0.0024$, **: $10^{-10} \leq p < 10^{-5}$, ***: $p < 10^{-10}$. (**A**) Intracranial volume. (**B**,**C**) Visual cortical areas: V1 (**B**) and V3 (**C**). (**D**,**E**) Dorsal attention network (DAN) ROIs: LIP (**D**) and FEF (**E**). (**F**,**G**) Ventral attention network (VAN) ROIs: TPJ (**F**) and vlPFC (**G**). (**H**,**I**) Superior temporal sulcus (STS) ROIs: TPOc (**H**) and PGa (**I**).

A

Intracranial volume (ICV)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.07*					
8wk	1.24***	1.15***				
12wk	1.30***	1.21***	1.05*			
16wk	1.33***	1.24***	1.08*	1.02		
20wk	1.37***	1.28***	1.10*	1.05	1.03	
24wk	1.38***	1.28***	1.11**	1.06*	1.03	1.01

0.9-0.99
1-1.09
1.1-1.19
1.2-1.29
1.3-1.39
1.4-1.49
1.5-1.59
1.6-1.69
1.7-1.79

B

Primary visual cortex (V1)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.10**					
8wk	1.33***	1.20**				
12wk	1.36***	1.24***	1.03*			
16wk	1.38***	1.25***	1.04*	1.01		
20wk	1.37***	1.24***	1.03	1.01	1.00	
24wk	1.32***	1.20***	0.99	0.97**	0.96*	0.96*

C

Extrastriate visual area (V3)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.06*					
8wk	1.37***	1.29***				
12wk	1.41***	1.33***	1.03*			
16wk	1.41***	1.33***	1.03**	1.00		
20wk	1.57***	1.48***	1.14***	1.11***	1.11***	
24wk	1.57***	1.48***	1.14***	1.11***	1.11***	1.00

D

Lateral intraparietal area (LIP)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.05*					
8wk	1.29***	1.23***				
12wk	1.35***	1.29***	1.05**			
16wk	1.40***	1.33***	1.08***	1.03**		
20wk	1.63***	1.56***	1.26***	1.20***	1.17***	
24wk	1.63***	1.56***	1.26***	1.21***	1.17***	1.00

E

Frontal eye field (FEF)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.07*					
8wk	1.33***	1.25***				
12wk	1.36***	1.27***	1.02			
16wk	1.35***	1.27***	1.02	0.99		
20wk	1.46**	1.37***	1.10***	1.07***	1.08**	
24wk	1.47***	1.37***	1.10***	1.08***	1.08**	1.00

F

Temporoparietal junction (TPJ)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.10**					
8wk	1.12**	1.02				
12wk	1.19***	1.09*	1.07**			
16wk	1.19***	1.09**	1.07**	1.00		
20wk	1.20***	1.10**	1.08**	1.01	1.01	
24wk	1.24***	1.13**	1.11***	1.04*	1.04	1.03

G

Ventrolateral prefrontal cortex (vlPFC)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.06*					
8wk	1.32***	1.24***				
12wk	1.29***	1.21***	0.97*			
16wk	1.23***	1.15***	0.93**	0.95*		
20wk	1.44***	1.35***	1.09***	1.12***	1.17***	
24wk	1.44***	1.35***	1.09***	1.12***	1.17***	1.00

H

Temporal parietooccipital area, caudal (TPOc)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.03					
8wk	1.51***	1.46***				
12wk	1.56***	1.51***	1.03*			
16wk	1.57***	1.52***	1.04**	1.01*		
20wk	1.69***	1.63***	1.12***	1.08**	1.08**	
24wk	1.74***	1.68***	1.15***	1.12***	1.11**	1.03

I

Area PG associated region of the STS (PGa)	2wk	4wk	8wk	12wk	16wk	20wk
2wk						
4wk	1.09					
8wk	1.70***	1.56***				
12wk	1.73***	1.59***	1.02			
16wk	1.72***	1.58***	1.01	0.99		
20wk	1.60***	1.47***	0.94*	0.92**	0.93**	
24wk	1.57***	1.45***	0.93*	0.91**	0.92*	0.98

Table 2: Comparison of ROI volumetric fold-increases.

Comparison ROI volumetric fold increases between age timepoints and across the first 6 months. Stars indicate significant volumetric changes; green indicates increase and purple indicates decreases.

ROI (ICV)	2-4 wk	4-8wk	8-12wk	12-16wk	16-20wk	20-24wk	Fold increase (2-24wks)
V1	★	★	★			★	1.32
V3	★	★	★		★		1.57
LIP	★	★	★	★	★		1.63
FEF	★	★			★		1.47
TPJ	★		★				1.24
vlPFC	★	★	★	★	★		1.44
TPOc		★	★	★	★		1.74
PGa		★			★		1.57

Table 3: Summary of jmSRS Scores. The group average for each jmSRS item ±SEM is reported at 3 months and 6 months of age. Items bolded and marked with an asterisk indicate significant changes with age ($p<0.05$). Note that "Avoids eye contact or has unusual eye contact" could not be analyzed as all subjects at both ages had the same "1" score (on 5-point Likert scale).

jmSRS Item	3 Month Average Score (±SEM)	6 Month Average Score (±SEM)
6. Avoids eye contact or has unusual eye contact	-	-
7. Plays appropriately with peers*	4(±0.2264)	5(±0.2236)
13. Stares or gazes off into space	1(±0.0909)	1(±0.1000)

References

Allison, T., Puce, A., and McCarthy, G. (2000). Social perception from visual cues: role of the STS region. Trends in Cognitive Sciences *4*, 267-278.

Altmann, S.A. (1962). A field study of the sociobiology of rhesus monkeys, Macaca mulatta. Annals of the New York Academy of Sciences *102*, 338-435.

American Psyciatric Association (2013). Autism Spectrum Disorder (Washington, DC).

Amso, D., and Johnson, S.P. (2008). Development of Visual Selection in 3- to 9-Month-Olds: Evidence From Saccades to Previously Ignored Locations. Infancy *13*, 675-686.

Aron, A., Robbins, T., and Poldrack, R. (2004). Inhibition and the right inferior frontal cortex. Trends in Cognitive Sciences *8*, 170-177.

Aziz-Zadeh, L., Koski, L., Zaidel, E., Mazziotta, J., and Iacoboni, M. (2006). Lateralization of the human mirror neuron system. J Neurosci *26*, 2964-2970.

Balzeau, A., Gilissen, E., and Grimaud-Hervé, D. (2012). Shared Pattern of Endocranial Shape Asymmetries among Great Apes, Anatomically Modern Humans, and Fossil Hominins. PLoS ONE *7*, e29581.

Barnéoud, P., and Van der Loos, H. (1993). Direction of handedness linked to hereditary asymmetry of a sensory system. Proc Natl Acad Sci U S A *90*, 3246-3250.

Bartolomeo, P. (2013). Attention disorders after right brain damage: Living in halved worlds (Springer).

Bauman, M.D., and Schumann, C.M. (2018). Advances in nonhuman primate models of autism: Integrating neuroscience and behavior. Exp Neurol *299*, 252-265.

Bekoff, M., and Allen, C. (2011). Intentional communication and social play: how and why animals negotiate and agree to play. In Readings in Zoosemiotics (De Gruyter Mouton), pp. 175-194.

Bisiach, E., and Luzzatti, C. (1978). Unilateral neglect of representational space. Cortex *14*, 129-133.

Bisley, J.W., and Goldberg, M.E. (2003). The role of the parietal cortex in the neural processing of saccadic eye movements. Adv Neurol *93*, 141-157.

Bisley, J.W., and Goldberg, M.E. (2010). Attention, intention, and priority in the parietal lobe. Annu Rev Neurosci *33*, 1-21.

Bisley, J.W., Mirpour, K., Arcizet, F., and Ong, W.S. (2011). The role of the lateral intraparietal area in orienting attention and its implications for visual search. European Journal of Neuroscience *33*, 1982-1990.

Black, M., Freeman, B.J., and Montgomery, J. (1975). Systematic observation of play behavior in autistic children. Journal of autism and childhood schizophrenia *5*, 363-371.

Blaser, E., Sperling, G., and Lu, Z.-L. (1999). Measuring the amplification of attention. Proceedings of the National Academy of Sciences *96*, 11681-11686.

Bogadhi, A.R., Bollimunta, A., Leopold, D.A., and Krauzlis, R.J. (2018). Brain regions modulated during covert visual attention in the macaque. Sci Rep *8*, 15237.

Bogadhi, A.R., Bollimunta, A., Leopold, D.A., and Krauzlis, R.J. (2019). Spatial Attention Deficits Are Causally Linked to an Area in Macaque Temporal Cortex. Curr Biol *29*, 726-736.e724.

Bogart, S.L., Mangin, J.F., Schapiro, S.J., Reamer, L., Bennett, A.J., Pierre, P.J., and Hopkins, W.D. (2012). Cortical sulci asymmetries in chimpanzees and macaques: a new look at an old idea. Neuroimage *61*, 533-541.

Bourgeois, J.P., and Rakic, P. (1993). Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci *13*, 2801-2820.

Braddick, O., and Atkinson, J. (2011). Development of human visual function. Vision Research *51*, 1588-1609.

Brazelton, T. (1973). Neonatal Behavioral Assessment Scale. Clinics in Developmental Medicine, No 50.

Budday, S., Steinmann, P., and Kuhl, E. (2015). Physical biology of human brain development. Front Cell Neurosci *9*, 257.

Burghardt, G.M. (2005). The genesis of animal play: Testing the limits (Mit Press).

Cárdenas-de-la-Parra, A., Lewis, J.D., Fonov, V.S., Botteron, K.N., McKinstry, R.C., Gerig, G., Pruett, J.R., Jr., Dager, S.R., Elison, J.T., Styner, M.A.*, et al.* (2021). A voxel-wise assessment of growth differences in infants developing autism spectrum disorder. Neuroimage Clin *29*, 102551.

Cardinal, R.N., Parkinson, J.A., Hall, J., and Everitt, B.J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience & Biobehavioral Reviews *26*, 321-352.

Chang, S.W.C., Brent, L.J.N., Adams, G.K., Klein, J.T., Pearson, J.M., Watson, K.K., and Platt, M.L. (2013). Neuroethology of primate social behavior. Proceedings of the National Academy of Sciences *110*, 10387-10394.

Chawarska, K., Macari, S., and Shic, F. (2013). Decreased Spontaneous Attention to Social Scenes in 6-Month-Old Infants Later Diagnosed with Autism Spectrum Disorders. Biological Psychiatry *74*, 195-203.

Colombo, J. (2001). The Development of Visual Attention in Infancy. Annual Review of Psychology *52*, 337-367.

Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., Metzger, L.M., Shoushtari, C.S., Splinter, R., and Reich, W. (2003). Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord *33*, 427-433.

Constantino, J.N., and Gruber, C.P. (2012). Social Responsiveness Scale Second Edition (SRS-2): Manual (Western Psychological Services (WPS)).

Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., and Shulman, G.L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci *3*, 292-297.

Corbetta, M., Patel, G., and Shulman, G.L. (2008). The reorienting system of the human brain: from environment to theory of mind. Neuron *58*, 306-324.

Corbetta, M., and Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci *3*, 201-215.

Courchesne, E., Carper, R., and Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. Jama *290*, 337-344.

Cusick, C.G., Seltzer, B., Cola, M., and Griggs, E. (1995). Chemoarchitectonics and corticocortical terminations within the superior temporal sulcus of the rhesus monkey: Evidence for

subdivisions of superior temporal polysensory cortex. The Journal of Comparative Neurology *360*, 513-535.

Davranche, K., Nazarian, B., Vidal, F., and Coull, J. (2011). Orienting attention in time activates left intraparietal sulcus for both perceptual and motor task goals. J Cogn Neurosci *23*, 3318-3330.

De Winter, F.L., Zhu, Q., Van den Stock, J., Nelissen, K., Peeters, R., de Gelder, B., Vanduffel, W., and Vandenbulcke, M. (2015). Lateralization for dynamic facial expressions in human superior temporal sulcus. Neuroimage *106*, 340-352.

Dekkers, M.P., Nikoletopoulou, V., and Barde, Y.A. (2013). Cell biology in neuroscience: Death of developing neurons: new insights and implications for connectivity. J Cell Biol *203*, 385-393.

Distler, C., Bachevalier, J., Kennedy, C., Mishkin, M., and Ungerleider, L.G. (1996). Functional Development of the Corticocortical Pathway for Motion Analysis in the Macaque Monkey: A 14C-2-Deoxyglucose Study. Cerebral Cortex *6*, 184-195.

Farrant, K., and Uddin, L.Q. (2016). Atypical developmental of dorsal and ventral attention networks in autism. Dev Sci *19*, 550-563.

Feczko, E.J., Bliss-Moreau, E., Walum, H., Pruett, J.R., Jr., and Parr, L.A. (2016). The Macaque Social Responsiveness Scale (mSRS): A Rapid Screening Tool for Assessing Variability in the Social Responsiveness of Rhesus Monkeys (Macaca mulatta). PLoS One *11*, e0145956.

Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M*, et al.* (2012). 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging *30:1323–1341*.

Ferrari, P.F., Paukner, A., Ionica, C., and Suomi, S.J. (2009). Reciprocal face-to-face communication between rhesus macaque mothers and their newborn infants. Curr Biol *19*, 1768-1772.

Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B.T.T., Mohlberg, H., Amunts, K., and Zilles, K. (2008). Cortical Folding Patterns and Predicting Cytoarchitecture. Cerebral Cortex *18*, 1973-1980.

Frank, M.C., Amso, D., and Johnson, S.P. (2014). Visual search and attention to faces during early infancy. J Exp Child Psychol *118*, 13-26.

Freiwald, W.A., and Tsao, D.Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. Science *330*, 845-851.

Frintrop, S., Backer, G., and Rome, E. (2005). Goal-directed search with a top-down modulated computational attention system. Paper presented at: Joint Pattern Recognition Symposium (Springer).

Funahashi, S., and Andreau, J.M. (2013). Prefrontal cortex and neural mechanisms of executive function. J Physiol Paris *107*, 471-482.

Gazzaniga, M.S., Ivry, R.B., and Mangun, G.R. (2018). Attention. In Cognitive Neuroscience: The Biology of the Mind, Fifth Edition (New York: W.W. Norton & Company).

Gilmore, J.H., Shi, F., Woolson, S.L., Knickmeyer, R.C., Short, S.J., Lin, W., Zhu, H., Hamer, R.M., Styner, M., and Shen, D. (2012). Longitudinal development of cortical and subcortical gray matter from birth to 2 years. Cereb Cortex *22*, 2478-2485.

Ginsburg, K.R. (2007). The importance of play in promoting healthy child development and maintaining strong parent-child bonds. Pediatrics *119*, 182-191.

Gipson, C.D., and Olive, M.F. (2017). Structural and functional plasticity of dendritic spines - root or result of behavior? Genes Brain Behav *16*, 101-117.

Glasel, H., Leroy, F., Dubois, J., Hertz-Pannier, L., Mangin, J.F., and Dehaene-Lambertz, G. (2011). A robust cerebral asymmetry in the infant brain: the rightward superior temporal sulcus. Neuroimage *58*, 716-723.

Gnadt, J.W., and Andersen, R.A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. Exp Brain Res *70*, 216-220.

Gogtay, N., and Thompson, P.M. (2010). Mapping gray matter development: implications for typical development and vulnerability to psychopathology. Brain Cogn *72*, 6-15.

Goldberg, M.E., Bisley, J.W., Powell, K.D., and Gottlieb, J. (2006). Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. Prog Brain Res *155*, 157-175.

Goldman-Rakic, P.S. (1987). Development of cortical circuitry and cognitive function. Child development *58*, 601-622.

Gómez-Robles, A., Hopkins, W.D., and Sherwood, C.C. (2013). Increased morphological asymmetry, evolvability and plasticity in human brain evolution. Proc Biol Sci *280*, 20130575.

Gray, P. (2011). The Special Value of Children's Age-Mixed Play. American Journal of Play *3*, 500-522.

Grefkes, C., and Fink, G.R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. J Anat *207*, 3-17.

Gregoriou, G.G., Borra, E., Matelli, M., and Luppino, G. (2006). Architectonic organization of the inferior parietal convexity of the macaque monkey. The Journal of Comparative Neurology *496*, 422-451.

Grossman, E., Donnelly, M., Price, R., Pickens, D., Morgan, V., Neighbor, G., and Blake, R. (2000). Brain areas involved in perception of biological motion. J Cogn Neurosci *12*, 711-720.

Halligan, P.W., and Marshall, J.C. (1994). Toward a principled explanation of unilateral neglect. Cognitive Neuropsychology *11*, 167-206.

Hazlett, H.C., Gu, H., Munsell, B.C., Kim, S.H., Styner, M., Wolff, J.J., Elison, J.T., Swanson, M.R., Zhu, H., Botteron, K.N.*, et al.* (2017). Early brain development in infants at high risk for autism spectrum disorder. Nature *542*, 348-351.

Herrington, J.D., Nymberg, C., and Schultz, R.T. (2011). Biological motion task performance predicts superior temporal sulcus activity. Brain Cogn *77*, 372-381.

Hinde, R.A., and Spencer-Booth, Y. (1967). The behaviour of socially living rhesus monkeys in their first two and a half years. Animal Behaviour *15*, 169-196.

Hoffman, E.A., and Haxby, J.V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. Nature Neuroscience *3*, 80-84.

Hutchins, J.B., and Barger, S.W. (1998). Why neurons die: cell death in the nervous system. Anat Rec *253*, 79-90.

Huttenlocher, P.R., and Dabholkar, A.S. (1997). Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol *387*, 167-178.

Iacoboni, M., and Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. Nature Reviews Neuroscience *7*, 942-951.

Itti, L., Koch, C., and Niebur, E. (1998). A model of saliency-based visual attention for rapid scene analysis. IEEE Transactions on pattern analysis and machine intelligence *20*, 1254-1259.

Johnson, H., Harris, G., and Williams, K. (2007). BRAINSFit: Mutual Information Registrations of Whole-Brain 3D Images, Using the Insight Toolkit. . The Insight Journal: 180.

Jones, W., Carr, K., and Klin, A. (2008). Absence of Preferential Looking to the Eyes of Approaching Adults Predicts Level of Social Disability in 2-Year-Old Toddlers With Autism Spectrum Disorder. Archives of General Psychiatry *65*, 946.

Jones, W., and Klin, A. (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature *504*, 427-431.

Kanemura, H., Aihara, M., Aoki, S., Araki, T., and Nakazawa, S. (2003). Development of the prefrontal lobe in infants and children: a three-dimensional magnetic resonance volumetric study. Brain and Development *25*, 195-199.

Kanner, L. (1943). Autistic disturbances of affective contact. Nervous child *2*, 217-250.

Kiorpes, L. (2015). Visual development in primates: Neural mechanisms and critical periods. Dev Neurobiol *75*, 1080-1090.

Klin, A., Jones, W., Schultz, R., and Volkmar, F. (2003). The enactive mind, or from actions to cognition: lessons from autism. Philosophical Transactions of the Royal Society of London Series B: Biological Sciences *358*, 345-360.

Klin, A., Jones, W., Schultz, R., Volkmar, F., and Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry *59*, 809-816.

Klin, A., Lin, D.J., Gorrindo, P., Ramsay, G., and Jones, W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. Nature *459*, 257-261.

Knickmeyer, R.C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J.K., Hamer, R.M., Lin, W., Gerig, G., and Gilmore, J.H. (2008). A structural MRI study of human brain development from birth to 2 years. J Neurosci *28*, 12176-12182.

Knickmeyer, R.C., Styner, M., Short, S.J., Lubach, G.R., Kang, C., Hamer, R., Coe, C.L., and Gilmore, J.H. (2010). Maturational trajectories of cortical brain development through the pubertal transition: unique species and sex differences in the monkey revealed through structural magnetic resonance imaging. Cereb Cortex *20*, 1053-1063.

Kovacs-Balint, Z., Feczko, E., Pincus, M., Earl, E., Miranda-Dominguez, O., Howell, B., Morin, E., Maltbie, E., Li, L., Steele, J.*, et al.* (2019). Early Developmental Trajectories of Functional Connectivity Along the Visual Pathways in Rhesus Monkeys. Cereb Cortex *29*, 3514-3526.

Kovacs-Balint, Z.A., Payne, C., Steele, J., Li, L., Styner, M., Bachevalier, J., and Sanchez, M.M. (2021). Structural development of cortical lobes during the first 6 months of life in infant macaques. Developmental Cognitive Neuroscience *48*, 100906.

Kovacs Balint, Z., Raper, J., Michopoulos, V., Howell, L.H., Gunter, C., Bachevalier, J., and Sanchez, M.M. (2020). Validation of the Social Responsiveness Scale (SRS) to screen for atypical social behaviors in juvenile macaques. bioRxiv, 2020.2006.2026.173161.

Kraemer, P.M., Görner, M., Ramezanpour, H., Dicke, P.W., and Thier, P. (2020). Frontal, Parietal, and Temporal Brain Areas Are Differentially Activated When Disambiguating Potential Objects of Joint Attention. eNeuro *7*.

Krall, S.C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P.T., Eickhoff, S.B., Fink, G.R., and Konrad, K. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. Brain Struct Funct *220*, 587-604.

Kwon, M.K., Setoodehnia, M., Baek, J., Luck, S.J., and Oakes, L.M. (2016). The development of visual search in infancy: Attention to faces versus salience. Dev Psychol *52*, 537-555.

Lai, M.-C., Lombardo, M.V., and Baron-Cohen, S. (2014). Autism. The Lancet *383*, 896-910.

Leopold, D.A., and Krauzlis, R.J. (2020). How the brain pays attention to others' attention. Proc Natl Acad Sci U S A *117*, 3901-3903.

Levy, B.J., and Wagner, A.D. (2011). Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. Annals of the New York Academy of Sciences *1224*, 40-62.

Lewis, D. (2000). The organization of cortical circuitry. In The neuropathology of schizophrenia: Progress and interpretation, P.J. Harrison, and G.W. Roberts, eds. (Oxford, New York: Oxford University Press).

Liu, C., Tian, X., Liu, H., Mo, Y., Bai, F., Zhao, X., Ma, Y., and Wang, J. (2015). Rhesus monkey brain development during late infancy and the effect of phencyclidine: a longitudinal MRI and DTI study. Neuroimage *107*, 65-75.

Liu, Y., Yttri, E.A., and Snyder, L.H. (2010). Intention and attention: different functional roles for LIPd and LIPv. Nat Neurosci *13*, 495-500.

Loomes, R., Hull, L., and Mandy, W.P.L. (2017). What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry *56*, 466-474.

Luo, L., and O'Leary, D. (2005). Axon Retraction and Degeneration in Development and Disease. Annual Review of Neuroscience *28*, 127-156.

Machado, C.J., Bliss-Moreau, E., Platt, M.L., and Amaral, D.G. (2011). Social and Nonsocial Content Differentially Modulates Visual Attention and Autonomic Arousal in Rhesus Macaques. PLoS One *6*, e26598.

Maenner, M.J., Shaw, K.A., Baio, J., EdS, Washington, A., Patrick, M., DiRienzo, M., Christensen, D.L., Wiggins, L.D., Pettygrove, S.*, et al.* (2020). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ *69*, 1-12.

Malkova, L., Heuer, E., and Saunders, R.C. (2006). Longitudinal magnetic resonance imaging study of rhesus monkey brain development. Eur J Neurosci *24*, 3204-3212.

Marciniak, K., Atabaki, A., Dicke, P.W., and Thier, P. (2014). Disparate substrates for head gaze following and face perception in the monkey superior temporal sulcus. Elife *3*.

Marquardt, K., Ramezanpour, H., Dicke, P.W., and Thier, P. (2017). Following Eye Gaze Activates a Patch in the Posterior Temporal Cortex That Is not Part of the Human "Face Patch" System. eNeuro *4*.

Marrus, N., Faughn, C., Shuman, J., Petersen, S.E., Constantino, J.N., Povinelli, D.J., and Pruett, J.R., Jr. (2011). Initial description of a quantitative, cross-species (chimpanzee-human) social responsiveness measure. J Am Acad Child Adolesc Psychiatry *50*, 508-518.

Mars, R.B., Sallet, J., Schuffelgen, U., Jbabdi, S., Toni, I., and Rushworth, M.F.S. (2012a). Connectivity-Based Subdivisions of the Human Right "Temporoparietal Junction Area": Evidence for Different Areas Participating in Different Cortical Networks. Cerebral Cortex *22*, 1894-1903.

Mars, R.B., Sallet, J., Schuffelgen, U., Jbabdi, S., Toni, I., and Rushworth, M.F.S. (2012b). Connectivity-Based Subdivisions of the Human Right ‘‘Temporoparietal Junction Area’’: Evidence for Different Areas Participating in Different Cortical Networks. Cerebral Cortex *22*, 1894-1903.

McCormack, K., Howell, B.R., Guzman, D., Villongco, C., Pears, K., Kim, H., Gunnar, M.R., and Sanchez, M.M. (2015). The development of an instrument to measure global dimensions of maternal care in rhesus macaques (Macaca mulatta). Am J Primatol *77*, 20-33.

McCormack, K., Newman, T.K., Higley, J.D., Maestripieri, D., and Sanchez, M.M. (2009). Serotonin transporter gene variation, infant abuse, and responsiveness to stress in rhesus macaque mothers and infants. Horm Behav *55*, 538-547.

McCormack, K., Sanchez, M.M., Bardi, M., and Maestripieri, D. (2006). Maternal care patterns and behavioral development of rhesus macaque abused infants in the first 6 months of life. Dev Psychobiol *48*, 537-550.

Miller, E.K., and Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annu Rev Neurosci *24*, 167-202.

Mills, K.L., and Tamnes, C.K. (2014). Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci *9*, 172-190.

Monosov, I.E., and Thompson, K.G. (2009). Frontal eye field activity enhances object identification during covert visual search. J Neurophysiol *102*, 3656-3672.

Morin, E.L., Howell, B.R., Meyer, J.S., and Sanchez, M.M. (2019). Effects of early maternal care on adolescent attention bias to threat in nonhuman primates. Developmental Cognitive Neuroscience *38*, 100643.

Moriuchi, J.M., Klin, A., and Jones, W. (2017). Mechanisms of Diminished Attention to Eyes in Autism. Am J Psychiatry *174*, 26-35.

Muschinski, J., Feczko, E., Brooks, J.M., Collantes, M., Heitz, T.R., and Parr, L.A. (2016). The development of visual preferences for direct versus averted gaze faces in infant macaques (Macaca mulatta). Developmental Psychobiology *58*, 926-936.

Naber, F.B., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., Swinkels, S.H., Buitelaar, J.K., Dietz, C., van Daalen, E., and van Engeland, H. (2008). Play behavior and attachment in toddlers with autism. J Autism Dev Disord *38*, 857-866.

Navalpakkam, V., and Itti, L. (2005). Modeling the influence of task on attention. Vision research *45*, 205-231.

Neubauer, S., Gunz, P., Scott, N.A., Hublin, J.-J., and Mitteroecker, P. (2020). Evolution of brain lateralization: A shared hominid pattern of endocranial asymmetry is much more variable in humans than in great apes. Science Advances *6*, eaax9935.

Nijhof, S.L., Vinkers, C.H., van Geelen, S.M., Duijff, S.N., Achterberg, E.J.M., van der Net, J., Veltkamp, R.C., Grootenhuis, M.A., van de Putte, E.M., Hillegers, M.H.J.*, et al.* (2018). Healthy play, better coping: The importance of play for the development of children in health and disease. Neuroscience & Biobehavioral Reviews *95*, 421-429.

Nye, C. (2014). A Child's Vision. Pediatric Clinics of North America *61*, 495-503.

O'Leary, D.D. (1992). Development of connectional diversity and specificity in the mammalian brain by the pruning of collateral projections. Curr Opin Neurobiol *2*, 70-77.

Oliva, A., and Torralba, A. (2007). The role of context in object recognition. Trends in cognitive sciences *11*, 520-527.

Oppenheim, R.W. (1991). Cell death during development of the nervous system. Annu Rev Neurosci *14*, 453-501.

Ozonoff, S., Iosif, A.-M., Baguio, F., Cook, I.C., Hill, M.M., Hutman, T., Rogers, S.J., Rozga, A., Sangha, S., Sigman, M.*, et al.* (2010). A prospective study of the emergence of early behavioral signs of autism. Journal of the American Academy of Child and Adolescent Psychiatry *49*, 256-266.e662.

Papagiannopoulou, E.A., Chitty, K.M., Hermens, D.F., Hickie, I.B., and Lagopoulos, J. (2014). A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders. Social Neuroscience, 1-23.

Parten, M.B. (1932). Social participation among pre-school children. The Journal of Abnormal and Social Psychology *27*, 243.

Patel, C.I., Garg, S., Zaveri, T., and Banerjee, A. (2014). Top-Down and Bottom-Up Cues Based Moving Object Detection for Varied Background Video Sequences. Advances in Multimedia *2014*, 879070.

Paxinos, G., Huang, X., and Toga, A.W. (2000). The Rhesus Monkey Brain in Stereotaxic Coordinates. Faculty of Health and Behavioural Sciences - Papers (Archive)

Pelphrey, K.A., and Morris, J.P. (2006). Brain Mechanisms for Interpreting the Actions of Others From Biological-Motion Cues. Curr Dir Psychol Sci *15*, 136-140.

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. Phil Trans R Soc B *360*, 781-795.

Petrides, M., and Pandya, D. (1994). Comparative architectonic analysis of the human and the macaque frontal cortex. Handbook of neuropsychology *11*, 17-58.

Petrides, M., and Pandya, D.N. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. European Journal of Neuroscience *16*, 291-310.

Petrides, M., and Pandya, D.N. (2007). Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J Neurosci *27*, 11573-11586.

Postema, M.C., van Rooij, D., Anagnostou, E., Arango, C., Auzias, G., Behrmann, M., Filho, G.B., Calderoni, S., Calvo, R., Daly, E.*, et al.* (2019). Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets. Nat Commun *10*, 4958.

Pulvermüller, F., and Mohr, B. (1996). The Concept of Transcortical Cell Assemblies: a Key to the Understanding of Cortical Lateralization and Interhemispheric Interaction. Neuroscience & Biobehavioral Reviews *20*, 557-566.

Rakic, P., Bourgeois, J.P., Eckenhoff, M.F., Zecevic, N., and Goldman-Rakic, P.S. (1986). Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science *232*, 232-235.

Ramezanpour, H., and Thier, P. (2020). Decoding of the other's focus of attention by a temporal cortex module. Proc Natl Acad Sci U S A *117*, 2663-2670.

Raper, J., Stephens, S.B., Sanchez, M., Bachevalier, J., and Wallen, K. (2014). Neonatal amygdala lesions alter mother-infant interactions in rhesus monkeys living in a species-typical social environment. Dev Psychobiol *56*, 1711-1722.

Riccomagno, M.M., and Kolodkin, A.L. (2015). Sculpting neural circuits by axon and dendrite pruning. Annu Rev Cell Dev Biol *31*, 779-805.

Richards, J. (2001). Cortical Indexes of Saccade Planning Following Covert Orienting in 20-Week-Old Infants. Infancy *2*.

Richards, J.E. (2000). Localizing the development of covert attention in infants with scalp event-related potentials. Dev Psychol *36*, 91-108.

Rizzolatti, G., and Craighero, L. (2004). THE MIRROR-NEURON SYSTEM. Annual Review of Neuroscience *27*, 169-192.

Rosenholtz, R. (1999). A simple saliency model predicts a number of motion popout phenomena. Vision research *39*, 3157-3163.

Rushworth, M.F.S., Johansen-Berg, H., Göbel, S.M., and Devlin, J.T. (2003). The left parietal and premotor cortices: motor attention and selection. NeuroImage *20*, S89-S100.

Saleem, K., and Logothetis, N. (2006). A Combined MRI and Histology Atlas of the Rhesus Monkey Brain in Stereotaxic Coordinates, 1st ed (Boston: Academic Press).

Salminen-Vaparanta, N., Koivisto, M., Vorobyev, V., Alakurtti, K., and Revonsuo, A. (2019). Does TMS on V3 block conscious visual perception? Neuropsychologia *128*, 223-231.

Samonds, J.M., and Priebe, N.J. (2020). 1.22 - The Primary Visual Cortex. In The Senses: A Comprehensive Reference (Second Edition), B. Fritzsch, ed. (Oxford: Elsevier), pp. 392-412.

Sapountzis, P., Paneri, S., and Gregoriou, G.G. (2018). Distinct roles of prefrontal and parietal areas in the encoding of attentional priority. Proceedings of the National Academy of Sciences *115*, E8755-E8764.

Schall, J., Morel, A., King, D., and Bullier, J. (1995). Topography of visual cortex connections with frontal eye field in macaque: convergence and segregation of processing streams. Paper presented at: The Journal of neuroscience : the official journal of the Society for Neuroscience.

Schneider, M.L., and Suomi, S.J. (1992). Neurobehavioral assessment in rhesus monkey neonates (Macaca mulatta): developmental changes, behavioral stability, and early experience. Infant Behavior and Development *15*, 155-177.

Sclafani, V., Del Rosso, L.A., Seil, S.K., Calonder, L.A., Madrid, J.E., Bone, K.J., Sherr, E.H., Garner, J.P., Capitanio, J.P., and Parker, K.J. (2016). Early Predictors of Impaired Social Functioning in Male Rhesus Macaques (Macaca mulatta). PLOS ONE *11*, e0165401.

Scott, J.A., Grayson, D., Fletcher, E., Lee, A., Bauman, M.D., Schumann, C.M., Buonocore, M.H., and Amaral, D.G. (2016). Longitudinal analysis of the developing rhesus monkey brain using magnetic resonance imaging: birth to adulthood. Brain Struct Funct *221*, 2847-2871.

Seltzer, B., and Pandya, D.N. (1978). Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. Brain Research *149*, 1-24.

Seltzer, B., and Pandya, D.N. (1989). Frontal lobe connections of the superior temporal sulcus in the rhesus monkey. The Journal of Comparative Neurology *281*, 97-113.

Shaw, K.A., Maenner, M.J., Baio, J., Washington, A., Christensen, D.L., Wiggins, L.D., Pettygrove, S., Andrews, J.G., White, T., Rosenberg, C.R.*, et al.* (2020). Early Identification of Autism Spectrum Disorder Among Children Aged 4 Years - Early Autism and Developmental Disabilities Monitoring Network, Six Sites, United States, 2016. MMWR Surveill Summ *69*, 1-11.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Constable, R.T., Skudlarski, P., Fulbright, R.K., Bronen, R.A., Fletcher, J.M., Shankweiler, D.P., Katz, L.*, et al.* (1995). Sex differences in the functional organization of the brain for language. Nature *373*, 607-609.

Shen, M.D., Nordahl, C.W., Young, G.S., Wootton-Gorges, S.L., Lee, A., Liston, S.E., Harrington, K.R., Ozonoff, S., and Amaral, D.G. (2013). Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. Brain *136*, 2825-2835.

Shi, Y., Budin, F., Yapuncich, E., Rumple, A., Young, J.T., Payne, C., Zhang, X., Hu, X., Godfrey, J., Howell, B.*, et al.* (2017). UNC-Emory Infant Atlases for Macaque Brain Image Analysis: Postnatal Brain Development through 12 Months. Front Neurosci *10*, 617.

Sigaard, R.K., Kjær, M., and Pakkenberg, B. (2016). Development of the Cell Population in the Brain White Matter of Young Children. Cereb Cortex *26*, 89-95.

Silbereis, J.C., Pochareddy, S., Zhu, Y., Li, M., and Sestan, N. (2016). The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. Neuron *89*, 248-268.

Sliwa, J., and Freiwald, W.A. (2017). A dedicated network for social interaction processing in the primate brain. Science *356*, 745-749.

Smith, E. (2012). Social play in primates (Elsevier).

Styner M, Knickmeyer R, Joshi S, Coe C, Short SJ, and J, G. (2007). Automatic brain segmentation in rhesus monkeys. . In (Pluim JPW, Reinhardt JM, eds), pp 65122L.

Syal, S., and Finlay, B.L. (2011). Thinking outside the cortex: social motivation in the evolution and development of language. Developmental Science *14*, 417-430.

Toga, A.W., and Thompson, P.M. (2003). Mapping brain asymmetry. Nature Reviews Neuroscience *4*, 37-48.

Tustison, N.J., and Avants, B.B. (2013). Explicit B-spline regularization in diffeomorphic image registration. Front Neuroinform *7*, 39.

Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., and Gee, J.C. (2010). N4ITK: improved N3 bias correction. IEEE Trans Med Imaging *29*, 1310-1320.

Ungerer, J.A., and Sigman, M. (1981). Symbolic play and language comprehension in autistic children. J Am Acad Child Psychiatry *20*, 318-337.

Van Essen, D., Newsome, W., Maunsell, J., and Bixby, J. (1986). The projections from striate cortex (V1) to areas V2 and V3 in the macaque monkey: asymmetries, areal boundaries, and patchy connections. Journal of Comparative Neurology *244*, 451-480.

Volkmar, F.R. (2014). Editorial: the importance of early intervention. J Autism Dev Disord *44*, 2979-2980.

Vossel, S., Geng, J.J., and Fink, G.R. (2014). Dorsal and Ventral Attention Systems. The Neuroscientist *20*, 150-159.

Vossel, S., Weidner, R., Driver, J., Friston, K.J., and Fink, G.R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. J Neurosci *32*, 10637-10648.

Walker, A.E. (1940). A cytoarchitectural study of the prefrontal area of the macaque monkey. Journal of Comparative Neurology *73*, 59-86.

Wang, A., Payne, C., Moss, S., Jones, W.R., and Bachevalier, J. (2020). Early developmental changes in visual social engagement in infant rhesus monkeys. Dev Cogn Neurosci *43*, 100778.

Wang, J., Vachet, C., Rumple, A., Gouttard, S., Ouziel, C., Perrot, E., Du, G., Huang, X., Gerig, G., and Styner, M. (2014). Multi-atlas segmentation of subcortical brain structures via the AutoSeg software pipeline. Front Neuroinform *8*, 7.

Wardak, C., Olivier, E., and Duhamel, J.R. (2002). Saccadic target selection deficits after lateral intraparietal area inactivation in monkeys. J Neurosci *22*, 9877-9884.

Watanabe, H., Homae, F., and Taga, G. (2010). General to specific development of functional activation in the cerebral cortexes of 2- to 3-month-old infants. NeuroImage *50*, 1536-1544.

Watts, M.E., Pocock, R., and Claudianos, C. (2018). Brain Energy and Oxygen Metabolism: Emerging Role in Normal Function and Disease. Front Mol Neurosci *11*, 216.

Yeterian, E.H., Pandya, D.N., Tomaiuolo, F., and Petrides, M. (2012). The cortical connectivity of the prefrontal cortex in the monkey brain. Cortex *48*, 58-81.

Yogman, M., Garner, A., Hutchinson, J., Hirsh-Pasek, K., and Golinkoff, R.M. (2018). The Power of Play: A Pediatric Role in Enhancing Development in Young Children. Pediatrics *142*, e20182058.

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., and Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. International Journal of Developmental Neuroscience *23*, 143-152.