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Sara E. Saavedra April 7, 2020

# Developmental trajectories in social reward and salience brain networks: A combined behavioral and structural MRI study in infant rhesus macaques

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Abstract

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Non-human primate (NHP) translational models are critical for understanding social deficits in neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD). The goal of this study was to map developmental trajectories of social reward and salience neurocircuits that support the maturation of early prosocial behaviors in infant rhesus macaques.

Longitudinal structural MRI scans were acquired at 2, 4, 8, 12, 24wks from 25 infant male macaques living with their mothers in social groups; 21 of 25 subjects were also scanned at 16, 20wks, and 4 were scanned at 6wks. T1- and T2-weighted images were acquired using a 3T MRI scanner and analyzed for volumetric changes in social reward and salience neurocircuits, which include the amygdala (AMY), nucleus accumbens (NAcc), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), ventromedial PFC (vmPFC) and insula (INS). Measures of social development were collected from a subset of subjects (n = 9), using: (1) focal observations and a rhesus ethogram, (2) rating scales of atypical social behaviors (adapted from the Social Responsiveness Scale (SRS) used for ASD diagnosis in humans). Associations between brain and social behavior developmental measures were examined in a subset of 4 animals with both sMRI and behavioral data.

Region-specific developmental trajectories were identified in these social salience and reward brain networks, although rapid growth was shown by most regions between 8-12 and 16-20 weeks. These changes were paralleled by a decline in frequency and duration of mother-infant affiliative, contact, and proximity behaviors by 8 weeks, when infants increase independence-seeking behaviors and social play. Finally, our preliminary analysis identified the ACC and subgenual cingulate (a subregion of the mPFC) developmental volume changes as significant predictors of changes in social behaviors.

Our findings suggest that during the first 24 weeks of life (equivalent to 2 years in humans), social salience and reward brain networks undergo robust structural changes that parallel the infant's maturation to independence and increased emotional awareness of appropriate social interaction. Understanding normative development of social behavior 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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## Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a range of behavioral deficits, including difficulty with communication and with social interactions, obsessive interests, and repetitive behaviors (American Psychiatric Association, 2013). As of 2014, 1 in 59 children are diagnosed with ASD in the US, and this number has been increasing for decades (Baio, 2018). Sex is an influential factor in the pathology of ASD, as male infants are four times more likely to be affected and diagnosed than females (Baio, 2018). It is increasingly important to understand how ASD develops in infants and its neurobiological underpinnings, as early diagnosis and intervention is critical in improving outcomes and managing the symptoms a child may have (Elder et al., 2017; Pasco, 2018).

Social interaction is a fundamental component of not just human society, but of other primate species, and the social deficits that characterize ASD have a huge impact on the daily lives of those affected. Unfortunately, these deficits do not become obvious until early childhood, about 2 years of age in most children, challenging diagnosis and intervention early on (Levy et al., 2009). Social deficits of ASD can be heterogeneous, with children exhibiting a range of behavioral symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), children with ASD tend to self-isolate: they do not interact with peers, form few friendships, and lack social reciprocity (American Psychiatric Association, 2013). They also may not have desire to share their interests with others (Levy et al., 2009). On the other hand, some children with ASD may be inappropriately affectionate with strangers and may become extremely attached to their mother, and refuse to be separated from her (Rapin, 1991).

Atypical eye gaze patterns also characterize ASD. Both children and adults avoid eye contact during social interaction, and this aversion to the eyes is an important biomarker for the disorder (Papagiannopoulou et al., 2014). Recent research has found that ASD atypical social engagement is already displayed during infancy, with preference to look at non-social stimuli over other people and avoidance of eye gaze detectable after 6 months of age (Klin et al., 2009; Jones and Klin, 2013). The study by Jones and Klin (2013) demonstrates that typically developing infants' attention to their caregiver's eyes shows a sharp increase from 2-10 months. By 8-10 months, infants pay more attention to the eyes than any other part of the face or body. In contrast, in the same study infants later diagnosed with ASD actually started showing higher attention to the eyes than the typically developing infants at 2 months of age; however, this pattern reversed later on, and attention to the eyes declined progressively between 4-8 months. These findings indicate that there may be neurodevelopmental changes underlying the social deficits of ASD present from as early as 2 months of age and that understanding these differences in neural and behavioral developmental trajectories of ASD versus typically developing infants is critical.

Given this evidence, and the striking importance of early diagnosis and intervention, it is imperative to further investigate the early stages of social development. The Bachevalier and Sanchez labs at the Yerkes National Primate Research Center (YNPRC) are collaborating with researchers at the Marcus Autism Center in an NIH-funded Autism Center of Excellence (ACE) study to explore cross-species neurodevelopmental alterations that lead to early social deficits seen in infants with ASD. Both human and nonhuman primate (NHP) infants such as macaques, show similar social and neural development trajectories and milestones. In both humans and

NHP infants there are also early neuromotor reflexes, such as grasping, that shift from reflexive to a conscious motor control (Capute, 1986; St John et al., 2016). One of the main hypotheses of the ACE study is that early social development may follow a similar process, transitioning from early reflexive to conscious control of visual attention (eye gaze) in parallel to the achievement of socioemotional milestones. Several brain networks and circuits may support this transition and socioemotional functioning in early life, including social visual engagement (object and motion pathways), attention, affiliation/reward and salience brain networks. The present study focuses specifically on one aspect of this project: the characterization of the development of social affiliation/reward and salience brain networks as predictors of social maturation in infant rhesus monkeys.

The social affiliation/reward network is important for deriving perceived reward or pleasure for social interaction, motivation towards social interaction, and attachment; within this network we are studying the amygdala (AMY), nucleus accumbens (NAcc), anterior cingulate cortex (ACC), insula (INS), and ventromedial prefrontal cortex (vmPFC), as well as their connections (Kohls et al., 2012; Atzil et al., 2014; Landers and Sullivan, 2012). The social salience network is known for its role in the detection of the valence of emotional and social cues and consists of the AMY, ACC, INS, NAcc and orbitofrontal cortex (OFC) (Seeley et al., 2007; Uddin et al., 2013; Rosen et al., 2018). The social affiliation/reward and social salience brain networks are depicted in Figure 1 (Courtesy of Dr. Jocelyne Bachevalier).

The AMY is part of both the social reward and social salience brain networks. Social value is encoded in the AMY, which greatly influences the social decision-making processes central to the OFC and ACC –with which it connects-, such as selection of social partners (Grabenhorst et

al., 2019). The AMY supports social affiliation, formed from positive emotions toward others, both locally and through its anatomical and functional connections with the mesolimbic reward system, which include projections from the ventral tegmental area –VTA- to the NAcc, in the ventral striatum (Bickart et al., 2014). As for the salience of social features, in both NHPs and humans the AMY plays an important role in processing facial expression and gaze. Patients with AMY damage tend to make less eye contact, and have more difficulty processing faces in general (Spezio et al., 2007). Additionally, in primate species with hierarchical dominance social structure, such as rhesus monkey societies, activity in specific AMY neurons encodes social rank information of the individuals (Munuera et al., 2018). In infant primates, the role of the AMY is less clear, although there is evidence that neonatal AMY lesions disrupt the normal mother-infant bond and increase social fear (Prather et al., 2001; Bauman et al., 2004; Raper et al., 2014). But, the role of healthy AMY development in infant social behavior is still unclear, and we hope to further investigate the social function of the AMY during infancy in this study.

The NAcc is well known as a central node in the reward pathways of the brain. Social interaction acts as a rewarding stimulus to produce feelings of pleasure from social interaction -or feelings of "liking"-, as well as motivation towards social interactions and approval –or feelings of "wanting" (Ikemoto and Panksepp, 1999; Reynolds and Berridge, 2002; Carlezon and Thomas, 2009). For example, an fMRI study found that positive social feedback, such as a smiling face, is rewarding and activates the NAcc (Spreckelmeyer et al., 2009). Social reward is modulated by neurotransmission in the NAcc, particularly through the actions of dopamine, serotonin, endogenous opioids, and oxytocin (Trezza et al., 2011; Dölen et al., 2013; Walsh et al., 2018). Interestingly, the NAcc mediates more than social reward. One study found that

aversion of social rejection may also be modulated by the NAcc (Kohls et al., 2012). Pair bonding and non-partner attachment (such as attachment between mother and child) in rodents and primates, is also dependent upon oxytocin effects on dopamine transmission in the NAcc (Young et al., 2001; Dölen et al., 2013). Finally, there is evidence that social play is rewarding, and is modulated by dopaminergic transmission in the NAcc (Manduca et al., 2016). In infant rodents, the NAcc also facilitates distress vocalizations in socially-isolated pups (Muller and Shair, 2016); however, the exact role of NAcc development in supporting social functioning in infant primates is unclear.

The ACC is involved in both social reward and salience, in part by receiving input from the OFC regarding social reward and unrewarding outcomes, and also through its connections with the AMY and INS facilitating attention, awareness, and information processing (Van Hoesen et al., 1993; Rolls, 2000; Medford and Critchley, 2010; White et al., 2010; Kujawa et al., 2016). Given its important role in error detection and conflict-monitoring some studies suggest that the ACC is involved in assessing the error between expected social rewards and actual reward (Diaconescu et al., 2017; Will et al., 2017; Lockwood and Wittmann, 2018). Additionally, specific subdivisions of the cingulate cortex, including the subgenual cingulate and perigenual ACC, are known to mediate the opposite of social reward: social pain, derived from rejection, exclusion or loss (Rotge et al., 2015). The ACC is also involved in tracking the salience of social cues. For example, in macaques, the anterior cingulate gyrus seems to be necessary for determining the social value of other animals; thus, macaques with an intact anterior cingulate gyrus paid more attention to certain social cues such as the faces of large, aggressive males, whereas those with lesions to this area did not attend to those stimuli (Rudebeck, 2006). In humans, the ACC

responds to discordance in social cues such as pupil dilation. Thus, during tasks measuring pupillary reflex synchrony between two individuals, the ACC is activated when the observer's pupil reflexes do not match those of the observed (Harrison et al., 2009). Finally, there is evidence that the ACC is responsible for modulating the salience of cues based on the value of the stimulus reward, combining functions between salience and reward networks (Hickey et al., 2010), as well as in social cognitive reward-based learning processes (Jones et al., 2011; Wallis and Kennerley, 2011). A study conducted on human infants found that the ACC is activated during a visual preference task , so there is some evidence that the ACC is also critical to support salience in the very early stages of life (Reynolds et al., 2010). However, the role of early development of the ACC on infant social functions is still poorly understood; therefore, this study hopes to elucidate this question of ACC developmental trajectory in NHPs.

Primates have more developed, complex and enlarged PFCs compared to other mammals, and there have been several studies suggesting that this may be due to increased social complexity (Dunbar and Shultz, 2007). The mPFC, in particular, has been shown to modulate social reward. The mPFC, including the dorsal mPFC and ventral mPFC, receives input from the NAcc, integrates information about social reward into plans for future actions and into judgements and perceptions of others; for example, learning socially-rewarding cues activates the mPFC (Forbes and Grafman, 2010). Without the dorsal mPFC (including Brodmann's Areas 25, 32, and parts of 10) and the vmPFC Brodmann's Areas 14humans show decreased levels of social interest and do not make prosocial decisions (Bicks et al., 2015). Furthermore, social acceptance -a socially rewarding stimulus- activates the vmPFC (Gunther Moor et al., 2010). The mPFC is also involved in modulating social attention, and vmPFC function is disrupted in those

with social deficits such as ASD (Bicks et al., 2015). For example, healthy adults show dorsal mPFC activation during a face-to-face joint attention task, but adults with ASD did not (Redcay et al., 2013). Overall, the mPFC works to integrate social reward, salience, and other aspects of social cognition, and there is some evidence that these cognitive processes begin during infancy in humans (Grossmann, 2013). Yet, the exact developmental timeline of the social behaviors supported by mPFC and vmPFC in primates is still unclear.

The INS is an important component of both social salience and social reward networks, and there is evidence of functional specificity of its ventral and dorsal anterior parts, so that the ventral anterior insula mediates socio-emotional perception, whereas the dorsal anterior insula may be more important for salience of social cues (Odriozola et al., 2016). Several studies have reported that the INS integrates emotion with social behavioral outcomes. For example, stimulation of different areas of the macaque INS results in either a change in emotional facial expression or social affiliation behavior (Caruana et al., 2011). Recent evidence shows that reward derived from both pleasant and emotionally neutral social touch is mediated by the INS (Morrison et al., 2011; Davidovic et al., 2017). The INS also modulates social attention, particularly toward emotional cues. Resection of the human INS in epilepsy patients results in an inability to recognize emotional facial expressions (Uddin et al., 2017). Both healthy children and children with ASD engage the INS during a social salience task, but children with ASD show less activity in salience regions outside the INS (Odriozola et al., 2016). The functional role of the INS in infant social development is not yet well characterized, although one study suggests that the INS may already play a role in processing emotional vocal cues in 7 month-old human

infants (Blasi et al., 2011); the present study aims to further characterize how early INS development supports social functioning in primates.

The OFC has a clear role in reward processing and social behavior, in part related to its involvement in decision making, goal-directed behavior, emotional appraisal and inhibitory control of behavior (Beer et al., 2006; Rempel-Clower, 2007; Azzi et al., 2012; Hughes and Beer, 2012). Macaques with OFC lesions not only have difficulty with learning reward-based tasks, but the lesion may also cause socioemotional changes, such as increased aggression (Rolls, 2000). Social reward value may also be encoded in the OFC. Motivation toward an expected reward can be influenced depending on whether or not that reward is shared with a partner, and neuronal firing in the OFC modulates this change in socially-oriented motivation (Isoda et al., 2018). As for attentional cues, the OFC is part of a salience network monitoring both social and nonsocial cues. An example of social stimuli that engage the OFC are facial expressions, and patients with OFC damage have impaired ability to recognize emotional expression, along with other deficits in social interaction (Watson and Platt, 2012; Munuera et al., 2018); lesions in the macaque OFC also result in altered patterns of facial scanning and face perception (Goursaud and Bachevalier, 2020). While the role of the OFC in adult social behavior has been characterized, it remains unclear how the early development in OFC during infancy may support the development of early social behaviors.

Working together, the social salience and reward networks support social functioning in the healthy individual. Yet, the early developmental trajectories of these networks in either typically developing children or those with ASD social deficits, has not yet been fully characterized. In order to push the age of diagnosis for these social disorders to earlier ages, it

is crucial to understand the development of the social brain and the relationship to social behavior in very young age groups. Therefore, the main question of this study is: what neural changes occur during early development in these social networks that support the development of social skills in infants? This relationship between brain networks and behavior is ideally studied using magnetic resonance imaging (MRI) techniques in parallel to intense social behavior analysis during development. However, conducting longitudinal, in depth MRI studies on human infants may not be possible due to ethical, procedural, and health concerns (Bauman and Schuman, 2017). Due to limitations of early and repeated experiments of human infants and lack of experimental control on important confounding factors (e.g. SES; diet; prenatal adverse exposure to stress, drugs or infection), the use of highly translational NHP animal models is critical. In particular, a NHP animal model for ASD-related social deficits would be useful as it would allow for future experimental manipulations of neural circuits during development using cutting-edge invasive techniques, such as chemogenetics or optogenetics.

Rhesus monkeys (*Macaca mulatta*) are an ideal animal model to study neural development. This is because phylogenetically, they are closer to humans than rodents, and their brains are much more similar to ours in regards to organization, neurochemistry and development. Rhesus monkeys are also a good choice for studying social behavior, as they show similar social behaviors compared to humans. They live in rich and complex social groups where infants acquire social skills necessary for their development first from their interactions with their mother and family, and then from play with peers and interactions with other members of their group. Like humans, infant macaques have an intense bond with their mother, and early social development of the infant macaque is heavily dependent on proper maternal care (Hinde and

Spencer-Booth, 1967; Suomi, 2005; McCormack et al., 2006, 2009, 2015; Raper et al., 2014). For the first month or so of life, the infant spends most of its time in close contact with its mother, usually in ventral-ventral contact (Hinde and Spencer-Booth, 1967). At this stage, the infant may attempt to explore its environment, but is restrained by the mother (Hinde and Spencer-Booth, 1967). By two months of age, approximately equivalent to 8 months in humans, the weaning period begins. Between 8-12 weeks infants increase the time exploring the environment and in social interactions with kin and non-kin animals, and engaging in social play so that fear and anxiety may also emerge during this time (Hinde and Spencer-Booth, 1967). The increased infant independence is paralleled by increased rejection by the mother, who may even show aggressive behaviors (slap, bite) toward clinging offspring (Hinde and Spencer-Booth, 1967). Finally, infant macaques experience even increased independence from the mother after 6 months (equivalent to 2 years in humans) and throughout the rest of infancy until the juvenile period (which begins around 12 months).

Altogether, this evidence highlights that rhesus monkeys are an ideal model for studying neurobehavioral development and ASD-related social deficits. In fact, within the last few years several NHP transgenic models of ASD have been created, targeting mutations in genes linked to ASD in humans, such as Shank-3 (Zhao et al., 2017; Tu et al., 2019; Zhou et al., 2019),MeCP-2 (Liu et al., 2016; Chen et al., 2017), and ABCA-3 (Iritani et al., 2018). However, limitations to these models include a lack of phenotype analysis tools, ethical concerns regarding the use of a "higher order" NHP animal model, technical challenges of gene editing, such as mosaicism and off-target effects, and financial concerns of creating and housing a sufficient number of mutant animals (Zhao et al., 2018). Therefore, this study will focus on characterizing the variation in

development of social behavior and neurocircuits of healthy, typically developing infant rhesus macaques housed in complex social environments at the YNPRC Field Station breeding colony.

The **goal** of this project is to examine early developmental changes in brain social salience and affiliation/reward networks in relation to social behaviors of relevance for ASD that can lead us to identify early neural markers of for later social behaviors and dysfunctions using a rhesus macaque model. To achieve this goal, I tracked the neural and behavioral development of 30 male infant rhesus macaques. Only males were included in the study, as human males are more likely to be diagnosed with ASD than human females (Baio, 2018). These infant monkeys lived with their mothers in large, socially complex groups at the YNPRC Field Station where they were able to interact with their mothers, families, and other group members.

This study utilized two main approaches. Throughout the first 6 months of the macaques' life (equivalent to toddlerhood in humans), sMRI methods were used to calculate the volumetric growth of several brain regions of interest (ROIs) related to social functioning (specifically the affiliation/reward and salience brain networks) and map their developmental trajectories. A subset of those animals underwent behavioral observations and analysis for two measures of social development in addition to the brain developmental methods. Twenty-one subjects underwent structural MRI (sMRI) scans only, 5 underwent only behavioral data collection, and both sMRI and behavioral data were collected in 4 other animals. First, we used an ethogram to code for social behaviors of interest. Second, we used a modified version of the macaque Social Responsiveness Scale (Feczko et al., 2016) as a translational rating scale of general social competency.

I **hypothesized** that the brain structures in the social salience and affiliation/reward networks would experience a period of rapid growth around 8 weeks of age, which coincides with the beginning of infant weaning from its mother, and subsequent independence and exploration of new social environment. We also hypothesized that periods of high acceleration of specific brain regional growth of these ROIs will predict specific developmental milestones or transitions in specific infant social behaviors, using regression models. Overall, in this study I will outline how the development of social competency, especially within the context of ASD-relevant social behavior, is supported by developmental changes in social salience and affiliation/reward neural networks.

## Methods

### Subjects

Thirty male infant rhesus monkeys (*Macaca Mulatta*) were studied as part of a larger project that also examined developmental trajectories of social perception using eye-tracking and resting state functional connectivity. Twenty-one subjects underwent structural MRI (sMRI) scans, 5 underwent only behavioral data collection, and both sMRI and behavioral data were collected in 4 other animals. All subjects were born and reared at the YNPRC Field Station in Lawrenceville, GA. They were housed in large outdoor/indoor compounds, where they lived in a complex social environment with their mothers, families and other group members. Data were collected from the subjects longitudinally, from 2 weeks to 6 months of age. Standard high fiber, low fat monkey chow (Purina Mills Int., Lab Diets, St. Louis, MO) and seasonal fruits and

vegetables were provided twice daily, in addition to enrichment items. Water was available *ad libitum.* Exclusionary criteria included: 1) infants of primiparous females and/or females with histories of infant physical abuse or neglect, and 2) infant birth weight <450g, to avoid confounding effects of prematurity/low birth weight on brain development (Scott et al. 2016). 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.

**sMRI**

***sMRI data Acquisition***

SMRI scans were collected at 2, 4, 8, 12, and 24 weeks in 25 subjects; a subgroup of infants (n=21) was also scanned at 16 and 20 weeks, and a separate subset (n=4) were scanned at 6 weeks. The day before or morning of the scheduled scan, the infants were transported with their mothers from the YNPRC Field Station to the YNPRC Main Center 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. The sMRI scans included both a single shot 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), as well as single shot T2-weighted scanning 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). Both T1 and T2 images were collected during the same session, as the inclusion of both

image types helps with registration to atlas space, and to more accurately define the contrast between grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) for tissue segmentation, and to delineate anatomical borders of both cortical and subcortical regions of interest (Knickmeyer et al., 2010).

To prevent motion artifacts, anesthesia was induced with telazol (2.89±0.60 mg/kg) and the subjects were intubated and kept anesthetized with isoflurane (0.8-1% inhalation) during scan collection. The physiological state of the animal was closely monitored with a blood pressure monitor, oximeter, electrocardiograph, and rectal thermometer during the scan. Body temperature was maintained with an MRI-compatible heating pad, and the animal was kept hydrated during the scan with intravenous delivery of dextrose/NaCl (0.45%). Head movement was limited using a custom-made head restraint with a mouth piece and ear bars. To identify the right side of the brain, a vitamin E capsule was placed over the infant's right temple. Following recovery from anesthesia, the infant was reunited with its mother, and the pair was returned to its group at the YNPRC Field Station the next 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, 4 and 6 week timepoints). These are open-source pipelines developed by the Neuro Image Research and Analysis Laboratories (NIRAL) of the University of North Carolina (Wang et al., 2014). AutoSeg and NeoSeg are atlas-based pipelines that use automatic segmentation of brain tissue based on probabilistic tissue maps (consisting of WM, GM, and CSF), and generate parcellations for cortical and subcortical

regions of interest (ROIs). ROIs for this study included the amygdala (AMY), insula (INS), anterior cingulate cortex (ACC) [Brodmann Area (BA) 24], nucleus accumbens (NAcc), medial prefrontal cortex (mPFC; BA10, 25, 32), ventromedial PFC (vmPFC; BA14) and orbitofrontal cortex (OFC; BA11, 13).

The AutoSeg pipeline follows six main steps to perform volumetric computations of WM, GM, CSF, and ROIs for each subject. The first step corrects for inhomogeneity in the MRI image's signal intensity, or low frequency undesirable signals, which results from imperfections in the coil radiofrequency. Inhomogeneity leads to inaccuracies in the tissue segmentation process, and AutoSeg employs N4-ITK bias field correction to address the issue (Tustison et al., 2010). AutoSeg then performs image registration to atlas space using a reference space algorithm, which aligns the subject image to a reference space using published protocols (Styner et al. 2007; Wang et al. 2014; Shi et al. 2016). AutoSeg performs this alignment using a tool called BRAINSFit in Slicer, another image processing software (Styner et al., 2007; Johnson, Harris, and Williams, 2007; Fedorov et al., 2012; Liu et al., 2015; Shi et al., 2017). The age-specific T1- and T2-weighted UNC-Emory infant MRI atlases developed by our group (Shi et al., 2017) were used for this study. These atlases are templates of scans acquired longitudinally from 2 weeks to 6 months in 40 infant rhesus monkeys from the YNPRC social colony, balanced by sex and social rank. Based on best match of neuroanatomical characteristics, we registered the earliest scan ages (2, 4 & 6 weeks) to the 2-week atlas, the 8, 12, and 16 week scans to the 3-month atlas, and the 20 and 24 week scans to the 6-month atlas. Once subject images are registered to the atlas, NeoSeg (for 2, 4, and 6 weeks) and AutoSeg (for 8, 12, 16, 20 and 24 weeks) were used for automatic atlas-based classification (ABC), which perform segmentation of the image into GM,

WM, and CSF tissue classes. The first round of ABC tissue segmentation is done including the skull, but a second round is done after skull-stripping the image (using automatic and then manually edited whole-brain masks to remove non-brain voxels: skull, muscle, blood vessels outside of the brain; (Tustison & Avants, 2013; Liu et al., 2015); this process improves registration to the atlas, tissue segmentation and ROI parcellations (Wang et al. 2014). Following the second round of ABC, AutoSeg was used at all ages to generate intracranial volume (ICV: GM+WM+CSF) and parcellations of cortical and subcortical ROIs, which includes computing their respective volumes. In this study, volumes were calculated for 10 ROIs by hemisphere (left and right AMY, INS, ACC [BA24], NAcc, mPFC [BA10, 25, 32], vmPFC [BA14], OFC [BA11, 13]). ROI volumes were also corrected by total ICV to account for individual differences in whole brain volume by adding ICV as a covariate in the statistical models.

ROIs were generated based on published macaque MRI anatomical parcellations (Knickmeyer et al, 2010; Paxinos, Huang, & Toga, 2000) mapped onto the UNC-Emory macaque brain atlases (Shi et al., 2017), and then manually edited to ensure accurate anatomical definition following published definitions (Paxinos et al, 2000; Saleem and Logothetis, 2006; Price et al, 1987; Amaral et al, 1987; Payne et al, 2010; Howell et al, 2014; Reding et al, 2020; Petrides and Pandya, 2001; Barbas and Pandya, 1989;  Gashaghaei et al, 2007; Cole et al, 2009; ). Editing of PFC, ACC and AMY ROIs was guided by an expert macaque neuroanatomist (Dr. Jocelyne Bachevalier). The mPFC, vmPFC, OFC, ACC and NAcc definitions were generated from the Paxinos, Huang and Toga (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- and ACC-specific macaque neuroanatomical landmarks

(Petrides and Pandya, 2001; Barbas and Pandya, 1989; Gashaghaei et al, 2007; Cole et al, 2009). The AMY was defined as follows, based on published macaque anatomical landmarks (Price et al., 1987; Amaral and Basset, 1989; Howell et al, 2014; Reding et al, 2020; Knickmeyer et al. 2010; Payne et al. 2010; Saleem and Logothetis 2012; Saleem and Logothetis, 2006): the superior boundary was defined by WM (including the internal capsule, optic and auditory radiation, and the anterior commissure) and the putamen; the posterior inferior boundary was defined by the lateral ventricle/temporal horn and the posterior boundary by the hippocampus (note that the AMY-hippocampal transition area was included in the AMY volume); the beginning of the periamygdaloid cortex was the anterior border, the anterior inferior boundary was defined by the temporal WM and, when not visible due to low contrast, the rhinal fissure that separates AMY from the entorhinal cortex; finally, the medial boundary was the meninges. INS subdivisions included the granular, dysgranular, agranular insula, and the insular proisocortex, with the retroinsular area as the caudal border, rostral border with the orbital proisocortex, and delimited medially and dorsally by WM, and laterally and ventrally by the lateral sulcus (Paxinos, Huang, & Toga, 2000; Seltzer and Pandya 1978; Stephani et al. 2011; Saleem and Logotethis, 2012).

**Behavior**

***Infant Socioemotional Behaviors***

In parallel to examining the longitudinal growth of social brain networks, the development of infants' social and emotional behaviors was also studied using two approaches: (1) infant focal behavioral observations (OBS) using a macaque ethogram -a catalogue of macaque behaviors

that are relevant to the study, and their operational definition -; and (2) rating scales of typical and atypical social behavior using a tool developed by our lab, the juvenile macaque social responsiveness scale (jmSRS; Kovacs Balint et al, in preparation).

OBS data were collected at 2, 4, 6, 8, 12, and 24 weeks for a subset of 9 subjects. This study used a modified version of a well-established macaque ethogram, adapted from Altman's 1962 (Altman, 1962) by our group for studies of infant rhesus social and emotional development and mother-infant interactions (McCormack et al, 2006, 2009, 2015; Morin et al, 2019; Raper et al, 2014). These behaviors are arranged by categories: (1) Prosocial and affiliative behaviors; (2) aggressive/submissive behaviors; (3) anxiety-like behaviors; and (4) vocalizations and standard behaviors such as eating and drinking are recorded as well. These data were collected by trained coders (inter-observer reliability >80% agreement, Cohen k>0.8) at the YNPRC Field Station, from observation towers over the social compounds. Coders used focal sampling technique, in which they collected behavioral frequency and duration data from a specific infant for 30 minutes by recording all behaviors in the ethogram initiated or received by that infant using an in-house program, "WinOBS". The coders performed 4 separate observations between 8am and 12pm on different days, except in cases which observations could not be performed on separate days, during which observations were performed once in the early morning and once in the early afternoon on the same day. Observations were 30 minute each, for a total of 2 hours of observation at each age. After the OBS data were collected and error-checked, the duration and frequency of each behavior were converted into time proportions (minutes per hour), or frequency rates (behavior counts per hour). From these values, the sum of each behavior's frequency rates or time proportions was calculated for each subject across the four observation

sessions at each age. Low occurrence behaviors (i.e. those that were performed by very few animals) were excluded from the analyses, following a cutoff rate of 50% (i.e., 50% of the subjects displayed the behavior at most ages). After the data processing and exclusion process, 14 unique behaviors remained in the dataset, and were included in the statistical analysis.

***Juvenile Macaque Social Responsiveness Scale (jmSRS)***

The second method used to study social development was a translational measurement tool, the jmSRS, which is a set of rating scales that quantifies individual differences in both typical and atypical social behaviors in juvenile macaques and was collected at 12 and 24 weeks for the same 9 subjects used for OBS. In humans, the SRS is a tool used in the diagnosis of ASD (Constantino et al., 2003). The human SRS has been adapted to chimpanzees (Marrus et al., 2011) and adult macaques (mSRS; Feczko et al., 2016); the jmSRS used in this project is a modified version of Feczko and colleagues' mSRS for use with juveniles (Kovacs-Balint et al., *in preparation*). The jmSRS consists of 17 items that rate each infant on typical and atypical social behaviors using a standard 5-point Likert scale (1="never true", 5="always true"). The same coder who collected the focal behavioral observation for each infant, completed the jmSRS assessment for each subject at 3 and 6 months of age. Each infant was scored at each age 2 to 4 times to increase reliability.

After the jmSRS was completed, the average score for each item was calculated for each individual. For the majority of items on the jmSRS a higher average score (closer to 5) is indicative of higher social impairment. However, 4 of the items (e.g. "Plays appropriately with peers") measure social competence/skills rather than impairment, such that a higher score

represents better social functioning. For these 4 items, scores were reverse-coded before averaging and analysis, in which a score of 5 became 1, 4 became 2, and so on, to ensure consistency with the rest of jmSRS items.

**Statistical Analysis**

***sMRI***

Normal distribution of variables was initially checked using the Shapiro-Wilks test and data was log-transformed if it failed ($p>0.05$). Linear Mixed Models (LMM) was used to examine significant developmental volume changes of brain ROIs [AMY, INS, ACC (BA24), NAcc, BA14, 25, 32, 11, 13, 10] across the first 6 months of life and to determine periods of specific growth acceleration or deceleration. As only 4 subjects were scanned at the 6 weeks age, LMM models were ran first including the 6 weeks timepoint and again excluding the 6 weeks timepoint, in order to determine if the inclusion of 6 weeks data would skew the results. For the initial analysis, AGE [2, 4, (6), 8, 12, 16, 20, 24 weeks] and HEMISPHERE [left, right] were used as fixed factors, with subject entered in the model as a random effect. For ROIs with significant volume changes due to age, a secondary analysis was performed adding ICV as a covariate to control for individual differences in total brain (ICV) volume. Note that, because AutoSeg does not compute ICV by hemisphere, ROI volumes were summed (total ROI volume = right + left ROI volume) for this LMM secondary analysis (i.e. HEMISPHERE was excluded). Post-hoc pairwise comparisons were performed with Bonferroni adjustments, when main AGE or AGE x HEMISPHERE interaction effects were detected. Outliers with ROI volumes greater than 2 standard deviations above or below the mean, or subjects missing multiple timepoints resulting

in a skewed polynomial curve were excluded from the figures. All analyses were performed using IBM SPSS version 26, and a significant p-value was set at $p<0.05$.

### *Infant Socioemotional Behaviors*

Two statistical methods were used to determine periods of significant behavioral changes in specific macaque socio-emotional behaviors across the first 6 months of life. The Shapiro-Wilk test was used to check normality of variables at each age; for normally distributed variables, LMM was used. For non-normally distributed behaviors, which violate the assumptions of LMM, a non-parametric Friedman's ANOVA was used, as it tests differences between related measures when normality is not assumed (Friedman, 1937; Field, 2017). All analyses were performed using IBM SPSS version 26, and a significant p-value was set at $p<0.05$.

### ***jmSRS***

To examine how scores on the jmSRS changed from 3 to 6 months of age, the Shapiro-Wilk test was first used to check normality of variables at 3 and 6 months. As 15 out of 17 variables on the jmSRS were non-normally distributed at one or both timepoints, the Wilcoxon signed-rank test was performed, as it does not assume normality like LMM (Field, 2017). A significant p-value was set at $p<0.05$.

### ***Exploratory Analysis***

Although our sample size was very small (n=4) for the subset of subjects with both sMRI and behavioral data (OBS, jmSRS), they were used for an exploratory analysis to examine whether

the brain ROIs showing significant developmental changes predicted the changes in social behavior. With the available sample, hierarchical linear regressions (HLM) were performed in a stepwise manner to determine how much of the variance in behavioral changes from 2 to 24 weeks was explained by specific (vs. combined) ROI growth, in addition to AGE. All analyses were performed using IBM SPSS version 26, and a significant p-value was set at $p<0.05$.

## Results

### sMRI Results

As only 4 subjects were scanned at the 6 weeks age, LMM models were ran first including the 6 weeks timepoint and again excluding the 6 weeks timepoint, to determine if the inclusion of 6 weeks data would skew the results. The inclusion of the 6-week timepoint caused skewness in the LMM results, so results excluding the 6-week timepoint should be considered accurate. While the text below describes the results of the analyses both including and excluding the 6-week timepoint, figure captions include statistics excluding the 6-week timepoint. Outliers with ROI volumes greater than 2 standard deviations above or below the mean, or subjects missing multiple timepoints resulting in a skewed polynomial curve were excluded from the figures.

#### *Intracranial Volume (ICV)*

As shown in Figure 2, total ICV increased over time, as demonstrated by a significant effect of AGE ($F(7,16.68)=94.58$; $p= 3.45 \times 10^{-12}$). When the 6 weeks data (4 subjects) was included, post-hoc tests detected a period of rapid ICV growth between 2 and 4 weeks ($p=0.008$), followed by

continuous but non-significant growth until about 20 weeks, and a plateau in growth after that. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6,46.26)=108.79$; $p= 1.41 \times 10^{-25}$), with post-hoc tests identifying periods of significant growth between 2 and 12 weeks (2 to 4 weeks: $p=3.00 \times 10^{-4}$; 4 to 8 weeks: $p=7.60 \times 10^{-12}$ ; 8 to 12 weeks: $p=0.01$).

***Insula (INS) Volume***

Absolute INS volume increased over time (Fig 3A, B), as shown by the significant effect of AGE ($F(7, 20.27)=95.91$; $p= 3.94 \times 10^{-14}$) on INS volume, but no effect of HEMISPHERE, or AGE x HEMISPHERE interaction effects were found. When the 6 weeks data of 4 subjects was included, post-hoc tests detected a period of rapid growth between 16 and 20 weeks ($p=3.09 \times 10^{-7}$), with non-significant increases in volume either before or after that period. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 70.55)=109.49$; $p=2.46 \times 10^{-36}$), although post-hoc tests now identified periods of significant growth between 4 and 8 weeks ($p=1.52 \times 10^{-17}$) and between 16 and 20 weeks ($p=2.32 \times 10^{-7}$).

When controlling for subject ICV as a covariate in the LMM model (Fig 3C), analyses of INS volume (bilateral: right + left) still resulted in a significant effect of AGE ($F(7, 17.18)=328.86$; $p= 5.04 \times 10^{-17}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid bilateral INS growth between 2 and 4 weeks of age ($p=0.02$), 6 and 8 weeks ($p=0.01$), 16 and 20 weeks ($p= 7.76 \times 10^{-15}$), with growth plateaus in between. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 31.986)=3.72$; $p=3.86 \times 10^{-28}$) on INS volume, although post-hoc tests identified periods of significant growth between

2 and 12 weeks (2 to 4 weeks: p=0.02; 4 to 8 weeks: p=9.40 $x10^{-31}$ ; 8 to 12 weeks: p=0.04) and 16 and 20 weeks (p=7.84 $x10^{-15}$).

***Amygdala (AMY) Volume***

Absolute AMY volume increased over time and by hemisphere (Fig 4A, B). There was a significant effect of AGE (F(7, 46.24)=316.63; p= 7.63 $x10^{-37}$) and HEMISPHERE (F(1, 223.65)=9.13; p= 3.0 $x10^{-3}$), but no significant AGE x HEMISPHERE interaction. When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth between 2 and 4 weeks (p=0.02), 6 and 8 weeks (p= 6.60 $x10^{-16}$), 16 and 20 weeks (p= 3.5 $x10^{-5}$), with plateaus in growth in between. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE (F(6, 78.86)=323.59; p=2.22 $x10^{-53}$), and HEMISPHERE (F(1, 70.55)=109.49; p=0.004) on AMY volume, although post-hoc tests identified periods of significant growth between 2 and 4 weeks (p=0.01), 4 and 8 weeks (p=8.01$x10^{-21}$) and 16 and 20 weeks (p=2.7 $x10^{-5}$).

Analyses of AMY volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 4C), still resulted in a significant effect of AGE (F(7, 7.16)=513.04; p=4.17 $x10^{-9}$). When the 6 weeks data of 4 subjects was included, there was a gradual increase in AMY volume, and post-hoc tests detected periods of rapid growth between 2 and 4 weeks (p=0.001), 6 and 8 weeks (p=0.006) and 16 and 20 weeks (p= 2.08 $x10^{-8}$E-8). When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE (F(6, 32.76)=590.10; p=6.55 $x10^{-32}$) on AMY volume, although post-hoc tests identified periods of significant growth between 2 and 4 weeks (p=0.001), 4 and 8 weeks (p=4.41 $x10^{-23}$ ), and 16

and 20 weeks ($p=1.49 \times 10^{-8}$). Two subjects was excluded from the figures due to missing timepoints causing skew in their polynomial curves.

***Nucleus Accumbens (NAcc) Volume***

Due to poor tissue contrast intensity at the early ages, the AutoSeg processing pipeline did not generate good quality boundaries for the NAcc at 2, 4 and 6 week timepoints, and its volume is not provided for those ages; thus, NAcc growth was only assessed from 8 to 24 weeks of age. Absolute NAcc volume changed over time and by hemisphere (Fig 5A, B). There was a significant effect of AGE ($F(4, 88.79)=20.03$; $p= 8.77 \times 10^{-12}$) and HEMISPHERE ($F(1, 194.53)=7.28$; $p=0.008$) on NAcc volume, but no AGE x HEMISPHERE interaction effect. Post-hoc tests revealed a significant growth period between 16 and 20 weeks ($p=0.001$).

Analyses of NAcc volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 5C), still resulted in a significant effect of AGE ($F(4, 29.92)=61.57$; $p=5.20 \times 10^{-14}$). A significant increase in volume was detected based on post-hoc analysis between 16 and 20 weeks ($p=2.00 \times 10^{-6}$), followed by steady growth until 24 weeks at the group level, but with high individual variability.

***Anterior Cingulate Cortex (ACC[BA24]) Volume***

Absolute ACC (BA24) volume changed over time and by hemisphere (Fig65A, B). There was a significant effect of AGE ($F(7, 31.36)=998.19$; $p= 5.42 \times 10^{-35}$) and of HEMISPHERE ($F(1, 91.51)=45.32$; $p= 1.43 \times 10^{-9}$) on ACC volume, but no significant AGE x HEMISPHERE interaction. When the 6 weeks data of 4 subjects was included, post-hoc tests detected a period of rapid growth between 6 and 8 weeks ($p= 7.97 \times 10^{-9}$), with non-significant volumetric growth either

before or after this period. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 81.79)=1160.86$; $p=6.29 \times 10^{-77}$) and HEMISPHERE ($F(1, 209.635)=33.824$; $p=2.23 \times 10^{-8}$) on ACC, although post-hoc tests identified a period of significant growth between 4 and 8 weeks ($p=1.29 \times 10^{-41}$).

Analyses of ACC volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 6C), still resulted in a significant effect of AGE ($F(7, 2.34)=985.94$; $p= 3.55 \times 10^{-4}$). When the 6 weeks data of 4 subjects was included, ACC volume increased rapidly with a peak around 16 weeks; post-hoc tests detected periods of rapid growth between 8 and 12 weeks ($p= 0.03$) and 12 and 16 weeks ($p=0.001$). This growth was followed by a slight decline in volume after 20 weeks of age. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 25.80)=1129.93$; $p=6.07 \times 10^{-30}$), although post-hoc tests identified periods of significant growth between 2 and 4 weeks ($p=0.001$), 4 and 8 weeks ($p=1.40 \times 10^{-32}$), 8 and 12 weeks ($p=0.026$), and 16 and 20 weeks ($p=0.001$). One subject was excluded from the figures due to missing timepoints causing skew in its polynomial curve.

***Prefrontal Cortex (PFC) Volumes***

*Anterior mPFC (BA10):* Absolute BA10 volume changed over time by hemisphere (Fig 7A, B). There was a significant effect of AGE ($F(7, 37.251)=488.688$; $p= 1.23 \times 10^{-34}$) and HEMISPHERE ($F(1,91.543)=24.855$; $p= 3.00 \times 10^{-6}$), and there was a significant interaction of AGE x HEMISPHERE ($F(7, 37.251)=5.088$; $p= 0.000402$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected a period of rapid growth between 6 and 8 weeks ($p= 3.75 \times 10^{-}$

$^{8}$), with non-significant volumetric growth increases either before or after this period. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 82.92)=566.635$; $p=4.40 \times 10^{-65}$), HEMISPHERE ($F(1, 211.32)=15.01$; $p=1.43 \times 10^{-4}$), and an AGE x HEMISPHERE interaction effect ($F(6, 82.92)=5.84$; $p=4.10 \times 10^{-5}$), although post-hoc tests identified a period of significant growth only between 4 and 8 weeks of age ($p=6.37 \times 10^{-35}$).

Analyses of BA10 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 7C), still resulted in a significant effect of AGE ($F(7, 2.41)=467.02$; $p=7.14 \times 10^{-4}$). When the 6 weeks data of 4 subjects was included, there was continuous growth from 2 weeks on, which reached a volume peak around 20 weeks, and was followed by a slight decline thereafter. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 39.79)=532.97$; $p=2.18 \times 10^{-36}$) on BA10 volume, although post-hoc tests identified a period of significant growth between 4 and 8 weeks ($p=1.43 \times 10^{-42}$). Two subjects were excluded from the figures due to missing timepoints causing skew in its polynomial curve, and one subject was excluded for being a statistical outlier.

*Ventromedial Prefrontal Cortex (BA14):* Absolute BA14 volume changed over time by hemisphere (Fig 8A, B). There was a significant effect of AGE ($F(7, 37.17)=1235.04$; $p= 5.30 \times 10^{-42}$) and HEMISPHERE ($F(1,137.61)=18.21$; $p= 3.7- \times 10^{-5}$) on BA14 volume, and there was a significant interaction of AGE x HEMISPHERE ($F(7, 37.17)=12.32$; $p=4.97 \times 10^{-8}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth between 6 and 8 weeks ($p= 2.24 \times 10^{-8}$) and 16 and 20 weeks ($p=5.69 \times 10^{-7}$). When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 83.41)=1436.29$; $p=6.17 \times 10^{-82}$) and HEMISPHERE ($F(1, 205.38)=6.45$; $p=0.012$), and an AGE x HEMISPHERE

interaction ($F(6, 83.41)=13.924$; $p=6.61 \times 10^{-11}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=9.38 \times 10^{-42}$) and 16 and 20 weeks ($p=4.27 \times 10^{-7}$).

Analyses of BA14 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 8C), still resulted in a significant effect of AGE ($F(7, 8.63)=1562.64$; $p= 1.09 \times 10^{-12}$). When the 6 weeks data of 4 subjects was included, post-hoc test detected periods of rapid growth between 2 and 4 weeks ($p= 3.10 \times 10^{-5}$), 6 and 8 weeks ($p=1.68 \times 10^{-21}$), and 16 and 20 weeks ($p=4.00 \times 10^{-6}$), with periods of slower growth in-between. BA14 volume peaked around 20 weeks of age. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 38.91)=1823.451$; $p=4.55 \times 10^{-46}$), although post-hoc tests identified periods of significant growth between 2 and 4 weeks ($p=1.7 \times 10^{-5}$), 4 and 8 weeks ($p=6.75 \times 10^{-22}$), and 16 and 20 weeks ($p=3.00 \times 10^{-6}$).

*Subgenual Cingulate -mPFC- (BA25):* Absolute BA25 volume changed over time by hemisphere (Fig 9A, B). There was a significant effect of AGE ($F(7, 38.26)=774.74$; $p= 3.61 \times 10^{-39}$) and HEMISPHERE ($F(1,85.76)=19.11$; $p=3.40 \times 10^{-5}$), and there was a significant interaction of AGE x HEMISPHERE ($F(7, 38.26)=9.84$; $p= 5.90 \times 10^{-7}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth in BA14 volume between 6 and 8 weeks ($p= 2.91 \times 10^{-7}$) and 16 and 20 weeks ($p=2.00 \times 10^{-7}$). When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 88.65)=892.66$; $p=5.45 \times 10^{-77}$) and HEMISPHERE ($F(1, 215.37)=30.95$; $p=7.82 \times 10^{-8}$), and an AGE x HEMISPHERE interaction ($F(6, 88.65)=10.81$; $p=5.32 \times 10^{-9}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=2.17 \times 10^{-49}$) and 16 and 20 weeks ($p=1.00 \times 10^{-7}$).

Analyses of BA25 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 9C), still resulted in a significant effect of AGE ($F(7, 9.95)=1113.80$; $p= 1.39 \times 10^{-13}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth between 6 and 8 weeks ($p=0.01$), and 16 and 20 weeks ($p=2.60 \times 10^{-9}$). Rapid growth reaches a volume peak around 20 weeks, followed by a plateau. When the 6 weeks timepoint was excluded, there was a still a significant effect of AGE ($F(6, 24.15)=1330.05$; $p=3.39 \times 10^{-29}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=3.28 \times 10^{-37}$ ), and 16 and 20 weeks ($p=6.71 \times 10^{-8}$).

*Caudal mPFC (BA32):* Absolute BA32 volume changed over time (Fig 10A, B). There was a significant effect of AGE ($F(7, 13.01)=352.45$; $p= 8.48 \times 10^{-14}$), but no effect of HEMISPHERE, nor interaction of AGE x HEMISPHERE. When the 6 weeks data was included, post-hoc tests detected a period of rapid growth in BA32 volume between 16 and 20 weeks ($p= 4.20 \times 10^{-7}$), with non-significant volumetric growth increases either before or after this period. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 89.17)=408.84$; $p=1.33 \times 10^{-62}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=1.04 \times 10^{-27}$), and 16 and 20 weeks ($p=3.15 \times 10^{-7}$).

Analyses of BA32 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Figure 10C), still resulted in a significant effect of AGE ($F(6, 28.39)=701.01$; $p= 1.69 \times 10^{-29}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth between 4 and 8 weeks ($p= 9.86 \times 10^{-24}$), and 16 and 20 weeks ($p= 3.60 \times 10^{-10}$). When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 28.39)=701.01$; $p=1.69 \times 10^{-29}$), although post-hoc tests identified

periods of significant growth between 4 and 8 weeks ($p=9.86 \times 10^{-24}$), and 16 and 20 weeks ($p=3.60 \times 10^{-10}$). One subject was excluded from the figures due to missing timepoints causing skew in its polynomial curve.

***Orbitofrontal Cortex (OFC) Volumes***

*BA11:* Absolute BA11 volume changed over time and by hemisphere (Fig 11A, B), as shown bythe significant effect of AGE ($F(7, 33.94)=388.38$; $p= 1.78 \times 10^{-30}$) and HEMISPHERE ($F(1, 85.70)=12.25$; $p=7.41 \times 10^{-4}$), but no significant AGE x HEMISPHERE interaction effect. When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth between 6 and 8 weeks ($p= 6.00 \times 10^{-6}$), and 16 to 20 weeks ($8.13 \times 10^{-7}$), with non-significant increases in volume before, after, and in-between these time periods. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 93.71)=437.37$; $p=3.27 \times 10^{-66}$) and HEMISPHERE ($F(1, 235.705)=19.12$; $p=1.80 \times 10^{-5}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=8.11 \times 10^{-34}$), and 16 and 20 weeks ($p=6.10 \times 10^{-37}$).

Analyses of BA11 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 11C), still resulted in a significant effect of AGE ($F(7, 7.199)=701.728$; $p= 1.22 \times 10^{-9}$). When the 6 weeks data of 4 subjects was included, post-hoc tests detected a period of rapid growth between 6 and 8 weeks ($p= 0.002$), and 16 to 20 weeks ($p=3.04 \times 10^{-14}$). There is a peak in volume around 20 weeks, then a plateau in growth until about 24 weeks. When the 6 weeks timepoint was excluded, there was still a significant

effect of AGE ($F(6, 35.52)=751.93$; $p=6.82 \times 10^{-36}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=1.74 \times 10^{-33}$), and 16 and 20 weeks ($p=2.43 \times 10^{-14}$).

*BA13:* Absolute BA13 volume changed over time (Fig 12A, B). There was a significant effect of AGE ($F(7, 25.55)=1128.96$; $p= 3.55 \times 10^{-30}$), but no effect of HEMISPHERE, nor interaction of AGE x HEMISPHERE. When the 6 weeks data of 4 subjects was included, post-hoc tests detected periods of rapid growth in BA13 volume between 6 and 12 weeks (6 to 8 weeks: $p= 5.68 \times 10^{-37}$; 8 to 12 weeks: $p= 0.012$), with non-significant volumetric growth increase before this period, and a plateau in growth after 12 weeks. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 79.67)=1303.59$; $p=2.47 \times 10^{-77}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=9.42 \times 10^{-38}$), and 8 and 12 weeks ($p=0.01$).

Analyses of BA13 volume (bilateral: right + left) revealed changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 12C), still resulted in a significant effect of AGE ($F(7, 14.90)=958.74$; $p= 1.29 \times 10^{-18}$). When the 6 weeks data of 4 subjects was included, post-hoc test detected periods of rapid growth between 6 and 12 weeks (6-8 weeks: $p=2.00 \times 10^{-4}$; 8-12 weeks: $p=4.0 \times 10^{-7}$), and again between 16 and 20 weeks ($p= 0.01$), reaching a volume peak between 16-20 weeks, followed by a plateau thereafter. When the 6 weeks timepoint was excluded, there was still a significant effect of AGE ($F(6, 31.59)=918.27$; $p=5.31 \times 10^{-34}$), although post-hoc tests identified periods of significant growth between 4 and 8 weeks ($p=1.51 \times 10^{-31}$), 8 and 12 weeks ($p=1.00 \times 10^{-6}$), and 16 and 20 weeks ($p=0.003$). Two subjects were excluded from the figures due to missing timepoints causing skew in its polynomial curve.

**Behavioral Results**

***Infant Socioemotional Behaviors Data***

*Infant Affiliative/Prosocial Behaviors:* The duration of several infant affiliative behaviors was measured across the first 6 months of life, as shown in Figure 13. These behaviors included "Contact", "Proximity", "Within 3 Meters", and "Leave Beyond." The proportion of time an infant spent with half or more of their body in contact with another animal ("Contact") - measured as minutes per hour- changed over time (Figure 13A), as indicated by a significant AGE effect ($F(5,13.78)=19.21$; $p= 9.00 \times 10^{-6}$). Following a continuous decline in "Contact" behavior from 2 to 6 weeks, post-hoc pairwise comparisons revealed significant decreases in "Contact" frequency between 8 and 24 weeks of age (8-12 weeks: $p=0.021$; 12-24 weeks: $p=0.03$).

The proportion of time an infant spent within arms-reach of another animal ("Proximity") – measured as minutes per hour- was not significantly affected by age (Figure 13B).

The proportion of time an infant spent within 3 meters of their mother ("Within 3 Meters") – min/hour- changed over time (Figure 13C), as shown by a significant effect of AGE ($F(5, 13.21)=40.25$; $p= 1.53 \times 10^{-7}$). There were rapid, significant increases in "Within 3 Meters" behavior between 6 and 12 weeks (6-8 weeks: $p=0.004$; 8-12 weeks: $p= 0.028$).

The frequency rate at which an infant moved further than 3 meters away from their mothers or another animal ("Leave Beyond") -measured as counts per hour- also changed over time. (Figure 13D), as indicated by the significant effect of AGE ($F(5, 14.18)=15.49$; $p= 2.6 \times 10^{-5}$).

*Infant Play Behaviors:* Figure 14 shows results for developmental changes of infant play behaviors, which included “Social Play Composite”, “Solitary Play”, and “Quiet Play”. The Social Play Composite score consists of several species-typical social play behaviors (“Rough and Tumble Play”, “Chase Play”, “Brief Contact Play”). The proportion of time the infants spent on these different types of social play -measured as min/hour-, changed over time (Figure 14A), significantly increasing over the first 6 months of life ($\chi^2(5)=23.41$; $p= 2.82 \times 10^{-4}$). Social play behaviors seemed to emerge between 6 and 8 weeks of age (p=0.03), followed by a non-significant increase in play behavior thereafter.

The proportion of time spent in vigorous play alone (“Solitary Play”) -measured as minutes per hour- changed over time (Figure 14B), significantly increasing over the first 6 months of life ($\chi^2(5)=27.39$; $p= 4.8 \times 10^{-5}$). Duration of “Solitary Play” also increased continuously from 2 weeks of age, with rapid and significant increases between 6 and 12 weeks of age. There was high individual variability from 8 to 24 weeks, but in most of the cases, this behavior reached a peak from 12 to 24 weeks of age.

The proportion of time spent in “Quiet Play” with objects or toys -measured as minutes per hour- also changed over time (Figure 14C), with a significant AGE effect ($F(5,16.35)=17.03$; $p= 6.00 \times 10^{-6}$). Post-hoc pairwise comparisons revealed significant increases between 2 and 4 weeks of age (p=0.04).

*Other Infant Prosocial Behaviors:* Figure 15 shows the developmental changes in “Eye Gaze”, “Touch”, and “Grooming” behaviors. Direct eye contact with another animal (“Eye Gaze”) -

measured as counts per hour- was not significantly affected by age (Figure 15A). However, this could be due to high inter-individual variability.

The frequency rate of "touching" other individuals -measured as counts per hour-, was not significantly affected by age either (Figure 15B). The figure shows a particularly high individual variability in this behavior at 2 weeks.

The proportion of time spent grooming other animals -measured as minutes per hour- changed over time (Figure 15C), significantly increasing over the first 6 months of life ($\chi^2(5)=19.92$; p= $0.001.29 \times 10^{-3}$). Post-hoc pairwise comparison revealed a significant increase in "Grooming" duration from 12 to 24 weeks of age (p=0.032).

*Infant Fear and Distress Behaviors:* Figure 16 shows several behaviors in this category. The Anxiety Composite score -measured as counts per hour- consists of summed frequencies rates of several species-typical anxiety behaviors ("Yawn", "Body Shake", "Scratch", "Self-directed Behavior") and changed with AGE (F(4,14.27)=8.60; p= 0.001; Fig 16A). Post-hoc pairwise comparison revealed significant increases in the frequency of anxiety-like behaviors between 4 and 6 weeks (p=0.007), and between 8 and 12 weeks (p=0.01), after which there was a plateau.

The frequency rate of infants avoiding another animal ("Withdraw") -measured as counts per hour- also changed over time (Figure 16B). "Withdraw" frequency rate significantly increased over the first 6 months of life ($\chi^2(5)=24.94$; $p=1.43 \times 10^{-4}$).

The frequency rate of infants "Scream" vocalizations -measured as counts per hour-, was not significantly affected by AGE (Figure 16C).

The frequency rate of infants' "Gecker" vocalizations, or loud, staccato burst vocalizations which commonly occur with a bodily jerk (Patel and Owren, 2007) -measured as counts per hour-, did not change significantly with AGE (Figure 16D).

### *Juvenile Macaque Social Responsiveness Scale (jmSRS) Data*

Table 1 shows the total summed score, the group average ±SEM, as well as significant AGE effects for all 17 jmSRS items at 3 and 6 months of age. Only 2 items, "Plays appropriately with Peers" and "Upset in Busy Environments", showed significant changes with AGE: "Plays appropriately with Peers" scores were significantly lower at 6 than at 3 months of age (as shown by the negative Z score, which indicates that the median of the earlier age was larger than the later one: z=-2.214, p=0.027); and "Becomes upset in Busy Environments" scores were significantly higher at 6 than at 3 months of age (as shown by the positive Z score: z=2.384, p=0.017).

## Exploratory Analysis Results

Models are reported for behaviors (frequency or duration) that were significantly predicted by either AGE or ROI growth, as shown in Figure 17.

### *Within 3 Meters*

AGE, BA11, ACC(BA24), BA32, and BA14 volumes were all tested as potential predictors of "Within 3 Meters" behavior developmental changes due to similar growth trends. AGE significantly predicted developmental changes in "Within 3 Meters" frequency ($F(1, 19)=10.35$, $p= 0.005$). In addition to AGE, ACC (BA24) volume across all ages (i.e. the growth trajectory of

ACC) significantly predicted developmental changes in "Within 3 Meters" frequency ($F(2, 18)=8.42$, $p=0.003$; Fig 17A). According to this model, AGE accounted for 31.9% of variance in occurrence of "Within 3 Meters" ($R^2=0.319$), and AGE and ACC (BA24) volume accounted for 42.6% of variance ($R^2= 0.426$).

***Leave Beyond***

AGE, BA13, BA10, BA25, and BA14 volumes were all tested as potential predictors of "Leave Beyond" behavior developmental changes due to similar growth trends. AGE significantly predicted developmental changes in "Leave Beyond" frequency ($F(1, 19)=11.42$, $p= 0.003$). In addition to AGE, BA25 volume across all ages (i.e. the growth trajectory of BA25) significantly predicted developmental changes in "Leave Beyond" frequency ($F(2,18)=10.68$, $p=0.001$; Fig 17B). According to this model, AGE accounted for 34.3% of variance in occurrences of "Leave Beyond" ($R^2= 0.343$), and AGE and BA25 volume accounted for 49.2% of variance in occurrences of "Leave Beyond" ($R^2= 0.492$).

***Quiet Play***

AGE, ACC (BA24), AMY, INS, and BA14 volumes were all tested as potential predictors of "Quiet Play" behavior developmental changes due to similar growth trends AGE significantly predicted developmental changes in "Quiet Play" duration ($F(1, 19)=5.08$, $p=0.04$), although none of the ROIs significantly predicted "Quiet Play" duration across development (Fig 17C). According to this model, AGE accounted for 21.1% of variance in duration of "Quiet Play" ($R^2= 0.211$).

***Contact***

AGE, BA24, BA13, and AMY volumes were all tested as potential predictors of "Contact" behavior developmental changes due to similar growth trends. AGE significantly predicted developmental changes in "Contact" frequency ($F(1, 19)=25.97$, $p= 6.40 \times 10^{-5}$), although none of the ROIs significantly predicted "Contact" frequency across development (Fig 17D). According to this model, AGE accounted for 57.7% of variance in occurrences of "Contact" ($R^2= 0.577$).

***Play Composite***

Although "Play Composite" violated normality at the 2-week time point, because all other ages were normally distributed, this variable was tested in the HLM regression models. AGE, INS, AMY, ACC(BA24) and BA32 volumes were all tested as potential predictors of "Play Composite" behavior developmental changes due to similar growth trends. AGE increases significantly predicted developmental changes in "Play Composite" duration ($F(1, 19)=17.22$, $p=0.001$), although none of the ROIs predicted changes in "Play Composite" duration across development (Fig 17E). According to this model, AGE accounted for 66.7% of variance in occurrences of "Play Composite" behaviors ($R^2= 0.666$).

## Discussion

The goal of this project was to examine early developmental changes in brain social salience and affiliation/reward networks in relation to social behaviors of relevance for ASD that can lead us to identify early neural markers of social behaviors using a rhesus macaque model. Using sMRI to map the developmental trajectories of brain ROIs throughout the first 6 months

of an infant macaque's life (equivalent to toddlerhood in humans), we found age-related volumetric growth in the social salience and affiliation/reward networks that followed region-specific developmental trajectories. Using behavioral observation methods to study development of early socioemotional behaviors in macaques, we found age-related changes in social affiliation, distress, and play behaviors that reflected reduced contact and proximity with the mother as the infant matures and more time spent playing and in proximity with other animals. Using the jmSRS as a translational tool to assess atypical social behaviors, we found that most scores did not change with age, with the exception of "Plays Appropriately with Peers" and "Upset in Busy Environments", suggesting that our subjects, selected from a healthy population, displayed normal social interaction as they developed. Finally, we found that ACC volumetric growth from 2-24 weeks was a significant predictor of changes in social behaviors during the same age period, specifically in distance from the mother and other animals ("Within 3 Meters") and play ("Quiet Play") behaviors; and the growth trajectory of the subgenual cingulate (BA25) was a significant predictor of breaking proximity with mom and other animals ("Leave Beyond" behavior), indicating that changes in these brain regions are important to support developmental changes in social behavior of macaques. Our findings suggest that during the first 24 weeks of life, social salience and reward brain networks undergo robust structural changes, presumably to support the infant's adjustment to independence and increasing emotional awareness of appropriate social interaction. Understanding how normative social behavior and the underlying social brain networks develop in a nonhuman primate model can help elucidate the roots of brain-behavior pathogenesis of human social deficits.

The first goal of this study was to examine longitudinally how social brain networks develop in infant rhesus macaques as they mature socially, with a focus on the development of areas involved in social salience, and affiliation/reward. Thus, it included the early developmental trajectories of AMY, INS, ACC (BA24), NAcc, mPFC (BA10, 25, 32), vmPFC (BA14) and OFC (BA11, 13), which was also analyzed in relation to overall total brain growth, measured as ICV and included as a covariate in the statistical models.

This study found rapid ICV growth across the first 3 months of life, and a steady volumetric growth following that period. Several other studies have examined the early neurodevelopmental trajectories of rhesus macaques, and have reported consistent findings of extensive total brain growth early in life with the most rapid growth in total brain volume (TBV; calculated as GM + WM) between 1 week and 1 month of age, followed by slower, but still significant growth up to 3 years (Malkova et al., 2006; Payne et al., 2010; Scott et al., 2016) It is important to note that the present study used ICV rather than TBV as a metric of whole brain growth also used in the field, as ICV accounts for CSF in addition to WM and GM. However, similar trends in ICV were observed in this study compared to others, which is not surprising as both ICV and TBV are related and considered appropriate measures of whole brain volume. In human infants, there also appears to be an early critical period for whole brain growth between birth and one year of age (Knickmeyer et al., 2008; Giedd et al. 2009), and there are numerous reports of increased brain volume in ASD (Hardan et al., 2001). However, one distinction between macaque and human infant brains is that total human brain volume increases at a faster rate (approximately 100% growth over the first year of life) than the macaque brain (50% growth in a comparable age span –over first 3 months postpartum-; Scott et al., 2016).

Absolute INS volume grew most rapidly between 4-8 weeks, and 16-20 weeks of age in both left and right hemispheres. ICV correction of total INS volume revealed a trajectory with significant growth between 2 and 4 weeks of age, 4 and 8 weeks, 8 and 12 weeks, and 16 and 20 weeks. This study found an approximate 1.5 fold in size from 2-24 weeks, which was comparably smaller than other cortical regions (between 2-6 fold for BA10, 11, 13, 14, 24, 25, 32). This is consistent with results from another macaque MRI study reporting a flatter INS growth trajectory compared to other cortical regions (Scott et al., 2016). Humans and macaque INS have a similar anatomical organization, including cytoarchitectural and cell-type specific congruences (Evrard, 2019). Further, in children, adolescents, and young adults with ASD, the volume and thickness of the anterior and posterior INS is reduced indicating the importance of this region in healthy social development (Kosaka et al., 2010; Parellada et al., 2017). However, there may be differences in very early development, as human INS is, in contrast to the macaque's, one of the most rapidly growing regions in the cortex during infancy (Gilmore et al., 2012; Bauernfeind et al., 2013). This difference may be functionally relevant, as human infants may have more abstract or complex emotional and cognitive challenges in early life that require recruitment of INS networks (Uddin et al., 2013; Evrard, 2019).

The AMY grew most rapidly in the early stages, between 2 and 8 weeks of age, and experienced an approximate 1.8-fold increase in volume by 24 weeks. ICV correction of total AMY volume revealed similar results with growth acceleration between 2 and 8 weeks, and an additional period of rapid growth from 16 to 20 weeks, which indicates amygdala-specific patterns of growth in relation to overall brain growth. These results are similar to other published data on AMY development in macaques, demonstrating that the amygdala grows most rapidly before 3

months of age, and has slower growth patterns afterwards (Payne et al., 2010; Chareyron et al., 2012; Schumann et al., 2019). Given an approximate 4 fold faster growth in rhesus monkeys' life span than humans', the early fast rhesus AMY development up to 3 months (equivalent to 12 months in human infants) seems similar to that reported in humans, where high growth rates have been found during the earliest stages of life, particularly during the first 2 years (Giedd et al., 1996; Uematsu et al., 2012; Avino et al., 2018). In humans, structural abnormalities in AMY development have been observed in children with ASD (Munson et al., 2006; (Mosconi et al., 2009; Schumann et al., 2009; Herrington et al., 2017); additionally, enlarged amygdala have been associated with social impairment in young children aged 1 to 4 years (Courchesne et al., 2007; Schumann et al., 2009), highlighting the importance of typical AMY development in supporting social functioning. Therefore, these early periods of AMY growth in macaques during the first 3 months of life, and in humans during the first two years, may underlie the healthy infant's social development in both species through weaning and increasing exploration and independence from the mother.

The NAcc grew most rapidly between 16 and 20 weeks of age, and this result was preserved after controlling for ICV growth. The NAcc experienced an approximate 1.2-fold increase in volume by 24 weeks. While to my knowledge there are no studies on the early volumetric development of the macaque NAcc, a recent macaque study of both dorsal and ventral striatum (including the NAcc) has also found significant general striatal growth between birth and the first month, and between the first month and first year of life (Martin and Cork, 2014). Although we were unable to analyze NAcc development in the first month, we found that group NAcc growth trajectory has a relatively flat curve between 8 and 16 weeks, and after 20 weeks of age; based on the findings

from Martin and Cork (2014), this may indicate that significant growth of the striatum occurs in the first month of life and between 24 weeks of age and one year. Not much is known about the volumetric development of the human NAcc during infancy, but there is evidence that early life experience, such as stress or maternal care, affects NAcc size, chemoarchitecture, and activity in early childhood and adolescence (Martin et al., 1991; Goff et al., 2013). Given this, perhaps differences in early social environment and experience, such as dominance rank and variable quality of maternal care, may explain some of the variability of NAcc volume observed in the present study. Functionally, the NAcc plays an important role in motivational behavior and reward (Olsen, 2011), including prosocial/affiliative, pair-bonding and maternal behavior (Young et al., 2001; Ross et al., 2009; Haruno et al., 2014; van der Meulen et al., 2016; Lei et al., 2017). In addition, the NAcc of children and young adults diagnosed with ASD shows atypical developmental trajectories (Langen et al., 2009; Langen et al., 2014), and abnormalities in NAcc volume during adolescence have also been reported in other psychiatric disorders with underlying social alterations, such as bipolar disorder and schizophrenia (Ballmaier et al., 2004; Dickstein et al., 2005). Therefore, understanding the typical development of the NAcc in a macaque model is particularly important for future studies modeling alterations in social functioning of relevance to ASD and other neurodevelopmental disorders, such as ADHD and schizophrenia.

Absolute ACC volume increased continuously until 20 weeks of age, with a robust 4-fold increase in size between 2-24 weeks -particularly between 4 and 8 weeks-, and showing a larger volumetric increase in the right-hemisphere than the left hemisphere. After controlling for total ICV growth, the ACC-specific volume peak was detected at 20 weeks with the most rapid growth

between 2 and 12 weeks, and 16 and 20 weeks. A previous study also found that the macaque cingulate cortex grows rapidly in early life and asymmetrically, with larger growth in the right than left hemisphere from one week of age (Scott et al., 2016). In macaques, the ACC plays a key role in various cognitive processes, such as decision-making and reward valuation; of particular interest for this study, the primate ACC is important for social valuation and salience, both in macaques (Paus, 2001; Rudebeck, 2006; Fouragnan et al., 2019; Ma et al., 2019) and in humans (Sanfey et al., 2003; Newman-Norlund et al., 2009; Gu et al., 2010; Rigoni et al., 2010; Etkin et al., 2011; Lavin et al., 2013; Whittle et al., 2014; Dudek et al., 2016). Although there are no studies which have expressly examined the role of the right ACC in macaques, there is evidence that macaques with bilateral ACC lesions may self-isolate (Myers et al., 1973; Hadland et al., 2003) and show a lack of interest in salient social cues, such as the face of another monkey (Rudebeck, 2006). Furthermore, the ACC in humans is part of the salience network (Seeley et al., 2007; Bressler and Menon, 2010), which underlies attention to various social cues such as faces of loved ones (Bartels and Zeki, 2004), and is activated during social rejection (Eisenberger et al., 2003). Taken together with the observed pattern of early and rapid right-hemisphere growth, the development of the ACC, particularly the right ACC, may be important for infants to attend to social cues and facilitate social decision-making within their colonies. In humans, the ACC is responsible for a variety of processes involving mood and emotional processing (Devinsky et al., 1995; Bush et al., 2000). In human children older than 7 years of age, absence of hemispheric asymmetry and small right ACC volumes have been associated with neurodevelopmental disorders and depressed mood (Marquardt et al., 2005; Boes et al., 2008). The ACC is part of several larger networks that contribute to its various functions. For example, social decision-

making in the ACC recruits the PFC, particularly the OFC and vmPFC, in order to determine the value of external stimuli and outcomes of potential actions (Buckley et al., 2009; Mullette-Gillman et al., 2011). Connections between the ACC and INS may be important for processing empathy and negative socioemotional stimuli (Ibanez et al., 2010; Jones et al., 2011; Kunz et al., 2011; Couto et al., 2013). The limbic system, including the AMY, is connected to the ACC as well, and these connections may be important for error-monitoring (Etkin et al., 2011; Cohen et al., 2005; Mansouri et al., 2009; Shackman et al., 2011). Therefore, individual differences in the development of the ACC during infancy and toddlerhood likely set the foundation for mood and behavioral disorders during childhood.

In the present study, we examined the growth trajectories of five different subregions of the mPFC: the ventromedial PFC (BA14), the subgenual cingulate (BA25), the caudal mPFC (BA32), and the anterior mPFC (BA10). Several of these regions showed similar developmental trajectories, with periods of significant growth acceleration between 4 and 8 weeks, and 16 and 20 weeks of age. When corrected for ICV, all of these regions had a volume peak between 20 and 24 weeks, followed by either a plateau or decline to 6 months of age. Additionally, BA14 displayed significant growth very early in development between 2 and 4 weeks of age after ICV correction. BA10 experienced an approximate 3-fold increase in volume by 24 weeks; BA14 a 5-fold increase; BA25 a 4.5-fold increase; and BA32 a 2-fold increase. A separate study of early development of the macaque PFC did not divided into subregions, unlike in the present study, and included both GM and WM; yet, there were similar findings of rapid PFC growth within the first 3 months, followed by a decrease in growth rate after 6 months of age (Scott et al., 2016). It is important to note that in humans the maturation of the PFC is delayed; there is a slower rate of PFC growth

during the first year of life, followed by a period of faster growth after year two, a large PFC growth spurt in late childhood, and continuous growth throughout adolescence (Kanemura et al., 2003; Gilmore et al., 2012). As PFC has roles in social and emotional regulation (Barbas and Zikopoulos 2007; Machado and Bachevalier 2003), this difference in developmental timeline between humans and macaques may be due to differences in the developmental milestones between the species. Human children do not become socially independent until preschool years and beyond (ages 4 and older) while macaques begin exploring their social environment at the time of weaning (2-3 months old; equivalent to 1 year in humans; (Hinde and Spencer-Booth, 1967); therefore, the earlier periods of rapid development in the macaque PFC may be important to support their earlier transition to a complex social environment. However, it is important to note that while macaques may transition to independence earlier than human children, their social behavior is not truly mature by 6 months of age; there is refinement of social skills that continue to mature beyond 6 months of age, along with their PFC. Several of these PFC subregions have been implicated in childhood neuropsychiatric disorders with underlying social and emotional alterations. The volume of vmPFC is decreased in children with post-traumatic stress disorder or bipolar disorder, two disorders in which social functioning is impaired (Morey et al., 2016; Wise et al., 2017). The subgenual cingulate is smaller in adults and adolescents with major depressive disorder, a disease often associated with a lack of social motivation (Botteron et al., 2002; Drevets et al., 2008). Children with ASD have a larger PFC in early childhood, but may have a smaller PFC in late childhood (Carper and Courchesne, 2005; Rojas et al., 2006; Courchesne et al., 2007; Stigler et al., 2011; van Rooij et al., 2018). The various subregions of the PFC are highly connected (Passingham et al., 2002), and the PFC itself is part of the “social brain”

network, involving regions, such as the AMY, NAcc, ventral tegmental area, and hypothalamus (Ongur and Price, 2000; Croxson et al., 2005; Wise, 2008). Social reward arises from a network involving the vmPFC, OFC, ACC, striatum, and AMY (Bicks et al., 2015); and social behaviors related to a self-other distinction, such as theory-of-mind tasks, also involve PFC circuits, specifically the mPFC and dorsal mPFC (Amodio and Frith, 2006; Bicks et al., 2015). Clearly, the PFC supports different aspects of social functioning, and alterations in its development are related to social deficits; by understanding how the PFC develops in infant macaques, we can then begin to investigate the relationship between PFC function as related to social behavior and structure using experimental manipulations.

Finally, the present study examined early OFC development in two subregions, BA11 and BA13. After ICV correction, BA11 showed specific periods of rapid growth between 4 and 8 weeks and 16 to 20 weeks and experienced an approximate 3-fold increase in volume by 24 weeks. For BA13, there was significant growth between 4 and 12 weeks, and again between 16 and 20 weeks after ICV correction; BA13 experienced an approximate 4-fold increase in volume by 24 weeks. In NHPs, neurons in the OFC help distinguish social stimuli, evaluate them, and categorize them by social status (Watson and Platt, 2012; Isoda et al., 2018). The rapid OFC development we observed around weaning, approximately 12 weeks, may support infant macaque's learning of the complex dominance hierarchy of its social group during this time of increased exploration and distance from mom. In humans, there is a similar pattern of rapid growth of OFC at one year of age (Gilmore et al., 2012). In healthy children, OFC supports cognitive processes essential to social interaction, such as empathy, executive function, inhibitory control, and goal-directed behaviors (Kerr and Zelazo, 2004; Elliott and Deakin, 2005; Furuyashiki and Gallagher, 2007; Brink

et al., 2011; Gremel and Costa, 2013). OFC structural and functional abnormalities have also been associated with psychiatric disease, such as bipolar disorder, ASD and social anxiety (Girgis et al., 2007; Najt et al., 2007; Hahn et al., 2011; Abrams et al., 2013).

All of these brain regions in the social salience and reward brain networks showed unique patterns of growth in comparison to each other. In some cases, the same ROI developed differentially by hemisphere, such as the ACC. This may be in part due to the functional specificity of each ROI; perhaps the unique growth trajectory of each ROI supports the emergence and development of distinct aspects of social behavior. Yet, it is important to consider that these regions do not work independently; they are interconnected in networks that support social behaviors. Social affiliation/reward is supported by regions including the AMY, NAcc, ACC, INS, and vmPFC, as well as their connections to each other (Kohls et al., 2012; Atzil et al., 2014; Landers and Sullivan, 2012); the development of these regions together, which all show rapid growth in the first 3 months of life, is important for deriving reward or pleasure from social interactions, motivation towards social interaction, and forming attachment with the mother. Social salience is supported by a network including the AMY, ACC, INS, and OFC (Seely et al., 2007; Uddin et al., 2013; Rosen et al., 2018); the development of this network, which also grows extensively during the first 3 months of life, supports the early detection of cues of emotional and social relevance. Working together, these networks support the development of social functioning in the healthy infant. If the growth of a single region is altered during the neonatal timeperiod (due to damage, lesions, or other structural abnormality), there is evidence of some plasticity, in which other regions compensate for the disruption early on in development, and healthy social functioning is preserved into adulthood (Raper et al., 2014)Yet, if several regions

experiences delayed or accelerated growth past infancy, the function of the whole network may be altered; evidence from multiple studies previously cited indicates that many children and adults with psychiatric disorders affecting social functioning (such as ASD) have developmental and volumetric abnormalities in just about all of these regions.

While the overall developmental trajectory of each of the brain regions in the social salience and affiliation/reward brain networks was unique, there seems to be some common patterns, particularly periods of rapid growth between 4 to 8 and 16 to 20 weeks of age. What is more interesting is that these periods of accelerated growth are preserved even after correction for ICV, indicating that most regions are experiencing growth spurts independent of the rest of the brain's growth pattern. One possible explanation for these conserved periods is that the social brain is growing rapidly at these timepoints to support the species-typical social milestones of a 8- and 20-week old infant. Prior to 8 weeks of age, the infant macaque spends most of its time interacting with its mother and in close proximity to her (Hinde and Spencer-Booth, 1967; Suomi, 2005). However, around 8 weeks, weaning has started and the infant gains gradual independence, and spends more time in exploration and playing with peers (Hinde and Spencer-Booth, 1967; Suomi, 2005). The infant must also learn the rules of the hierarchy, as macaques have a strict matrilineal dominance structure (Sade, 1967; Suomi, 2005). The rapid growth of the social salience and reward networks from 4to 8 weeks, prior to the weaning period, and from 16 to 20 weeks, during the period of social skill refinement post-weaning, is likely supporting the infant's transition to independence and subsequent motivation to explore a rich social environment and play and to seek the reward of intense interactions with other infants.

As these results reflect GM increases only, it is important to consider how GM proliferates during early life. Several cellular processes underlie the overall volumetric increases in ROI GM. GM is composed of neuronal cell bodies, axon tracts, capillaries, and neuropil (Sigaard et al., 2016). Although most neurogenesis is complete by birth, postnatal synaptogenesis contributes greatly to increases in grey matter in early life (Budday et al., 2015). An analysis of the macaque AMY revealed that postnatal neuron number and soma size did not change, while the slow dendritic development of immature neurons into mature neurons via increases in dendritic length and arborization led to an increase in volume (Chareyron et al., 2012). Studies of the PFC have found increases in synaptic density, dendritic length, and arborization during early development in both monkeys and humans; further, the amount of synaptic density depends on location of the synapse along the neuron (shaft vs. dendritic spine) in the PFC (Lund and Lewis, 1993; Lewis, 1997). In humans, prefrontal synaptic density peaks around 2 years of age . Synaptic density increases in the macaque striatum after birth and peak at approximately 1 month (Brand and Rakic, 1984). In both humans and macaques, there is an overproduction of synapses and an overall increase in dendritic arborization in infancy, explaining the rapid periods of GM growth observed in this study; however, it is important to note that this early synaptogenesis is countered by synaptic pruning in adolescence in healthy individuals (Huttenlocher and Dabholkar, 1997).

Additionally, in typically-developing humans, GM continues to increase in volume and peaks around puberty before experiencing a decline in volume due to synaptic pruning (Gogtay and Thompson, 2010), but in our sample of macaques, it appears that GM peaks by 24 weeks of age (before puberty, around 2 years in humans) and then declines. This apparent pattern in

macaques could be an artifact of the best-fitting curves we used to display the data, and may not be actually representative of what is occurring during development. There may just be a plateau in growth after 24 weeks followed by continued GM growth later, which would more accurately reflect the growth pattern seen in humans. The actual growth pattern of GM after 24 weeks could be revealed with the addition of later age points in the study.

The second goal of this project was to examine developmental trajectories of social behaviors in macaques that are of relevance for human infants with ASD using several behavioral methods, as well as to identify individual differences between infants in the frequencies and durations of these behaviors during the infant period (until 6 months of age). We investigated the early development of social behavior using two methods: infant focal observations with a macaque ethogram, and the jmSRS, a modified version of the macaque SRS (Feczko et al., 2016) as a translational rating scale of general social competency using typical and atypical social domains.

Several infant macaque species-typical behaviors were measured with our ethogram, including affiliative behaviors such as “Contact” and “Proximity”, and distance behaviors that infer breaking contact or proximity with animals, such as “Within 3 Meters”, and “Leave Beyond”. “Within 3 Meters” refers exclusively to an infant’s distance from its mother, and this behavior increased over time, particularly around the weaning period of 6-12 weeks. Similarly, “Leave Beyond”, which refers to the infant moving away, further than arms-reach (approximately 3 meters) from its mother or another animal, also increased over the first 6 months of life. This demonstrates that the infant is spending more time at arm’s reach of its mother or further beyond that 3 meter safe distance, rather than in close physical contact (e.g. on ventrum, or

being held by its mother) as it grows older. In macaques, the mother plays a substantial role in facilitating their infant's transition to independence. In early life, mothers will physically restrain their infants to keep them close, but as they grow older, the mother is less restrictive and may even become aggressive or forceful toward a clingy infant, pushing it away (Hinde and Spencer-Booth, 1967). "Eye Gaze", another important behavior for mother-infant bonding, did not change with age. This behavior may remain consistent across early development as the infant still depends on its mother even while maintaining spatial distance. "Proximity" behavior, in which the infant is within arm's reach of another animal that is not its mother, did not change over time. This indicates that, while animals spent increasingly less time in proximity (out of arm's reach of) with their mother, they spend more time in proximity with peers (playing) or other monkeys in the compound (likely family members). Following these behavioral patterns, there was also a decrease in "Contact" behavior, which is defined as two animals with half or more of their bodies touching. This decrease could be explained as 1) decrease body-to-body contact with their mothers as they gain independence and 2) other behaviors in which body-to-body contact is occurring later in development, such as play, were recorded as such, and not as "Contact". "Touch" requires less of the body to be touching another animal (more like a hand-to-body touch) and did not change with age.

Various types of play behavior were also recorded and analyzed. The "Play Composite" increased over time, particularly around 8 weeks of age, and consisted several types of social play, including intense rough-and-tumble play, chasing, and less intense contact play. This is consistent with reports that social play emerges for most individuals between 7 and 12 weeks (Hinde and Spencer-Booth, 1967). Two types of nonsocial play also changed over time. Vigorous and active

"Solitary Play" drastically increased from 6 to 12 weeks of age, and the more subtle and gentle "Quiet Play" emerged at 4 weeks of age, earlier than any other type of play. Play is an evolutionarily conserved behavior in human and NHPs and has important roles in the social development for both species. In macaques, social play helps to facilitate group cohesion, dominance/submission interactions, independence from the mother, and social communication, and nonsocial play may be beneficial for environmental exploration and for practicing skills like object manipulation (Smith, 2012). Like macaques, solitary play in humans emerges first, around or before 2 years of age (Parten, 1932). Truly cooperative social play with peers emerges around 3-4 years of age (Parten, 1932). Play is important in human children for many of the same reasons as macaques, including facilitation of peer-peer and infant-adult bonding, increasing general social competence, and developing social communication both within and between age groups (Gray, 2007; Uren and Stagnitti, 2009; Mos and Boodt, 2016). Deficits in social play, delayed emergence of play behavior, and differences in type of play behavior are also some of the hallmarks of ASD (Ungerer and Sigman, 1981; Van Berckelaer-Onnes, 2003; Naber et al., 2008; Wolfberg, 2015).

Grooming emerged in some individuals at 6 weeks and increased in duration for most subjects by 24 weeks. Grooming is a social behavior of great importance in macaque society as it provides hygiene benefits, but more importantly it helps to create and reinforce social bonds and hierarchy. Lower-ranked macaques will groom higher-ranked macaques in exchange for protection and acceptance in the group; macaques also tend to groom family members and allies more often than non-kin individuals (Thierry et al., 1990; Schino, 2007; Roubová et al., 2015). As infants are weaned and begin to learn their role in the social environment, they begin to groom

other adults and occasionally other infants in their colony (Hinde and Spencer-Booth, 1967). Therefore, it is not surprising that grooming behavior was high by 24 weeks for most subjects.

Anxiety-like behaviors were also code in the infant macaques, and included yawning, shaking, self-directed behaviors, and scratching oneself (Coleman and Pierre, 2014). These behaviors were combined into one "Anxiety Composite" score that increased from 4 to 6 weeks and from 8 to 12 weeks. As the infant begins to gain motility and tries to explore its environment around 1 month of age, it is restrained by its mother (many times by the tail); this restriction leads to tantrums and it may also be a potential source of the observed early anxiety spike. Additionally, by 8-12 weeks the infant will gradually experience weaning (i.e. the reverse reaction from its mother, with attempts to cling on being rejected), which is a period of changes that may be another source of anxiety for the infants and coincides with the second increase in anxiety behaviors observed. After this period, there is an increase in "Withdraw" behavior, or active avoidance of other animals, from 12 to 24 weeks of age. As the infant becomes more familiar with its social environment post-weaning, he will learn which monkeys are family members and which to avoid because they are higher in the social hierarchy. Anxiety in humans is similar to macaques in that there is no single behavioral trait that distinguishes this arousal state. While some level of anxiety is normal in human children, especially between ages of 7 months and 2 years when fear of strangers emerges, persistent childhood anxiety can interfere drastically with quality of life (Costello et al., 2005). Childhood anxiety disorders, especially social anxiety, are commonly comorbid with ASD (Myles et al., 2001).

The last category of behaviors studied were vocalizations: “Gecker” and “Scream”. “Gecker” is defined as a sharp, high pitch “gak” sound, and “Scream” is a high pitch, high intensity screech. Neither “Gecker” nor “Scream” significantly changed with age, likely due to the high variability between subjects in vocalization behaviors. This likely reflects the differences in environmental stimuli, especially the relationship with mother and/or negative interactions with other animals (e.g. being kidnapped, aggressed, punished by another individual). The purpose of “Gecker” is not well understood, although sometimes they gecker when their mother moves away from them, while adult macaques rarely gecker (Patel and Owren, 2007). Screaming, though, is a distress vocalization, in both infant and adult macaques, although in adults it may also be used as a submissive signal or used to recruit help (Gouzoules et al., 1984; Osterweis et al., 1984).

The second tool used to study social development was the jmSRS. The subjects were rated at 3 and 6 months using this 17-items rating scale that measures general social competency. Results indicated that scores on only 2 of 17 items changed over time: “Plays Appropriately with Peers” and “Upset in Busy Environments”. The reverse-coded jmSRS scores for the former were significantly lower at 6 than 3 months of age, indicating improvement in social play skills with ages. The jmSRS scores for the item “Upset in Busy situations” were higher at 6 than 3 months of age, which can be related to the increased independence with age from the mother (i.e. a 6-month-old infant may not feel as secure in stressful situations, whereas a 3-month-old infant may still feel protection from the mother).

There are several possible explanations to the lack of developmental changes in the remaining 15 jmSRS items. The most obvious explanation is that the jmSRS measures social impairment,

rather than social competency (Constantino et al., 2003; Feczko et al., 2016) and the infants in our sample were selected from typically developing populations with normal social functioning. Another potential explanation is the small sample size; there were 9 subjects tested with this jmSRS. The distribution for most of the items on the jmSRS was not normal, and therefore had to be statistically analyzed using nonparametric tests. In the original macaque SRS by Feczko et al. (2016), the scores for their sample of 105 adult monkeys were normally distributed. Therefore, we are likely underpowered to detect significant effects. It is reasonable to assume that with a larger sample size, the jmSRS scores would also be normally distributed, and a more robust statistical model could be used to detect developmental changes. A third explanation for the lack of sensitivity of these 15 jmSRS items to detect developmental changes could be that the items are not well suited to measure infant macaque social competence and will more accurately measure changes in social competency at later ages, when the subjects reach the juvenile period; following this logic, investigating the difference in scores from 6 months to one year of age is a future plan for our group. Finally, the original macaque SRS by Feczko et al. (2016) found differences in scores by dominance rank of the animal. The present study did not examine rank as a factor; grouping both high- and low-ranking infants together may have erased any potential group-level differences between the ages. We plan to further investigate effects of dominance rank on jmSRS scores, as well as brain and behavioral development once we increase our sample size and add subjects to the studies.

The third and final goal was to determine the relationship between neural and behavioral development measures during infancy to identify neural predictors of social maturation across the first six months of life. There was a small subset of subjects for which we collected and

analyzed both sMRI and OBS data; therefore, we examined the predictive value of ROIs volume changes on behavioral outcomes in this group. It is important to recognize that because the sample is so small, these results should be considered as preliminary and used to guide future in-depth investigations.

The results from this exploratory analysis indicated that developmental changes in ACC (BA24) volume was the most significant predictor of age changes in "Within 3 Meters" rates, accounting for 47.5% of variance. Additionally, developmental increases in the subgenual cingulate (BA25) volume, another subregion of the cingulate cortex, was a significant predictor of developmental changes in "Leave Beyond" rates, with BA25 volume accounting for 51.6% of the variance. There are likely other brain regions involved in supporting complex behaviors. These results, which singled out specific ROIs, may have stemmed from inflated effects from statistical analyses completed with a very small sample size; nevertheless, the preliminary findings may still highlight important ROIs which support socioemotional behaviors.

There is a large body of existing evidence indicating a strong role of the ACC driving social behaviors (Lockwood and Wittmann, 2018). In particular, the ACC is known for its role in social decision-making in both humans and NHPs. Lesions of the ACC in primates lead to decreased interest in other con-specifics, and neuronal firing from the ACC is activated during encoding of social reward (Rudebeck, 2006; Chang et al., 2013). Different subregions of the ACC have different roles in social-emotional behavior, which may be why the results from our study suggest that the developmental volumetric changes of the ACC vs. subgenual cingulate predict different behaviors.

The dorsal ACC may be responsible for signaling prediction error, or discrepancy between expected and actual outcomes of behaviors in social situations (Holroyd et al., 2004; Critchley et al., 2005; Polli et al., 2005). Additionally, research suggests that individuals with ASD or social anxiety disorders may experience deficits in social prediction error (Balsters et al., 2017; Koban et al., 2017). The dorsal ACC and perigenual ACC (includes BA32 and 24) are associated with self-other distinction (Kelley et al., 2002; Ruff and Fehr, 2014; Perini et al., 2018). Furthermore, the perigenual ACC seems to play a role in memory of past performances on certain tasks, which later will support future performances of that same behavior (Wittmann et al., 2016). The relationship of this subregion to "Quiet Play" may be particularly interesting to investigate further, as it appears that infants engaging in quiet play behavior do so in order to learn and practice skills such as object manipulation for the future (Smith, 1978).

On the other hand, several studies have found that emotional appraisal, fear response to faces, and action selection recruit the subgenual ACC (Stevens et al., 2011; Rudebeck et al., 2014). Depression and other neuropsychiatric disorders may also be modulated in part by subgenual ACC (Marquardt et al., 2005; Boes et al., 2008; Drevets et al., 2008; Holtzheimer and Mayberg, 2010). Given this evidence, the subgenual ACC may also be a relevant target for future studies of healthy social functioning and social deficits in a NHP model.

Overall, this study is unique and unprecedented, and the findings will contribute to the understanding of neurodevelopmental processes underlying typical and atypical social behavior in primates, including the development of a NHP model of ASD and other neurodevelopmental disorders. However, it is important to note several limitations of this study. The only control used

for ROI development was ICV, but no negative control ROI were included. Inclusion of a non-socially oriented ROI, such as the motor cortex or primary visual cortex, would have helped differentiate the specificity (or not) of the trajectories described here for the social salience and reward network ROIs. Another limitation is the small sample size for the behavioral data and the exploratory regression analysis. A larger sample size would increase statistical power and further highlight ROI growth that predicts behaviors of interest. Future iterations of this project plan to increase the sample size of infants used in all parts of the study (sMRI, OBS, and jmSRS). A third limitation was the low occurrence of several social behaviors collected. Nevertheless, we were able to analyze at least the most frequent and common social behaviors

Despite these limitations, the potential implications of the findings towards future studies should not be dismissed. The level of detail is unique in both the longitudinal sMRI analysis and behavioral data assessment. There are no previous studies in which social brain structural development is extensively measured with multiple age points across the first weeks of life; this detail allowed us to identify specific weeks, rather than years or months, in development when milestones occur. Additionally, the level of detail recorded in the behavioral data in socially-housed macaques paints a rich picture of the early stages of healthy social development in one of our closest relatives. Rhesus monkeys are an ideal model to study neural development and social behavior due to their similarities with human brain and behavior, and the use of this macaque model lends itself towards future experimental manipulation that would not be ethical in human infants. With the findings from this study, we hope to use this macaque model as a baseline for future investigations of social deficits and early development of ASD. As this project is part of a larger study conducted by the Sanchez and Bachevalier labs with the Marcus Autism

Center, we plan to use this data to further investigate the original hypothesis of the project, which was that early development of social behaviors and underlying neurocircuits parallels shift from early reflexive to conscious control of movement. Furthermore, this data creates a foundation for a NHP model of ASD; by understanding how social behavior develops in the typically developing infant, we can then begin to investigate social deficits which are deviations from the norm. Overall, understanding normative development of social behavior 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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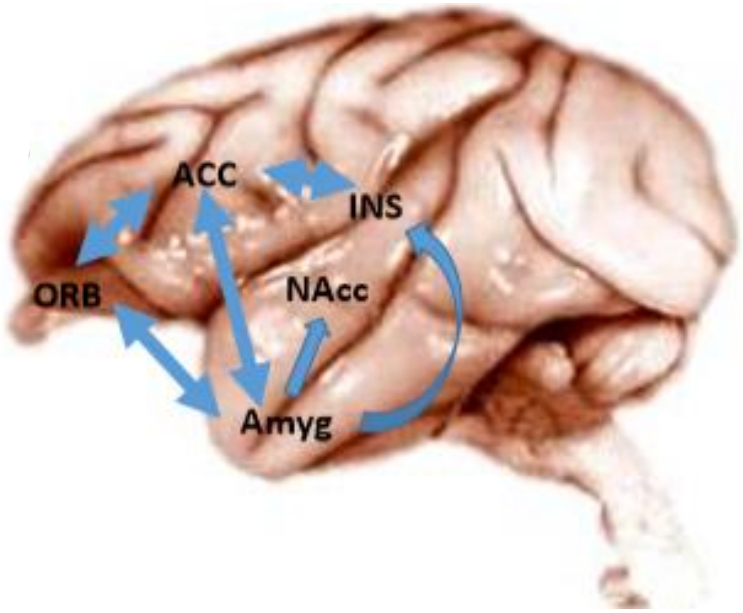


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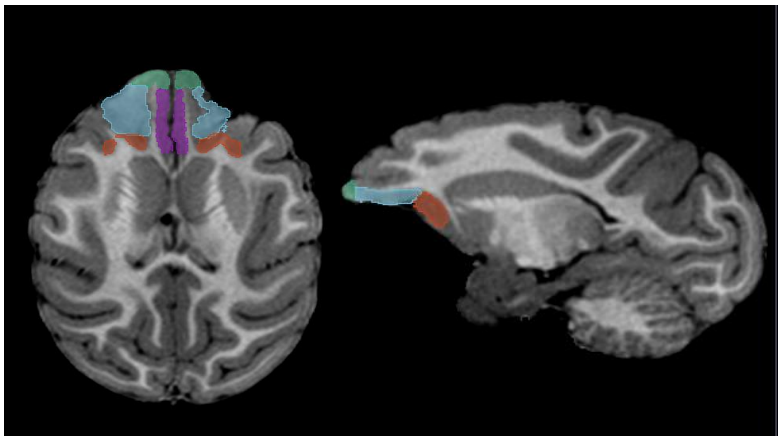


**Figure 1: Social Salience, Reward, and Affiliation Networks.** A) These networks include the amygdala (Amyg) and anterior cingulate cortex (ACC) and their connections with the insula (INS) and orbitofrontal cortex (ORB), and the nucleus accumbens (NAcc). Figure courtesy of Dr. Jocelyne Bachevalier. B) An example segmentation of the anterior prefrontal cortex (BA10: green), orbitofrontal cortex (BA11: blue; BA13: red), and the caudal medial prefrontal cortex (BA32, purple).

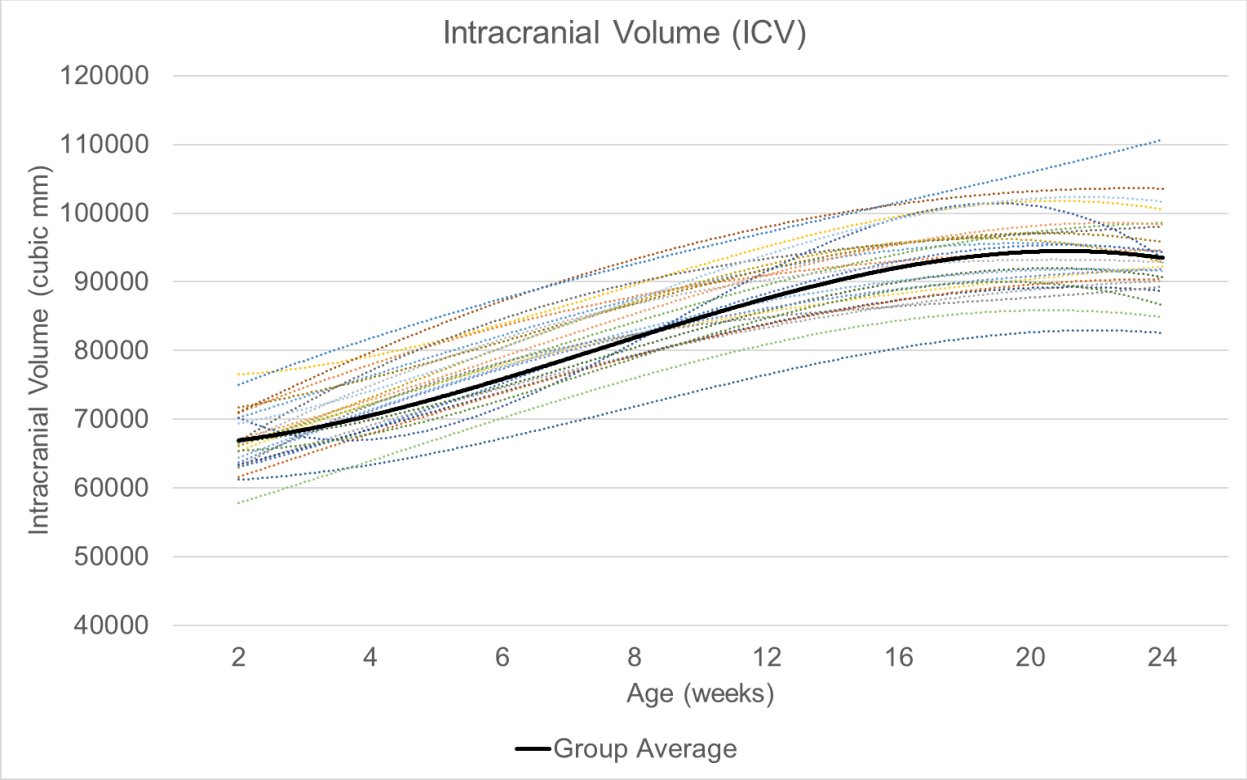
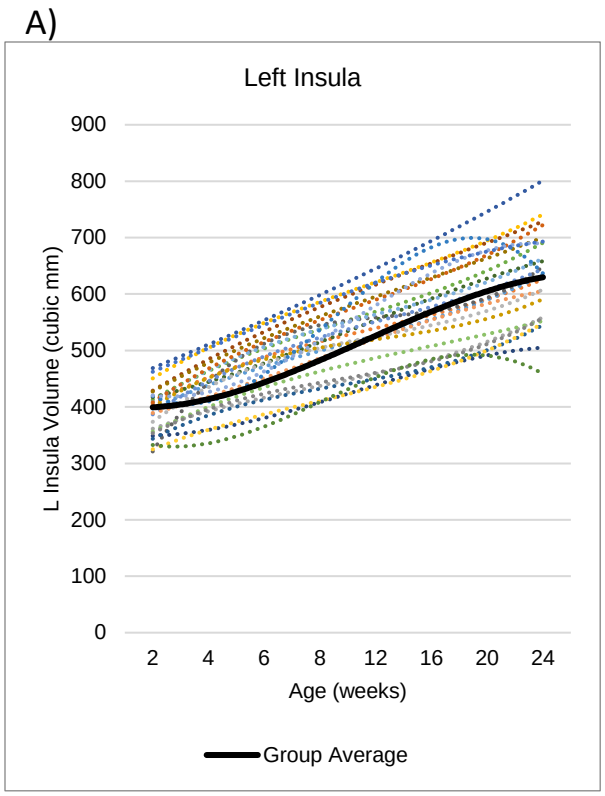
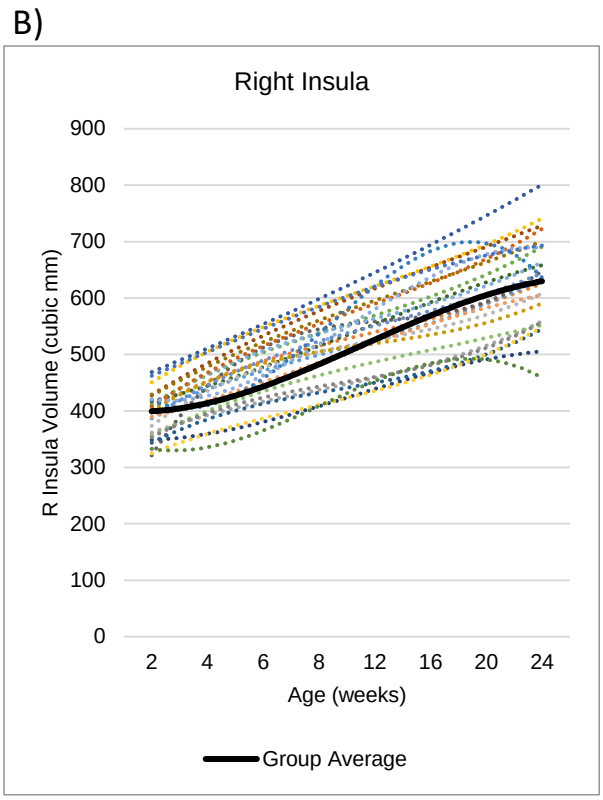



**Figure 2: Total ICV changed over time.** There was a significant effect of AGE (F(7,16.68)=94.58; p= 3.45 $x10^{-12}$) on ICV. Post-hoc tests detected a period of rapid ICV growth between 2 and 4 weeks (p=0.008), followed by continuous but non-significant growth until about 20 weeks, and a plateau in growth after that. Colored lines represent 3$^{rd}$ order polynomial trendlines (best fitting curves) for each subject; black line is the group average trendline. Data and statistical results presented include 6 weeks (n=4 subjects), although statistical results from LMM excluding 6 weeks are provided in the text.



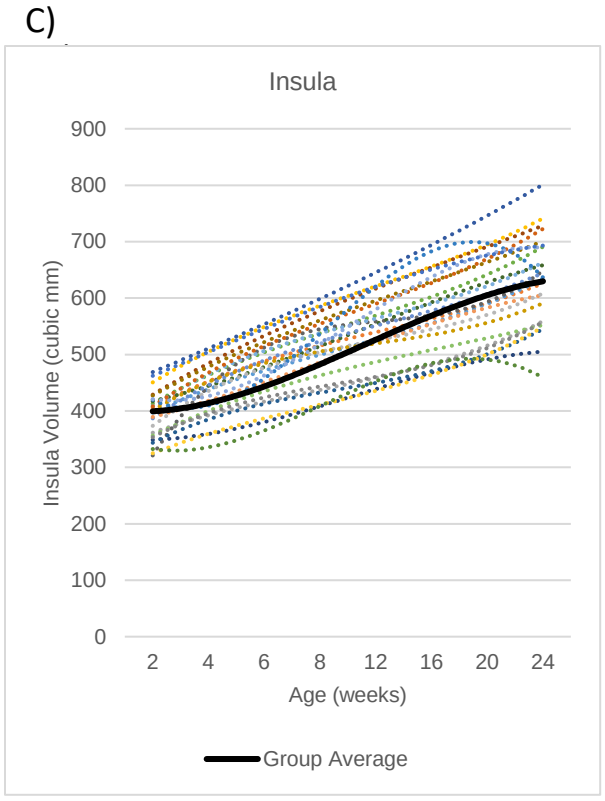




**Figure 3: INS volume changed over time.** A, B) There was a significant effect of AGE ($F(6, 70.55)=109.49$; $p=2.46 \times 10^{-36}$) on INS volume. Post-hoc tests detected periods of rapid growth between 4 and 8 weeks ($p=1.52 \times 10^{-17}$) and between 16 and 20 weeks ($p=2.32 \times 10^{-7}$). C) Volume of INS (bilateral: right + left) changes over time when controlling for subject ICV, still resulted in a significant effect of AGE ($F(6, 31.986)=3.72$; $p=3.86 \times 10^{-28}$); post-hoc tests identified periods of significant growth between 2 and 4 weeks ($p=0.02$) 4 and 8 weeks ( $p=9.40 \times 10^{-31}$), 8 and 12 weeks ($p=0.04$) and 16 and 20 weeks ($p=7.84 \times 10^{-15}$). Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented include 6 weeks (n=4 subjects); statistical results from LMM excluding 6 weeks are provided in the text

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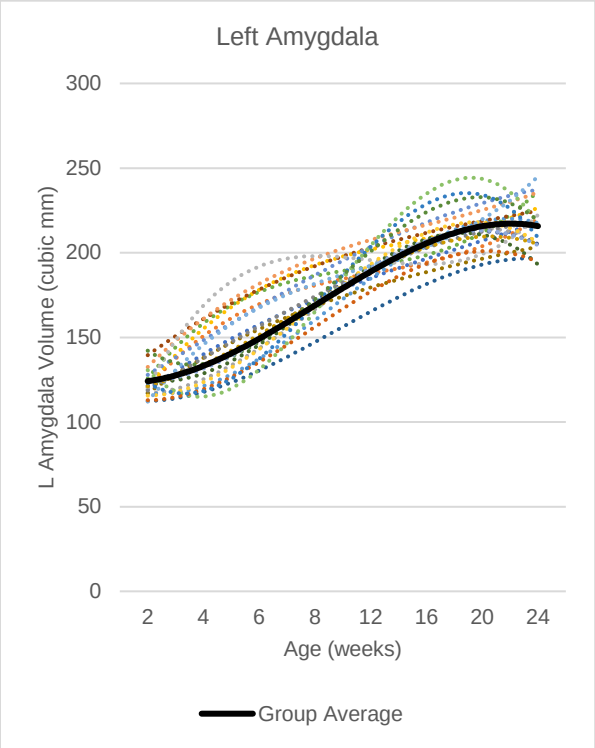


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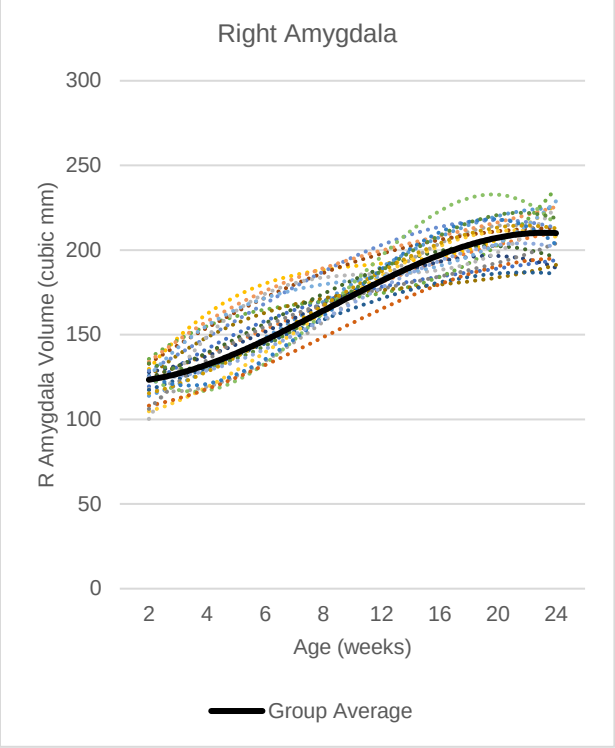


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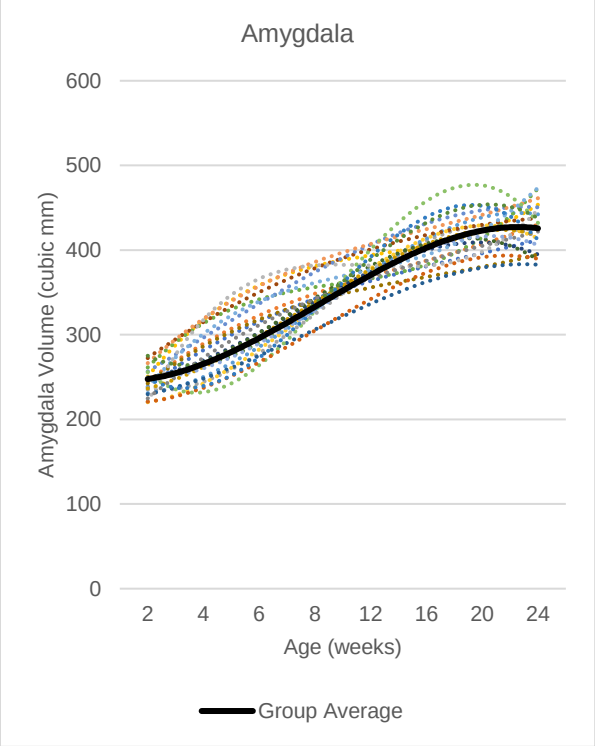
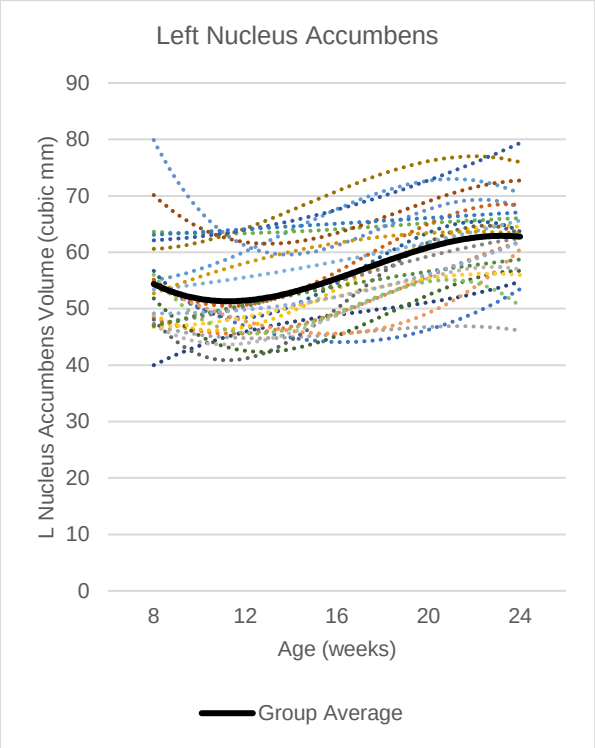



**Figure 4: AMY volume changed over time.** A,B) There was a significant effect of AGE (F(6, 78.86)=323.59; p=2.22 x10$^{-53}$), and HEMISPHERE (F(1, 70.55)=109.49; p=0.004) on AMY volume. Post-hoc tests detected periods of rapid growth between 2 and 4 weeks (p=0.01), 4 and 8 weeks (p=8.01x10$^{-21}$) and 16 and 20 weeks (p=2.7 x10$^{-5}$). C) Analyses of AMY volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 3C) still resulted in a significant effect of AGE (F(6, 32.76)=590.10; p=6.55 x10$^{-32}$) on AMY volume. Post-hoc tests detected periods of rapid growth between 2 and 4 weeks (p=0.001), 4 and 8 weeks (p=4.41 x10$^{-23}$ ), and 16 and 20 weeks (p=1.49 x10$^{-8}$). Colored lines represent 3$^{rd}$ order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)

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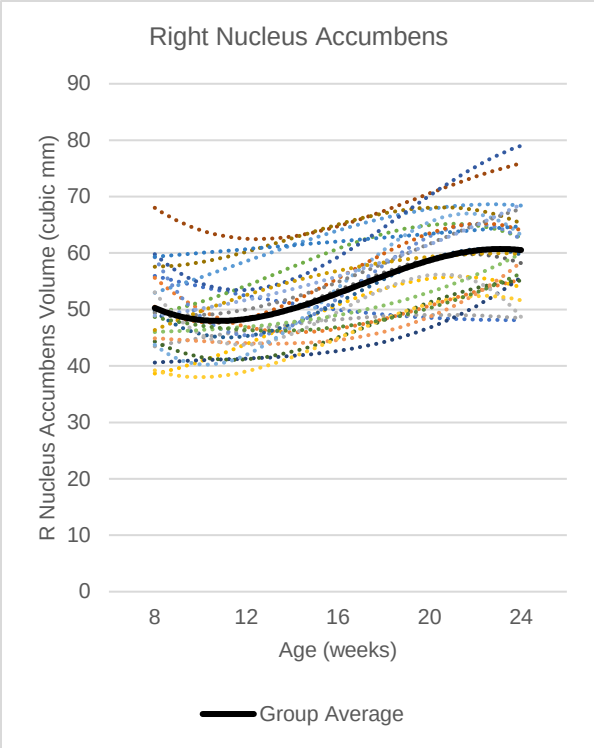


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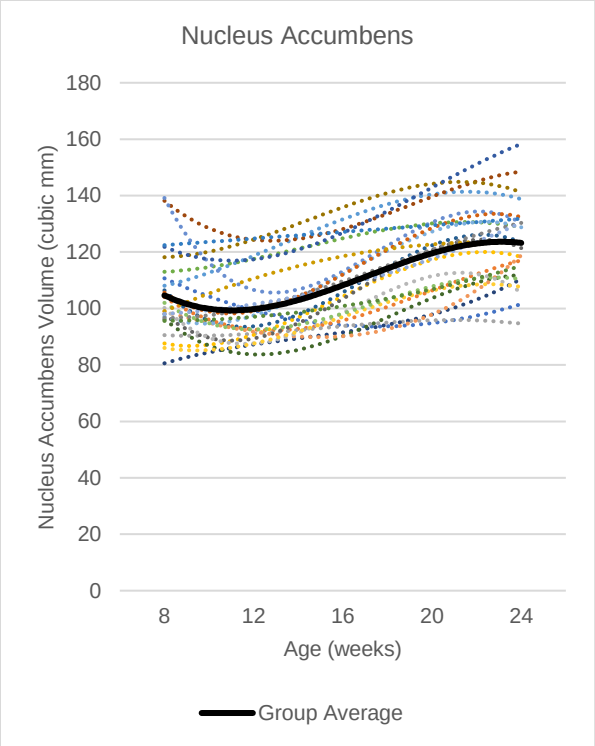
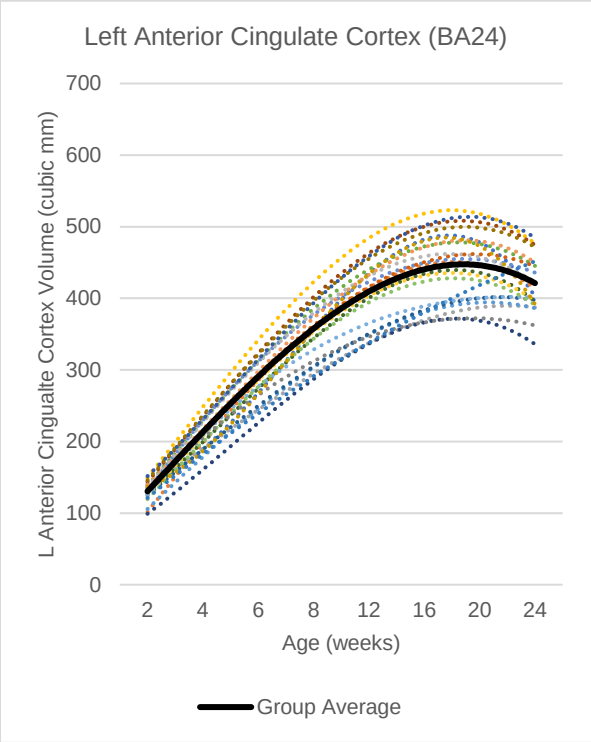



**Figure 5: NAcc volume changed over time.** A,B) There was a significant effect of AGE ($F(4, 88.79)=20.03$; $p= 8.77 \times 10^{-12}$) and HEMISPHERE ($F(1, 194.53)=7.28$; $p=0.008$) on NAcc. Post-hoc tests revealed a significant growth period between 16 and 20 weeks ($p=0.001$). C) Analyses of NAcc volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 4C) still resulted in a significant effect of AGE ($F(4, 29.92)=61.57$; $p=5.20 \times 10^{-14}$) on NAcc volume. A significant increase in volume was detected based on post-hoc analysis between 16 and 20 weeks. Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline.

A)

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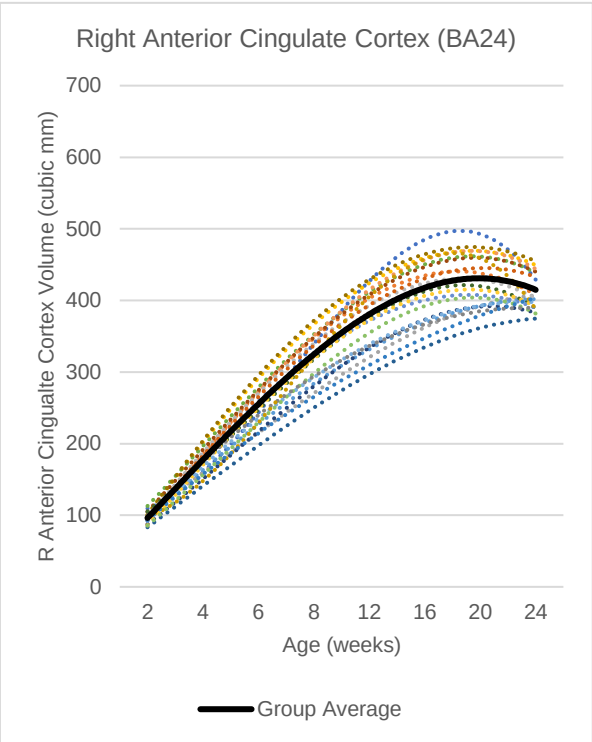


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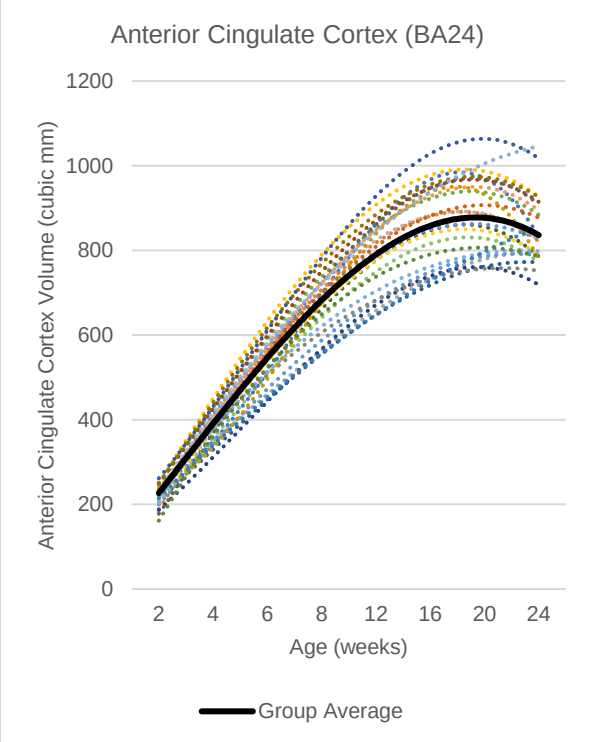



**Figure 6: ACC(BA24) volume changed over time.** A,B) There was a significant effect of AGE ($F(6, 81.79)=1160.86$; $p=6.29 \times 10^{-77}$) and HEMISPHERE ($F(1, 209.635)=33.824$; $p=2.23 \times 10^{-8}$) on ACC volume. Post-hoc tests detected a period of rapid growth between 4 and 8 weeks ($p=1.29 \times 10^{-41}$). C) Analyses of ACC volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model still resulted in a significant effect of AGE ($F(6, 25.80)=1129.93$; $p=6.07 \times 10^{-30}$) on ACC volume. Post-hoc tests detected periods of rapid growth growth between 2 and 4 weeks ($p=0.001$), 4 and 8 weeks ($p=1.40 \times 10^{-32}$), 8 and 12 weeks ($p=0.026$), and 16 and 20 weeks ($p=0.001$). Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

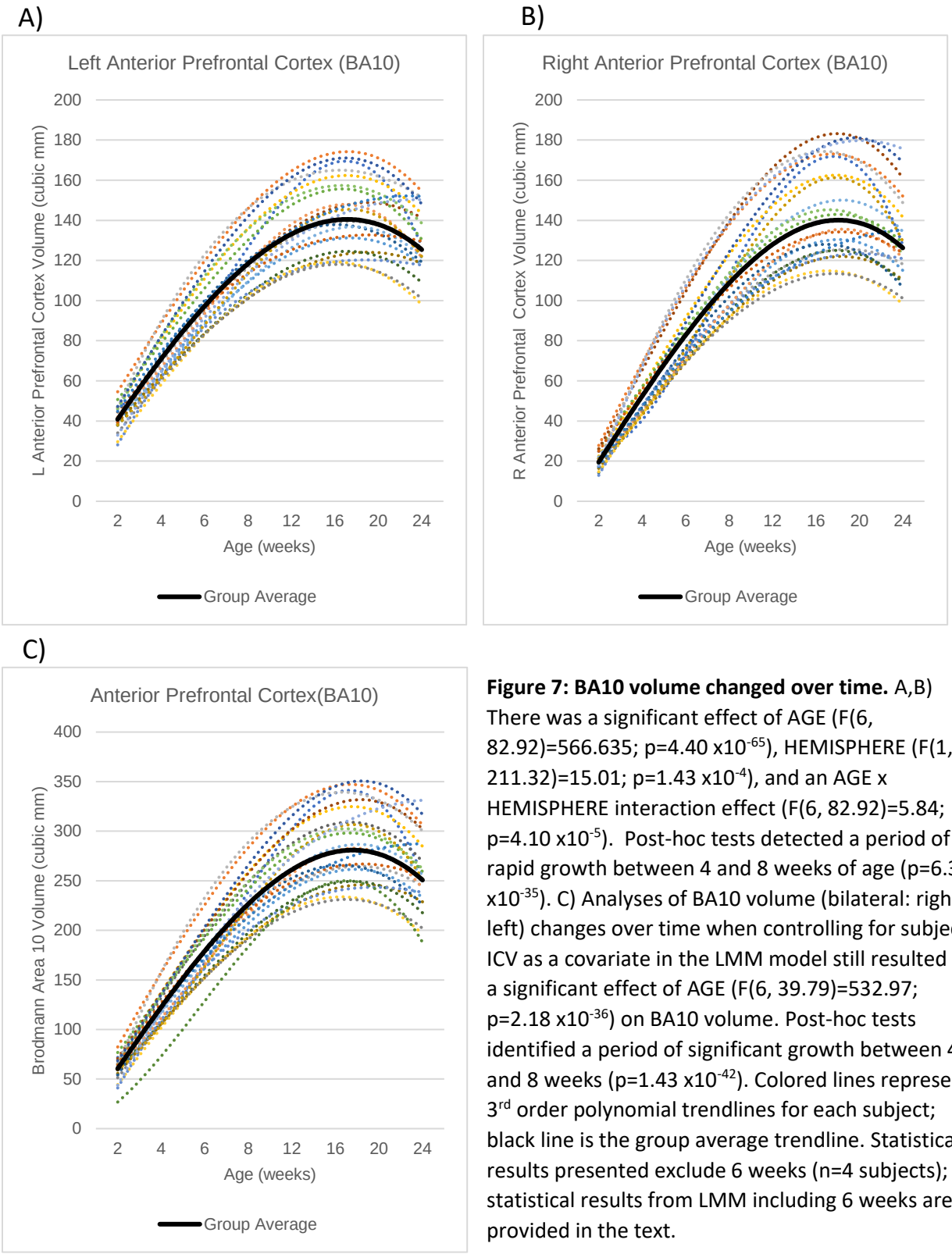
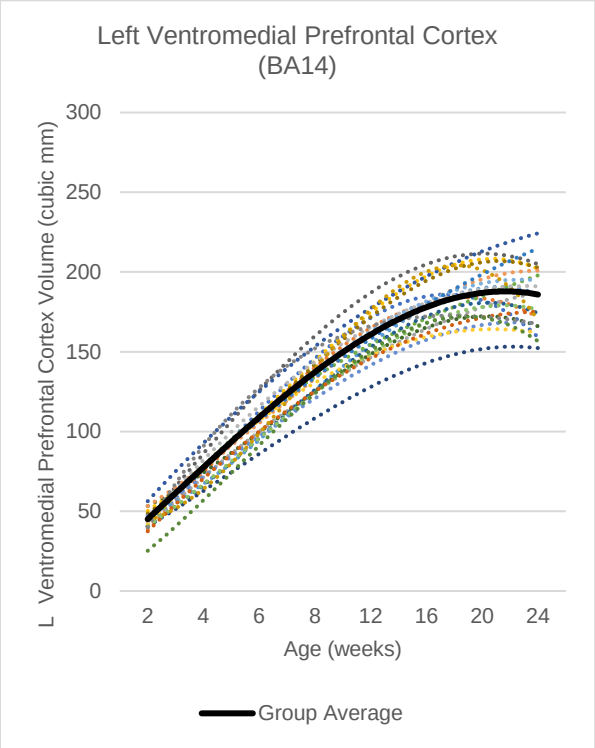
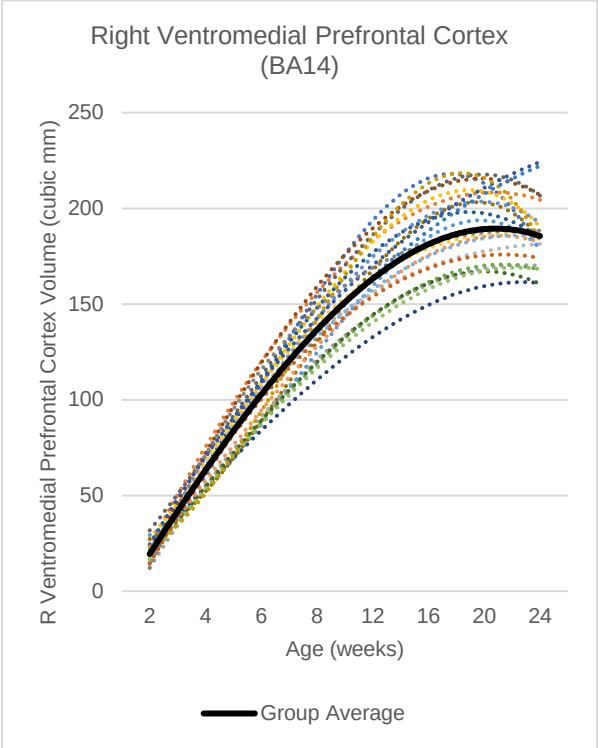



**Figure 7: BA10 volume changed over time.** A,B) There was a significant effect of AGE ($F(6, 82.92)=566.635$; $p=4.40 \times 10^{-65}$), HEMISPHERE ($F(1, 211.32)=15.01$; $p=1.43 \times 10^{-4}$), and an AGE x HEMISPHERE interaction effect ($F(6, 82.92)=5.84$; $p=4.10 \times 10^{-5}$). Post-hoc tests detected a period of rapid growth between 4 and 8 weeks of age ($p=6.37 \times 10^{-35}$). C) Analyses of BA10 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model still resulted in a significant effect of AGE ($F(6, 39.79)=532.97$; $p=2.18 \times 10^{-36}$) on BA10 volume. Post-hoc tests identified a period of significant growth between 4 and 8 weeks ($p=1.43 \times 10^{-42}$). Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)




B)




C)

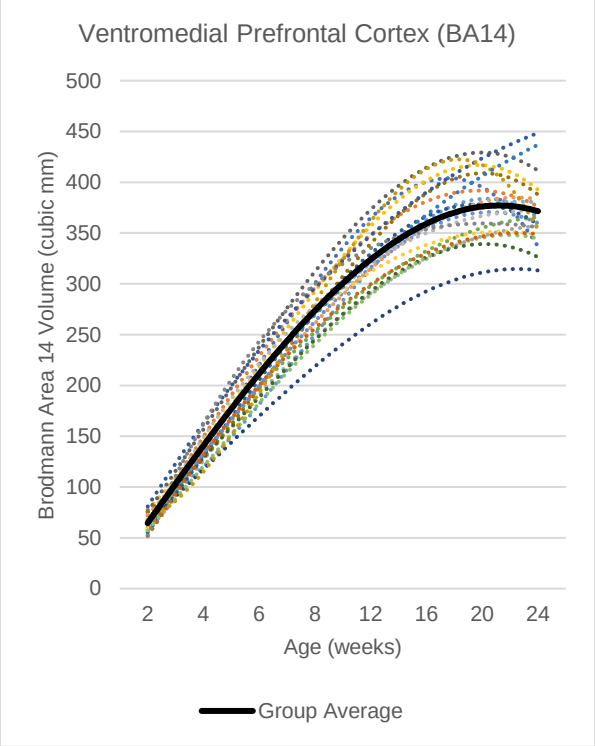
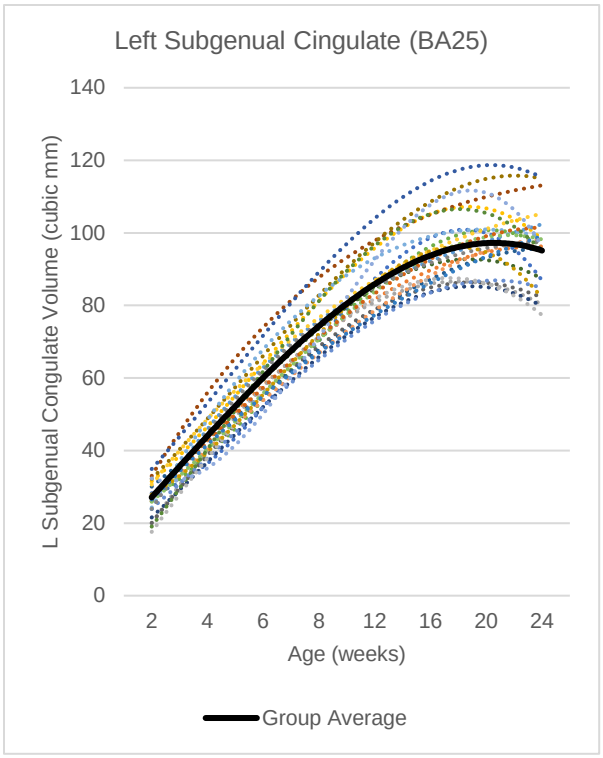



**Figure 8: BA14 volume changed over time.** A,B) There was a significant effect of F(6, 83.41)=1436.29; p=6.17 x$10^{-82}$) and HEMISPHERE (F(1, 205.38)=6.45; p=0.012), and an AGE x HEMISPHERE interaction (F(6, 83.41)=13.924; p=6.61 x$10^{-11}$). Post-hoc tests detected periods of rapid growth between 4 and 8 weeks (p=9.38x$10^{-42}$) and 16 and 20 weeks (p=4.27x$10^{-7}$). C) Analyses of BA14 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 7C) still resulted in a significant effect of AGE (F(6, 38.91)=1823.451; p=4.55 x$10^{-46}$), on BA14 volume. Post-hoc tests detected periods of rapid growth between 2 and 4 weeks (p=1.7 x$10^{-5}$), 4 and 8 weeks (p=6.75 x$10^{-22}$), and 16 and 20 weeks (p=3.00 x$10^{-6}$). Colored lines represent 3$^{rd}$ order polynomial trendlines for each subject; black line is the group average trendline. . Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)

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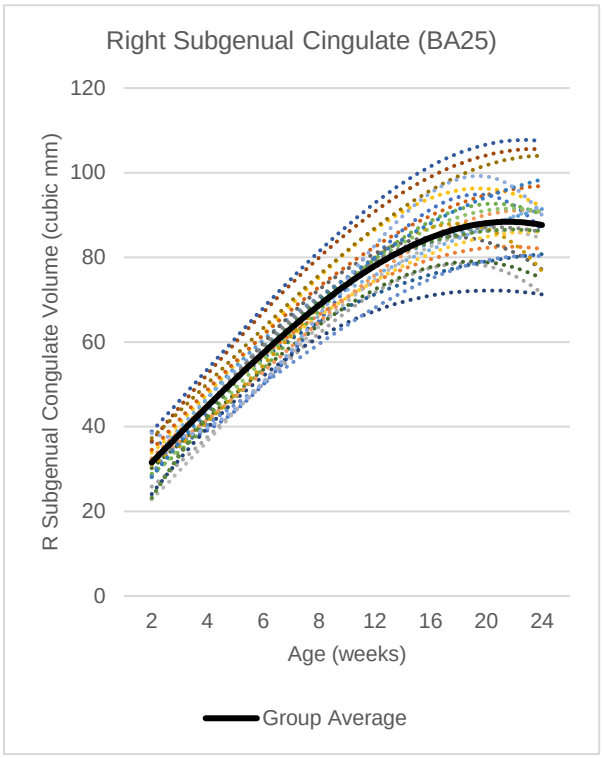



C)

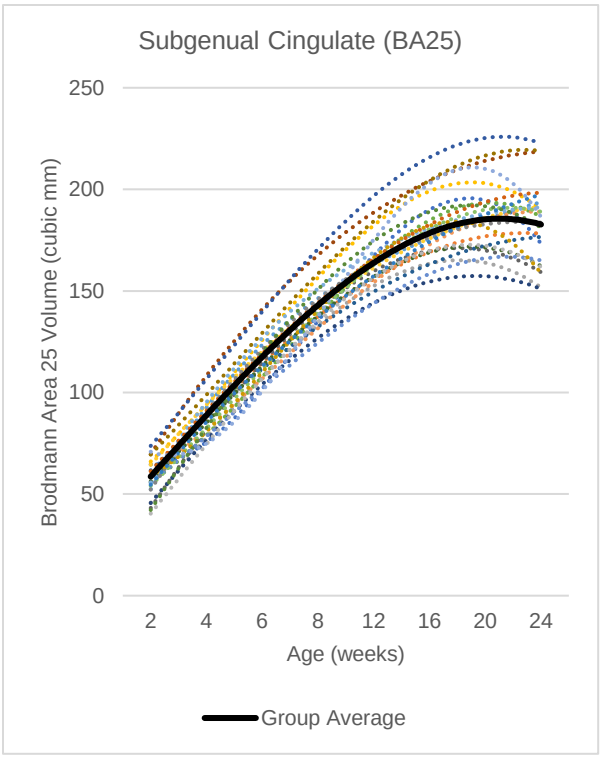
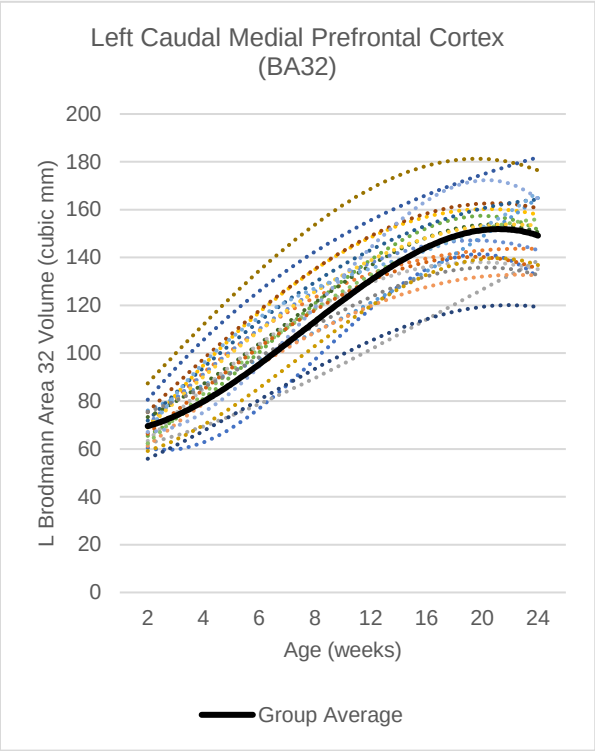



**Figure 9: BA25 volume changed over time** A,B) There was a significant effect of AGE ($F(6, 88.65)=892.66$; $p=5.45 \times 10^{-77}$) and HEMISPHERE ($F(1, 215.37)=30.95$; $p=7.82 \times 10^{-8}$), and an AGE x HEMISPHERE interaction ($F(6, 88.65)=10.81$; $p=5.32 \times 10^{-9}$). Post-hoc tests detected periods of rapid growth in BA14 between 4 and 8 weeks ($p=2.17 \times 10^{-49}$) and 16 and 20 weeks ($p=1.00 \times 10^{-7}$). C) Analyses of BA25 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model still resulted in a significant effect of AGE ($F(6, 24.15)=1330.05$; $p=3.39 \times 10^{-29}$), on BA25 volume. Post-hoc tests detected periods of rapid growth between 4 and 8 weeks ($p=3.28 \times 10^{-37}$), and 16 and 20 weeks ($p=6.71 \times 10^{-8}$).Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. . Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)

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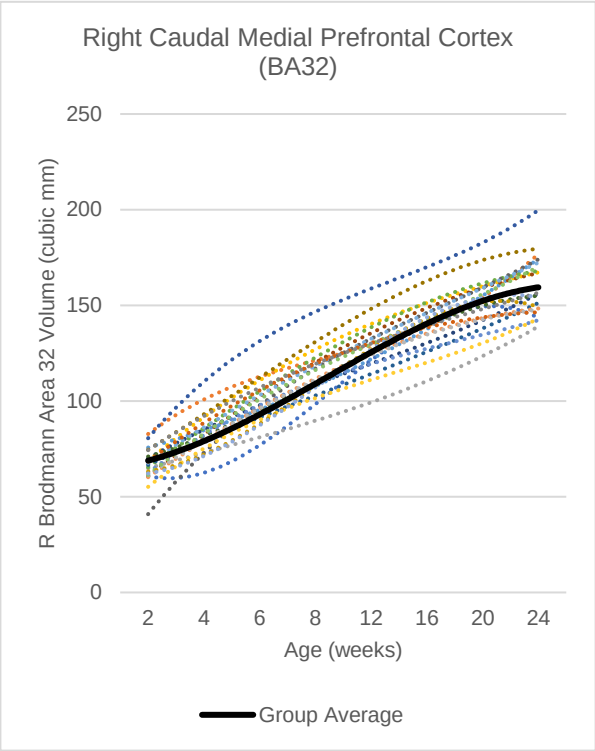



C)

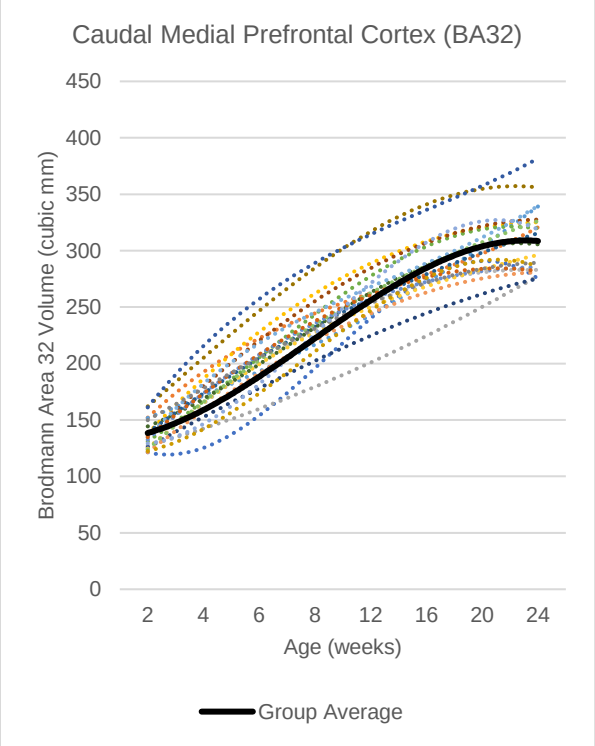
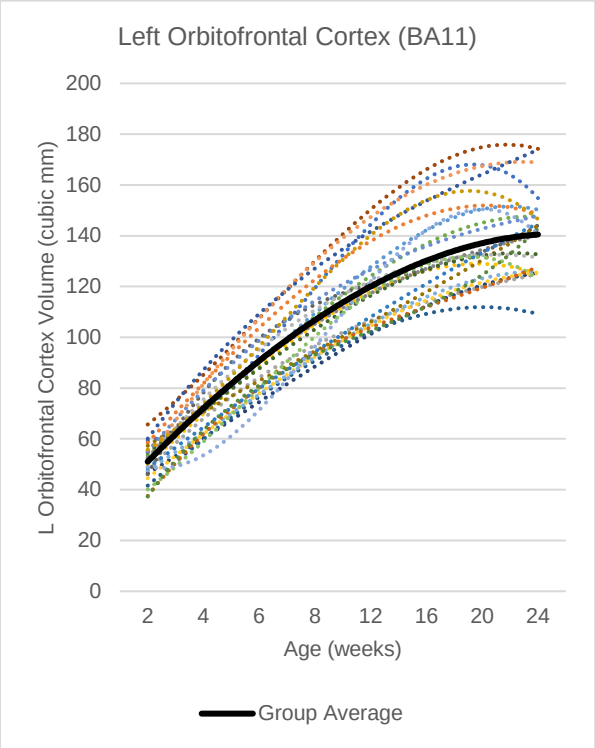
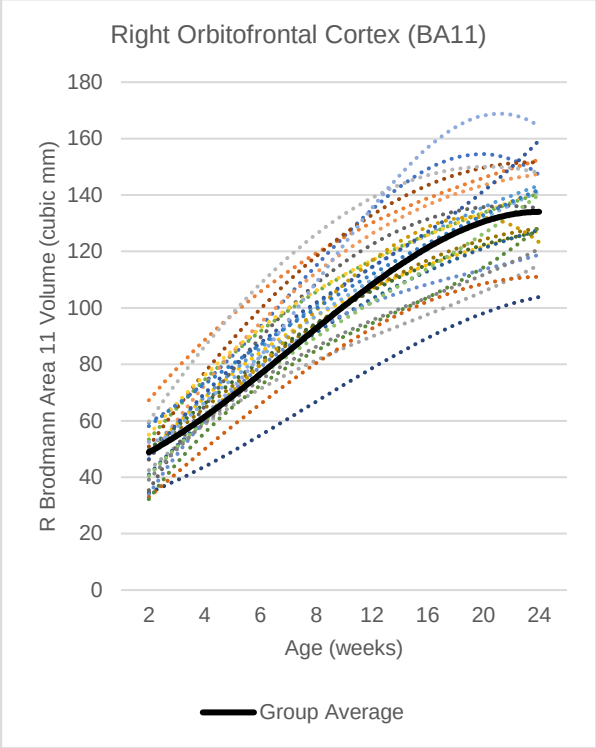



**Figure 10: BA32 volume changed over time.** A,B) There was a significant effect of AGE ($F(6, 89.17)=408.84$; $p=1.33 \times 10^{-62}$), on BA32 volume. Post-hoc tests detected periods of rapid growth in BA32 volume between 4 and 8 weeks ($p=1.04 \times 10^{-27}$), and 16 and 20 weeks ($p=3.15 \times 10^{-7}$). C) Analyses of BA32 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model still resulted in a significant effect of AGE ($F(6, 28.39)=701.01$; $p=1.69 \times 10^{-29}$) on BA32 volume. Post-hoc tests detected periods of rapid growth growth between 4 and 8 weeks ($p=9.86 \times 10^{-24}$), and 16 and 20 weeks ($p=3.60 \times 10^{-10}$). Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)




B)

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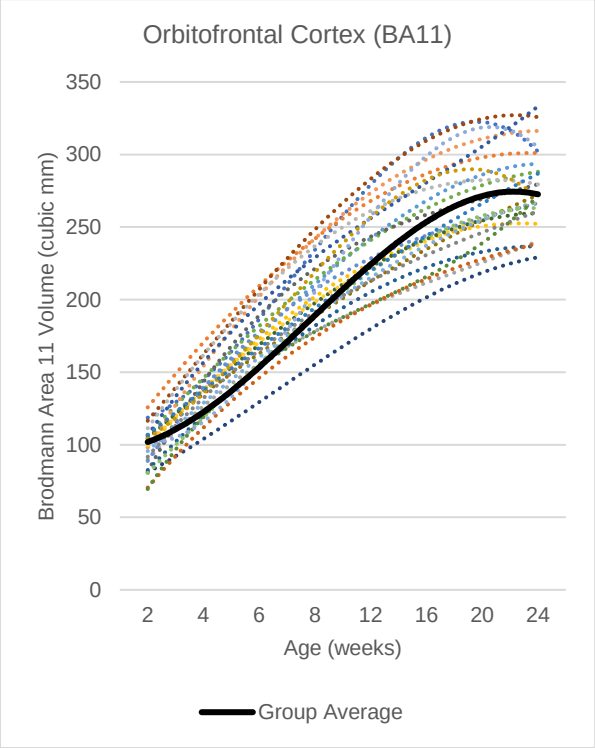
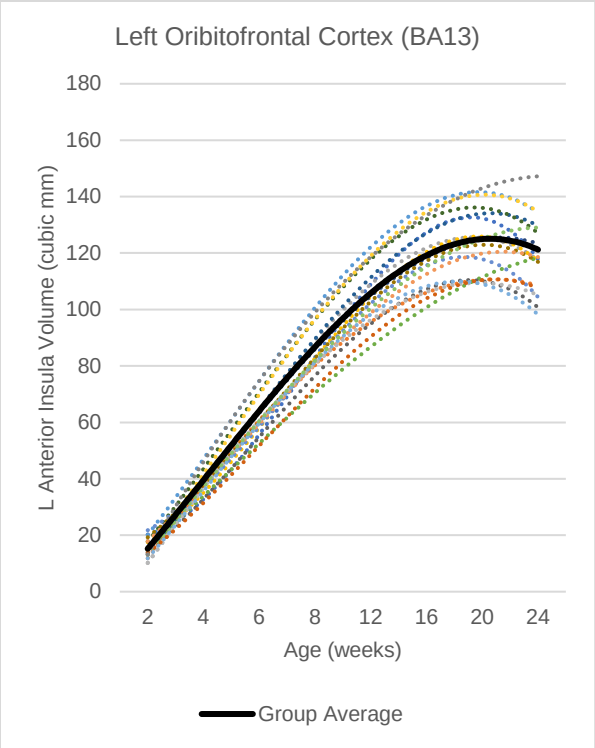
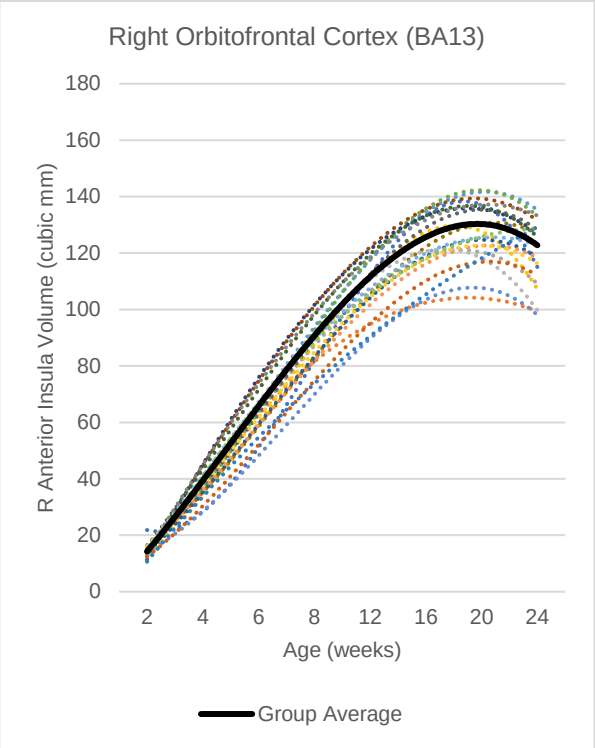



**Figure 11: BA11 volume changed over time.** A,B) There was a significant effect of AGE ($F(6, 93.71)=437.37$; $p=3.27 \times 10^{-66}$) and HEMISPHERE ($F(1, 235.705)=19.12$; $p=1.80 \times 10^{-5}$)on BA11 volume. Post-hoc tests detected periods of rapid growth between 4 and 8 weeks ($p=8.11 \times 10^{-34}$), and 16 and 20 weeks ($p=6.10 \times 10^{-37}$) with non-significant increases in volume before, after, and in-between these timeframes. C) Analyses of BA11 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 10C) still resulted in a significant effect of AGE ($F(7, 7.199)=701.728$; $p= 1.22 \times 10^{-9}$) on BA11 volume. Post-hoc tests detected a period of rapid growth between 4 and 8 weeks ($p=1.74 \times 10^{-33}$), and 16 and 20 weeks ($p=2.43 \times 10^{-14}$). Colored lines represent 3$^{rd}$ order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

A)




B)




C)

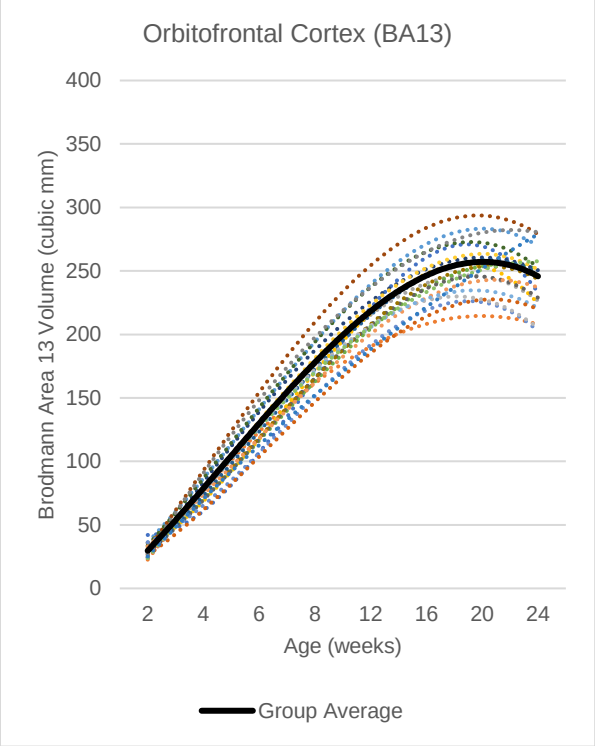



**Figure 12: BA13 volume changed over time.** A,B) There was a significant effect of AGE ($F(6, 79.67)=1303.59$; $p=2.47 \times 10^{-77}$) on BA13 volume. Post-hoc tests detected periods of rapid growth in BA13 volume between 4 and 8 weeks ($p=9.42 \times 10^{-38}$), and 8 and 12 weeks ($p=0.01$). C) Analyses of BA13 volume (bilateral: right + left) changes over time when controlling for subject ICV as a covariate in the LMM model (Fig 11C) still resulted in a significant effect of AGE ($F(6, 31.59)=918.27$; $p=5.31 \times 10^{-34}$) on BA13 volume. Post-hoc tests detected periods of rapid growth between 4 and 8 weeks ($p=1.51 \times 10^{-31}$), 8 and 12 weeks ($p=1.00 \times 10^{-6}$), and 16 and 20 weeks ($p=0.003$). Colored lines represent 3rd order polynomial trendlines for each subject; black line is the group average trendline. Statistical results presented exclude 6 weeks (n=4 subjects); statistical results from LMM including 6 weeks are provided in the text.

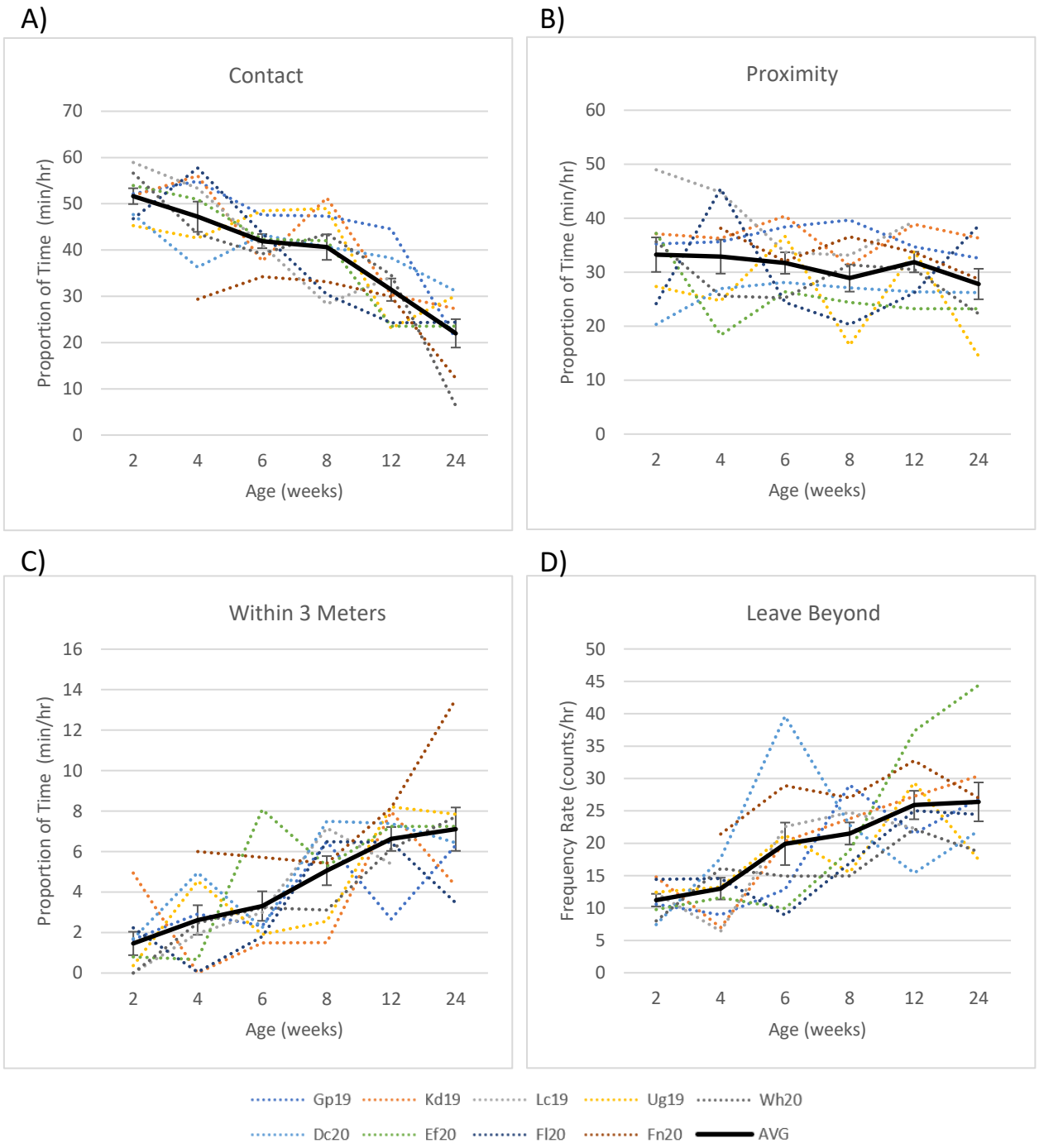



**Figure 13: Infant affiliative/prosocial behaviors over time.** Average rate (min/hr or counts/hr) of affiliative behaviors. A) There was a significant effect of AGE ($F(5,13.78)=19.21$; $p= 9.00 \times 10^{-6}$) on "Contact" duration. B) There was no significant effect of AGE on "Proximity" duration. C) There was a significant effect of AGE ($F(5, 13.21)=40.25$; $p= 1.53 \times 10^{-7}$) on "Within 3 Meters" duration. D) There was a significant effect of AGE ($F(5, 14.18)=15.49$; $p= 2.6 \times 10^{-5}$) on "Leave Beyond" frequency. Colored lines represent individual subjects; black line is the group average, with error bars ±SEM.

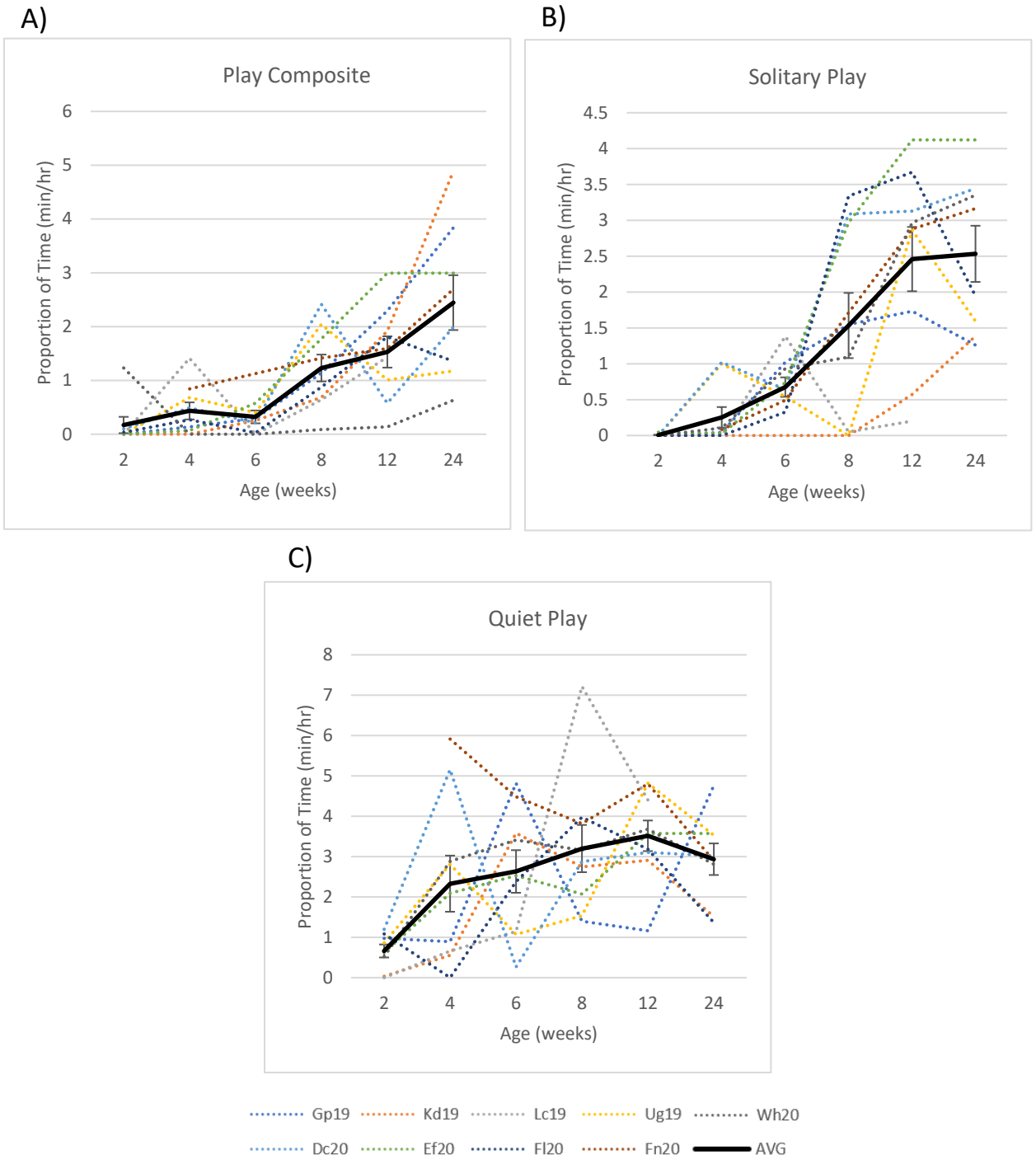



**Figure 14: Infant play behaviors over time**. Average rate (min/hr) of play behaviors. A) "Play Composite" changed with AGE ($\chi^2(5)=23.41$; p= 2.82 x$10^{-4}$). B) Solitary Play" changed with AGE ($\chi^2(5)=27.39$; p= 4.8 x$10^{-5}$). C) There was a significant effect of AGE ($F(5,16.35)=17.03$; p= 6.00 x$10^{-6}$) on "Quiet Play" duration. Colored lines represent individual subjects; black line is the group average, with error bars ±SEM

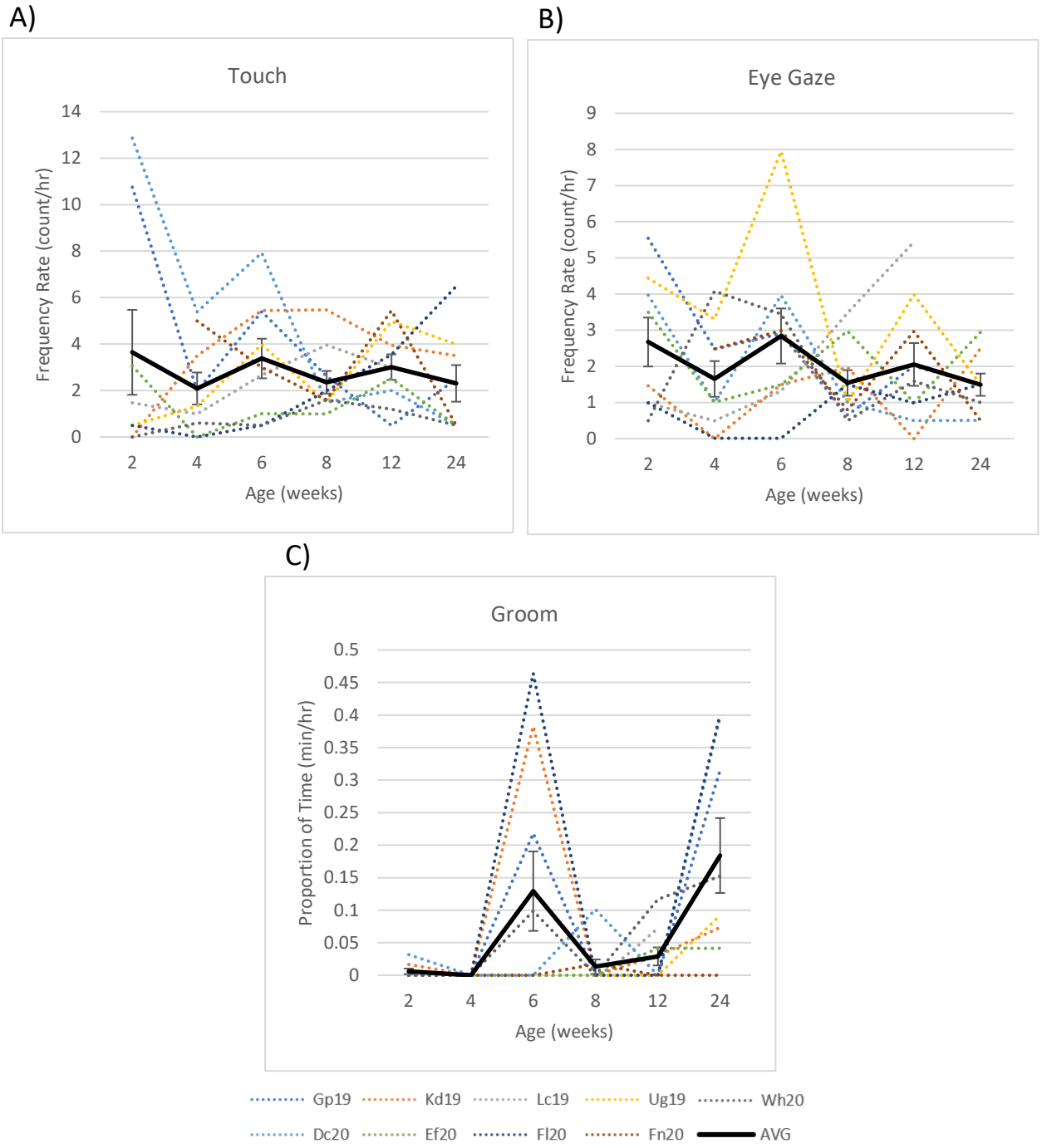



**Figure 15: Other infant prosocial behaviors over time.** Average rate (min/hr or counts/hr) of prosocial behaviors. A) There was no significant effect of AGE on "Eye Gaze" frequency. B) "Touch" behavior was not significantly affected by age. C) "Groom" increased with AGE ($\chi^2(5)=19.92$; p= $0.001.29 \times 10^{-3}$). Colored lines represent individual subjects; black line is the group average, with error bars ±SEM.

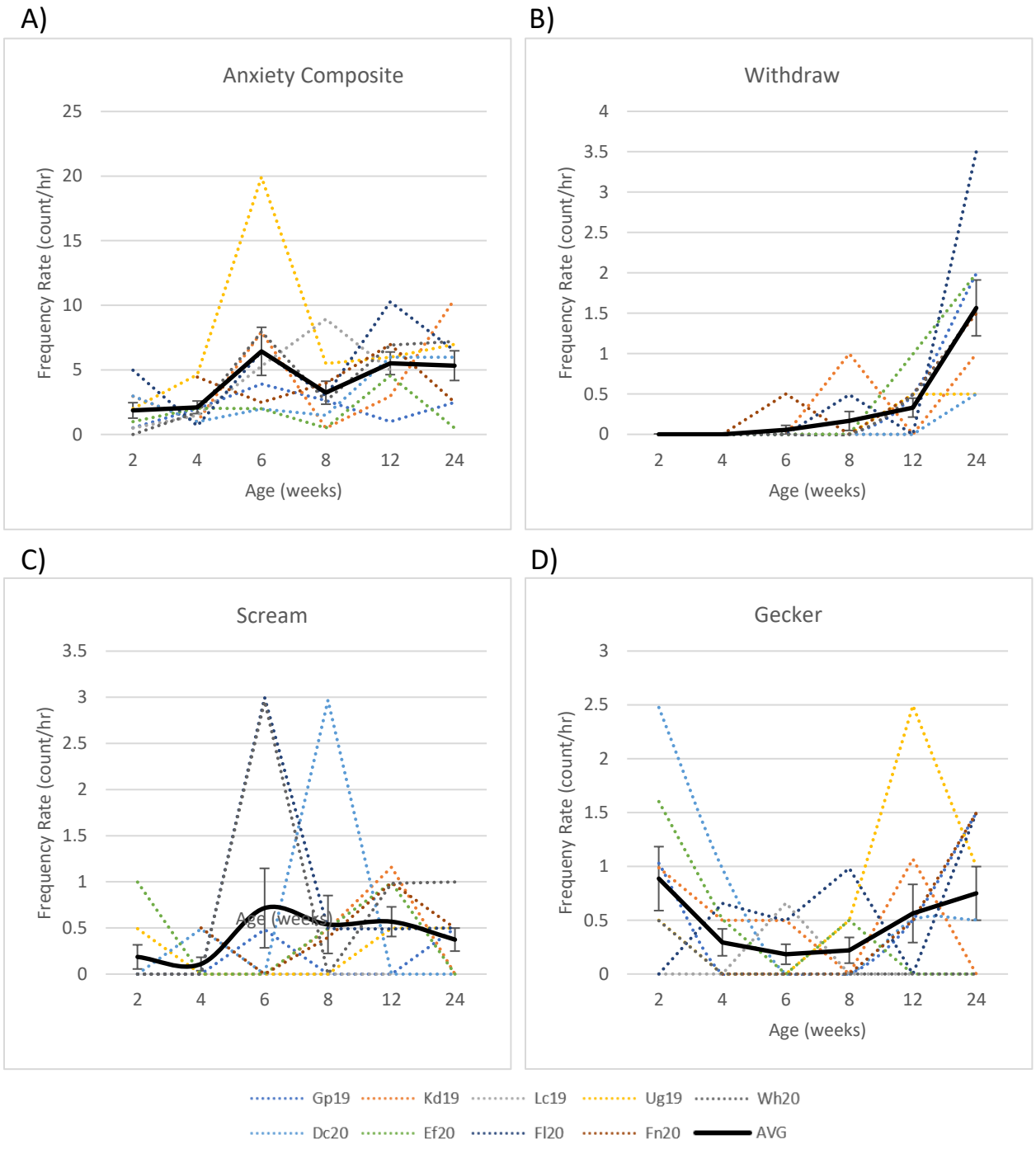



**Figure 16: Fear and distress behaviors over time.** Average rate (counts/hr) of fear and distress behaviors. A) There was a significant effect of AGE ($F(4,14.27)=8.60$; $p= 0.001$) on "Anxiety Composite" scores. B) "Withdraw" frequency changed with AGE ($\chi^2(5)=24.94$; $p=1.43 \times 10^{-4}$). C) "Scream" vocalizations were not significantly affected by AGE. D) "Gecker" vocalizations were not significantly affected by age.

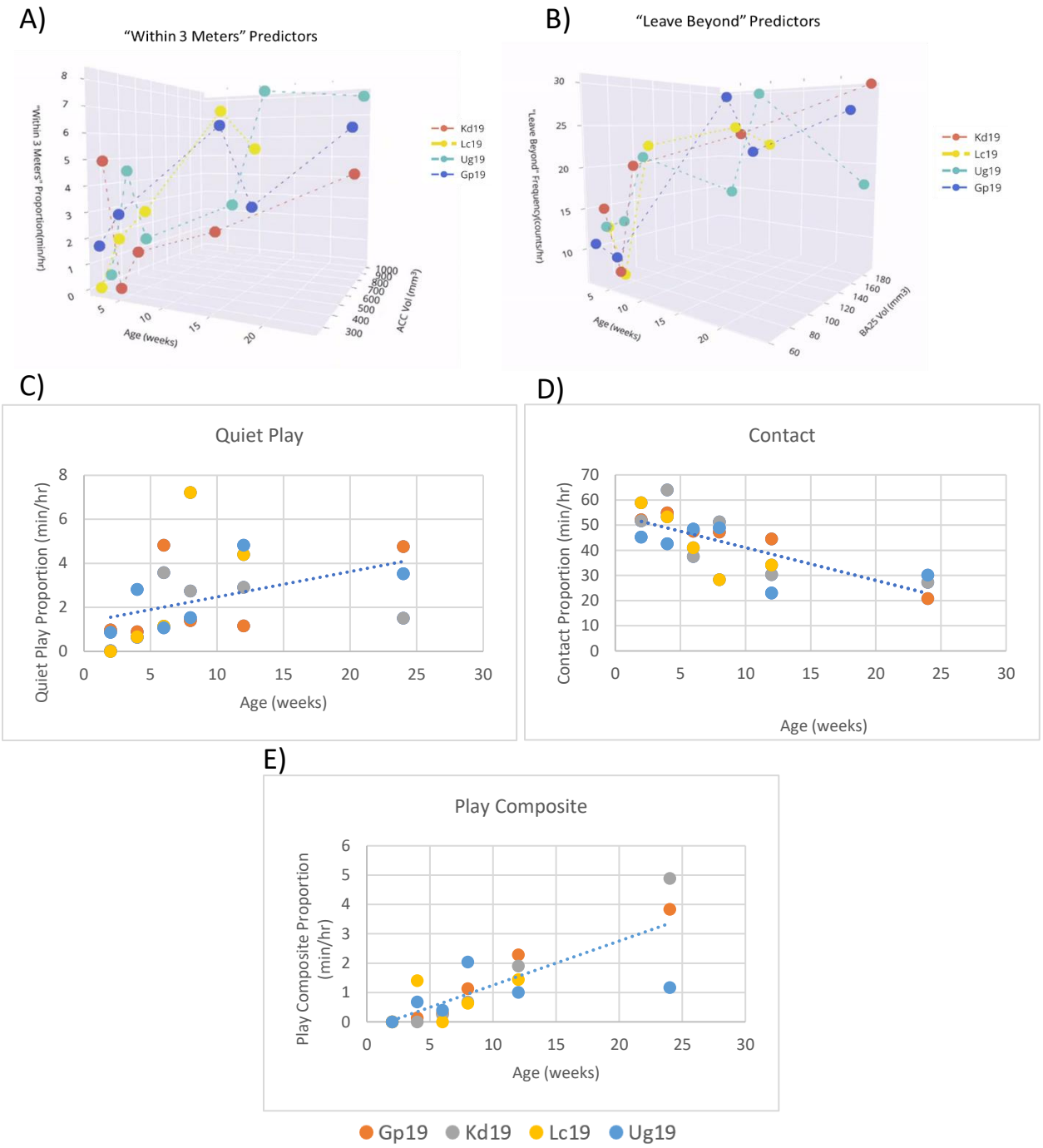



**Figure 17: Significant predictors of behavior.** A) ACC(BA24) volume significantly predicted "Within 3 Meters" behavior across age ($F(2, 18)=8.42$, $p=0.003$). B) BA25 significantly predicted "Leave Beyond" behavior across age ($F(2,18)=10.68$, $p=0.001$). C) AGE significantly predicted "Quiet Play" behavior ($F(1, 19)=5.08$, $p=0.04E$). D) Age was the most significant predictor of "Contact" duration ($F(1, 19)=25.97$, $p= 6.40 \times 10^{-5}$). E) Age significantly predicted "Play Composite" behavior ($F(1, 19)=17.22$, $p=0.001$). Colored dots represent individual subjects.

**Table 1: Summary of jmSRS Scores.** For each item on the jmSRS and the total summed score, the group average ±SEM is reported at 3 months and 6 months of age. Items bolded and marked with an asterisk indicate significant changes with age ($p<0.05$).

| jmSRS Item | 3 Month Average Score (±SEM) | 6 Month Average Score (±SEM) |
|---|---|---|
| 1. Self-Confident | 1.69(±0.19) | 1.90(±0.29) |
| 2. Prefers to Be Alone | 1.26(±0.10) | 1.40(±0.11) |
| 3. Strange/Bizarre Behavior | 1.15(±0.12) | 1.44(±0.20) |
| 4. Not Well Coordinated | 1.00(±0) | 1.00(±0) |
| 5. Responds Appropriately to Conspecific Vocalizations/Faces | 1.47(±0.20) | 1.15(±0.07) |
| 6. Avoids Eye Contact | 1.03(±0.03) | 1.00(±0.0) |
| **7. Plays Appropriately with Peers*** | **1.65(±0.15)** | **1.25(±0.19)** |
| 8. Avoids Social Interactions | 1.42(±0.21) | 1.10(±0.07) |
| 9. Is Socially Awkward | 1.31(±0.28) | 1.06(±0.06) |
| 10. Restricted/Narrow Interests | 1.08(±0.08) | 1.10(±0.07) |
| 11. Repetitive/Odd Behaviors | 1.00(±0) | 1.04(±0.04) |
| 12. Tense in Social Situations | 1.54(±0.32) | 1.15(±0.10) |
| 13. Stares or Gazes Off | 1.14(±0.06) | 1.10(±0.07) |
| 14. Species-Typical Reactions to Loss of Resources | 1.65(±0.11) | 1.42(±0.12) |
| **15. Upset in Busy Environments*** | **1.75(±0.28)** | **2.08(±0.22)** |
| 16. Overly Sensitive to Sensory Stimulation | 1.71(±0.30) | 1.81(±0.31) |
| 17. Overly Sensitive to Handling | 2.14(±0.39) | 2.04(±0.31) |

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