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Authors

Schumann, Cynthia M
Scott, Julia A
Lee, Aaron
et al.

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Amygdala growth from youth to adulthood in the macaque monkey

Cynthia M. Schumann[1,*], **Julia A. Scott**[2,*], **Aaron Lee**[3], **Melissa D. Bauman**[1,4], **David G. Amaral**[1,4]

[1]University of California, Davis School of Medicine; Department of Psychiatry and Behavioral Sciences; and the MIND Institute

[2]Santa Clara University; Department of Bioengineering

[3]University of California, Davis School of Medicine; Center for Virtual Care

[4]California National Primate Research Center; University of California, Davis

Abstract

Emerging evidence suggests that the human amygdala undergoes extensive growth through adolescence, coinciding with the acquisition of complex socioemotional learning. Our objective was to longitudinally map volumetric growth of the nonhuman primate amygdala in a controlled, naturalistic social environment from birth to adulthood. Magnetic resonance images were collected at 5 time-points in 24 male and female rhesus macaques from 6 months to adulthood at 5 years. We then compared amygdala growth to other brain regions, including newly collected isocortical gray and white matter volumes, and previously published data on the same cohort. We found that amygdala volume increases by nearly 50% from age 6 months to 5 years. This dramatic growth is in contrast to overall brain and hippocampal volume, which peak near 3 years, white matter, which slows from 3 to 5 years, and isocortical gray, which has a net decrease. Similar to isocortical gray and hippocampal volumes, amygdala volume is ~8% larger in males than females. Rate of growth does not differ by sex. Although the underlying neurobiological substrate for protracted amygdala growth into adulthood is unclear, we propose it may be due in part to the unique cellular development of immature neurons in paralaminar nucleus that mature in size and connectivity with age. Prolonged amygdala maturation raises the possibility that environmental and genetic perturbations that disrupt this trajectory may contribute to the emergence of psychiatric disorders, such as anxiety, depression, schizophrenia, and autism; all in which the amygdala is strongly implicated.

Graphical Abstract

Corresponding author: Cynthia Schumann, Ph.D., cschumann@ucdavis.edu, Phone: 916-703-0372, UC Davis MIND Institute 2805 50th Street, Sacramento, CA 95817.

*co-first authors

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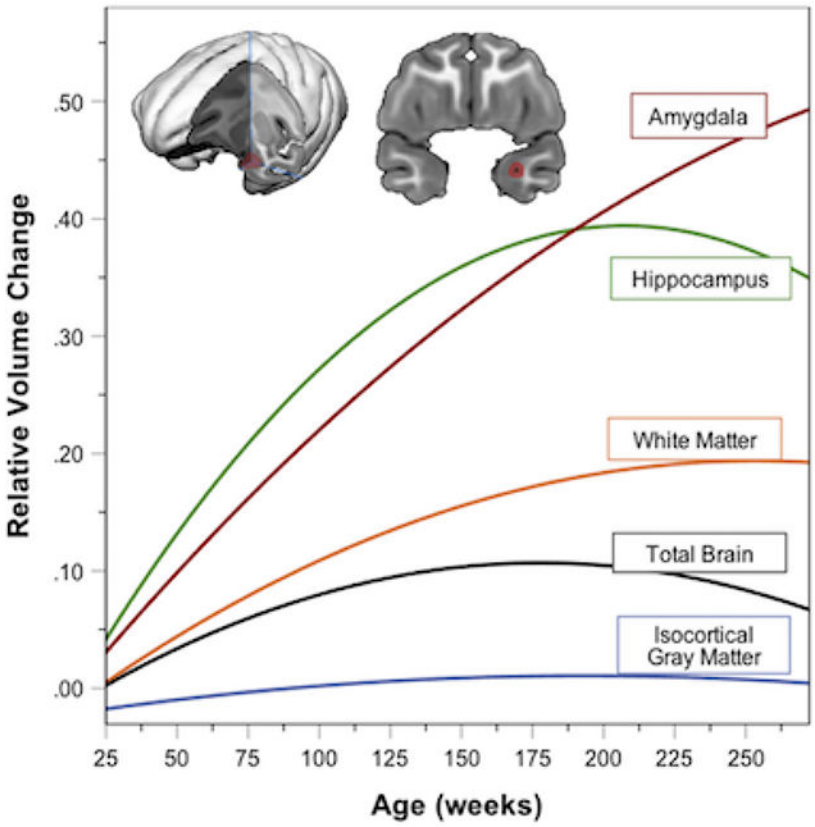

Amygdala, isocortical gray, and cerebral white matter volumes were measured longitudinally in 24 male and female rhesus macaques reared in a controlled, naturalistic social environment. Amygdala volume increases by nearly 50% from 6 months to five years. This dramatic growth is in contrast to overall brain and hippocampal volume, which peak near 3 years, white matter, which slows from 3 to 5 years, and isocortical gray, which has a net decrease. Prolonged amygdala maturation raises the possibility that environmental and genetic perturbations that disrupt this trajectory may contribute to the emergence of psychiatric disorders, such as anxiety, depression, schizophrenia, and autism; all in which the amygdala is strongly implicated.

Keywords

nonhuman primate; animal model; rhesus; magnetic resonance imaging; development; amygdaloid complex; neuroanatomy; MRI; volume; trajectory; autism; schizophrenia; anxiety
RRID:SCR_005988; RRID:SCR_004757

INTRODUCTION

The amygdala has been a central focus in the investigation of the neurobiology of primate social behavior and emotion for over 25 years (Brothers, Ring, & Kling, 1990; Rutishauser, Mamelak, & Adolphs, 2015). More accurately termed the amygdaloid complex, it is comprised of thirteen nuclei and cortical regions. The amygdala has widespread connections with cortical and subcortical brain regions that modulate social and emotional recognition

and response (Adhikari, 2014; Aggleton, Wright, Rosene, & Saunders, 2015; Del Casale et al., 2012; Fudge, deCampo, & Becoats, 2012; Schumann, 2016). Although the basic cellular architecture of the amygdala and pathways of amygdalocortical connectivity appear to be well established at the time of birth (Bauman & Amaral, 2005; Emery & Amaral, 2000), both cytoarchitectural and magnetic resonance imaging (MRI) studies demonstrate rapid postnatal enlargement of the nonhuman primate amygdala between birth and three months of age (Chareyron, Lavenex, Amaral, & Lavenex, 2012; Payne, Machado, Bliwise, & Bachevalier, 2010). Surprisingly, cross-sectional MRI studies indicate that the human amygdala continues to undergo substantial postnatal growth throughout childhood and well into adolescence, increasing by approximately 40% from 5 to 18 years of age in males (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; J. N. Giedd et al., 1996; Schumann et al., 2004; Uematsu et al., 2012). There appear to be sex differences in this remarkable growth trajectory, with female children showing somewhat earlier enlargement than males (Giedd et al., 1996; Giedd et al., 1997) that may be related to the age of pubertal maturity (Goddings et al., 2014).

Prolonged plasticity may promote beneficial experience-dependent refinement of amygdaloid structure and function. It may also lead to greater vulnerability to damage or alterations in the developmental trajectory, potentially contributing to the onset of psychiatric disorders. An extensive literature implicates the amygdala in virtually every psychiatric disorder from anxiety to schizophrenia to autism (Kalin, 2017; Schumann, Bauman, & Amaral, 2011; Varghese et al., 2017). Although the literature linking amygdala dysfunction and social impairment in psychiatric disease is vast, the underlying neurobiology of how and when this dysfunction arises is poorly understood. This is due, in part, to the relative paucity of information about the normal maturational trajectory of the human and nonhuman primate amygdala.

The goal of this study was to quantify the primate amygdala growth trajectory in a well-controlled, naturalistic social environment using the rhesus macaque (*Macaca mulatta*) as a model system to determine if the amygdala undergoes protracted development relative to other brain regions. Much like humans, rhesus macaques live in complex social groups and have evolved a sophisticated social communication system that includes a variety of facial expressions, body postures and vocalizations (Chang et al., 2013). Here we evaluate amygdala development in 24 male and female rhesus macaques, with MRI's collected longitudinally at 5 time points over a five-year period from 6 months to adulthood at 5 years of age. In addition, we compare amygdala growth relative to that of the developmental trajectory of previously published total brain and hippocampal volumes (Hunsaker, Scott, Bauman, Schumann, & Amaral, 2014; Scott et al., 2016) and newly collected data on isocortical gray matter volume and white matter volume on the same cohort. Importantly, the animals in this study were raised in a naturalistic social environment with numerous cage mates, providing opportunity to observe complex social interactions thought to influence neural functioning in human and nonhuman primates (Bickart, Wright, Dautoff, Dickerson, & Barrett, 2011; Sallet et al., 2011). These longitudinal data also provide an important baseline for primate models of psychiatric and neurodevelopmental disorders (Bauman & Schumann, 2018; Kalin, 2017).

MATERIALS AND METHODS

All experimental procedures were approved by the University of California, Davis, Institutional Animal Care and Use Committee. This study was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and developed through consultation with the veterinary staff at the California National Primate Research Center (CNPRC).

Subjects

Twenty-seven (14 males, 13 females, Table 1) infant rhesus monkeys (*Macaca mullata*) were selected from the outdoor breeding colony at the CNPRC. Infants were born and reared by mothers that resided in large, 2,000 m2 outdoor corrals. All seven of the corrals that housed study animals were chain-link and consisted of grass and gravel ground substrate and included a variety of hanging, climbing, and resting structures. The number of animals that lived in these corrals ranged from 70 to 155 individuals and all the kin relationships of all the primates were known. Primates were fed twice per day, in the morning and afternoon, with chow (Lab Diet 5047, PMI Nutrition International Inc., Brentwood, MO) and supplemented with fresh fruit and vegetables. Mothers were selected with attention to the following factors: (1) rank of matriline (high, n = 8; middle, n = 9; low, n = 10); (2) previous reproductive experience (multiparous, n = 24; primiparous, n = 3); (3) absence of previous medical problems such as diabetes or arthritis. Social rank of the mother was assessed monthly based on two, 30-minute observations by CNPRC behavioral specialists. Infant health was assessed at one and four weeks of age by a physical examination conducted by a veterinarian. Neurobehavioral tests of reflexes and sensorimotor abilities were also conducted. Infants were excluded from the study if there was: (1) loss in weight, (2) anomalies on MRI, such as edema or enlarged ventricles, or (3) other evidence of compromise in health status.

Animal transport

Animals underwent MRI scanning at postnatal weeks 1, 4, 8, 13, 26 (6 month), 39 (9 months), 52 (1 year), 156 (3 year), and 260 (5 year). Only scans from 6 months onward were used for the present study since stable, reliable contrast for amygdala boundaries emerged at this time point. For MRI scanning at 26 weeks of age, infants were temporarily removed with their mothers and housed together in a standard indoor housing cage (61 cm W by 66 cm D by 81 cm H). For MRI scans collected at 1, 4, 8, 13, and 26 weeks of age, rhesus macaque infants were relocated with their mothers and were housed together in a standard macaque indoor housing cage (61 cm in width by 66 cm in depth by 81 cm in height) 1 day before behavioral testing. On days when testing was to occur, mothers were lightly sedated with ketamine hydrochloride (7 to 8 mg/kg i.m.) and infants were temporarily removed from the cage for testing. Beginning at 39 weeks of age, each rhesus macaque subject was temporarily removed from its respective home enclosure without the mother the day before behavioral testing and was housed indoors as described above.

At the Imaging Research Center (IRC), infants were sedated with ketamine (1mg/kg IM) in preparation for placement of an indwelling intravenous (IV) catheter (22–24 gauge) and

intubation with an endotracheal tube (2.0–2.5 mm uncuffed, 3.0–3.5 mm cuffed). Infants were anesthetized with propofol (2 ml/kg/hr IV) for approximately 60 to 90 minutes and transported back to the CNPRC following the scan. The 6-month animals were first reunited with their mothers in holding cages and then returned together to their home enclosures; the older animals were returned directly to their home enclosures. All mothers immediately accepted their infants on each of the reunions. While the capture and anesthetic procedures used in this study undoubtedly induced some stress in the mothers and infants, these procedures are identical to those that are normally carried out for periodic health assessments of all animals at the CNPRC.

MRI acquisition

All subjects were imaged on a Siemen's 3T Trio MRI system using an 8-channel RF head array coil (Invivo, Inc., Gainesville Fl.). A 3D T1-weighted MP-RAGE sequence was collected in the sagittal plane [number of slices = 192; slice thickness = 0.7mm; number of excitations = 1; repetition time = 2200ms; echo time = 4.73ms; inversion time = 1100ms; flip angle = 7 degrees; field of view = 180 mm × 180 mm; matrix = 256 × 256; bandwidth = 140 hertz/pixel]. Subject 15 missed the 39-week time point due to scanner down time and data were lost for subject 7 at 52 weeks of age. Additional sequences were acquired at each time point but are not within the scope of this report. Procedures are described in further detail in our previous reports on this cohort (Hunsaker et al., 2014; Scott et al., 2016).

Volumetric measurements

Amygdala volume measures were obtained through manual tracing of the amygdala using Analyze 10 (Biomedical imaging resource, Rochester, MN; RRID:SCR_005988). Images were first converted to cubic voxel dimensions of 0.35 mm^3 using a cubic spline interpolation algorithm and reoriented so that the horizontal axis was parallel to a line from the rostral to the caudal pole of the hippocampus (Figure 1). Coronal sections were viewed perpendicular to the horizontal axis. On each coronal section running from caudal to rostral, the amygdala was manually outlined based on a detailed set of tracing guidelines modified from our previously published human protocol (Schumann et al., 2004). Briefly, the guidelines include the following: The rostral extent of the amygdala is defined in the sagittal plane, in which the tapering is more apparent and bound by white matter of the temporal lobe and the ventral claustrum. In rostral coronal sections, (Figure 1, panels 1 and 2), the lateral and ventral boundaries of the amygdala are formed by temporal lobe white matter. The medial surface is formed by white matter separating the amygdala from the entorhinal cortex. In midrostrocaudal sections (Figure 1, panel 3), the amygdala ventral boundary is formed by the temporal horn of the lateral ventricle. The lateral boundary is formed by white matter of the temporal lobe, which separates the amygdala from the ventral claustrum and amygdalostriatal transition area. In caudal sections (Figure 1, panels 4, 5 and 6), the amygdala is bound by the hippocampus or temporal horn of the lateral ventricle ventrally, the tail of the caudate nucleus laterally, and the substantia innominata and anterior commissure dorsolaterally. The amygdala boundary did not extend into the amygdalo-hippocampal transition zone located ventromedially or dorsally beyond the level of the optic tract.

Isocortical gray and white matter volumes were calculated for each image using an atlas-based tissue classification scheme (gray matter, white matter, and intra-and extra-cerebral CSF) (Figure 2). We also generated a regional atlas, which parcellated the brain into right and left cortical hemispheres, corpus callosum, subcortical structures, brainstem, and cerebellum. Total brain volume is defined as the sum of gray and white matter plus ventricular and extracerebral cerebral spinal fluid (CSF). Detailed image processing procedures and whole-brain anatomical parcellation may be obtained in Scott et al., 2016. Briefly, the ANTS-SyN symmetric normalization algorithm (Avants et al., 2011; RRID:SCR_004757) was used to obtain fully deformable parameters for spatially transforming age-specific templates. An initial parcellation and probability atlas was created by warping a validated adult rhesus macaque template (Knickmeyer et al., 2010; Styner, Smith, et al., 2007) to the minimal deformation template (MDT) of the brains at 5 years of age. The MDT for each age (3-year, 1-year, 9-month, and 26-month) was then registered to the 5-year template. The resulting deformation fields were used to propagate the gray/white segmentations and regional parcellation from the 5-year template onto each age-specific template (Scott et al., 2016). Lastly, regional tissue volumes were calculated from the segmented tissue masks intersected with the parcellation masks.

Hippocampal volumetric data was initially analyzed beginning at 1 week of age as previously reported in Hunsaker et al., (Hunsaker et al., 2014). Volumes were produced using semi-automated methodology in the SegAdapter function of ANTs based on user set landmarks (Hunsaker et al., 2014). Hippocampal volumetric growth data was reanalyzed in the current study specifically for comparison with amygdala growth from 6 months to 5 years of age.

Statistical Analyses

Growth trajectories were estimated using linear mixed models with linear and quadratic terms for age and random effect of subject (SPSS v.21) from 6 months to five years of age. Age-related changes in hemispheric volumes (amygdala, hippocampus, isocortical gray matter, cortical white matter) were first modelled to test for the effect of hemisphere on average volume and rate of change. Bilateral volumes were then modelled independently in male and female subgroups. Relative growth curves were estimated based on change in volume from six months for all regional volumes and total brain. Lastly, the effect of sex on average volume and the rate of change were modelled in all subjects while adjusting for total brain volume. It is important to note that hippocampal and total brain volumes for this data set were previously reported in Hunsaker et al. (2014) and Scott et al. (Scott et al., 2016) respectively from an earlier age than in the current study, and therefore the regression analyses were repeated to best fit the specific time period measured for the amygdala. Although the findings did not change, the shape and parameter estimates reported in the current paper beginning at 6 months of age differ from the previous reports. In addition, Hunsaker et al (2014) reported right and left hippocampal data separately, whereas here we report the sum of right and left hippocampus in our model.

RESULTS

Hemispheric asymmetry

Prior to fitting growth trajectory models to the amygdala from 6 months to 5 years, we tested for hemispheric differences in volume. Based on a linear mixed model, we found no significant difference in the absolute volume or rate of growth of the amygdala between hemispheres. Therefore, all further analyses were conducted with combined right and left amygdala volumes (total amygdala). Though left greater than right hemispheric asymmetry was found for isocortical gray matter ($p<0.001$), the hemispheres did not significantly differ in age-related change in volume. To be consistent, we report bilateral volumes of all structures.

Age-related changes in volume

Mean absolute volumes are presented in Table 2. Age-related changes in regional volume by a linear mixed model with linear and quadratic terms are presented in Table 3 and Figure 3. Average percent changes in volume relative to 26 weeks are listed in Table 4. Since the structures modeled (amygdala, gray matter, white matter, total brain, and hippocampus) vary greatly in absolute volume, we calculated and compared their relative growth rates from 6 months to 5 years (Figure 4). Total amygdala volume increases by approximately 48% with both linear and quadratic models fitting the data ($p<0.001$). Hippocampal growth, in contrast, rapidly increases from 6 months to 3 years by approximately 36% but then plateaus with little growth after that. As reported in Scott et al., total brain volume increases from six months to 3 years by 11% (+/−4%), then slightly decreases by 5 years, for a net gain of 8% (+/−6%). Gray matter slightly declines with age, such that a 2% (+/−3%) loss was observed from 6 months to 3 years followed by an additional average loss of 4% (+/−3%) by 5 years. Though the change in volume between consecutive age intervals was not significant, the change from 6 months to 5 years shows a significant age-related decline of 7% (+/−3%) ($p=0.001$). In contrast, white matter expands, gaining on average 20% (+/−4%) over its volume at 6 months during the same period. Further, the rate of white matter volume change declines with age, particularly after 3 years ($p<0.01$). Compared to all other regions, the amygdala displays the greatest relative growth from 6 months to 5 years, and did not have any detectable declines or plateaus.

Sexual dimorphisms

When adjusted for the global difference in total brain volume in males and females (7.2%, $p=0.001$), male amygdala volume is significantly larger than that of females (8.14%, $p=0.025$) in a linear mixed model testing for the main effect of sex. When the interaction between sex and age was included however, the effect of sex diminished ($p=0.093$) and the interaction was not significant. The rate of amygdala growth does not differ by sex, as it steadily increases by 48% in males and 47% in females from 6 months to 5 years of age. Whereas gray matter is larger in males than females on average (5.6%, $p=0.005$), the rate of change in both gray and white matter does not differ by sex.

DISCUSSION

We characterized normative amygdala development in a series of longitudinal MRI studies through juvenile, pubertal, and early adult phases of nonhuman primate life in 24 naturally-reared rhesus macaque monkeys. Here we present novel findings on the growth trajectory of the amygdala, isocortical gray matter, and white matter and compare these findings to our previously published data on total brain (Scott et al., 2016) and hippocampal (Hunsaker et al., 2014) volumes. The primary finding is that primate amygdala volume increases linearly by nearly 50% from 6 months to 5 years of age. This dramatic growth is in contrast to overall brain volume, which peaks near 3 years of age, white matter, which demonstrates a slowing of growth from 3 to 5 years of age and isocortical gray matter, which has a net decrease over this time period (Figure 4). The hippocampus grows at a similar rate to the amygdala up to 3 years of age, but then reaches a plateau while the amygdala continues to increase in volume. In the remainder of the discussion, we will first compare the amygdala volumetric growth results presented here with other MRI studies carried out in the macaque monkey. We will also discuss how these longitudinal findings compare to that of human MRI studies. Finally, we will discuss what underlying cellular factors may contribute to the protracted growth, and speculate on the functional implications of protracted amygdala development in the emergence of psychiatric disorders.

Nonhuman primate amygdala MRI studies.

To date, the only other semi-longitudinal MRI volumetric study to evaluate early development of the rhesus macaque amygdala was carried out by Payne et al. (Payne et al., 2010), in which hippocampal, amygdala, and total cerebral volumetric growth were evaluated in nursery-reared rhesus monkeys between 1 week and 2 years of age. Amygdala volume was calculated using 66 MRIs across ten developmental time points, using a combination of longitudinal and cross-sectional subjects. In this nursery-reared cohort, “amygdala maturation appears to stabilize earlier (around 8 months of age) than the total cerebrum or hippocampal formation (around 11.5 and 11 months, respectively)”, which is in contrast to the prolonged amygdala growth trajectories reported here for the 24 rhesus monkeys raised in a naturalistic environment. However, similar to our findings, protracted linear amygdala growth between 10–64 months of age has also been reported in a cross-sectional MRI study of 37 maternally-reared rhesus monkeys housed in small social groups (Knickmeyer et al., 2010). A number of factors likely contribute to the contradictory findings, including the age range evaluated (up to 2 years in Payne et al., and 5 years in both Knickmeyer et al. and in the current study) and the number of animals (relatively small sample of combined longitudinal and cross-sectional data for Payne et al., a large cross-sectional sample for Knickmeyer et al., and a large, longitudinal sample for the present study) which likely impacts the prospect of detecting protracted amygdala growth. A second factor may have been the higher resolution and contrast of current MRI scans (3.0T for Knickmeyer et al. and the present study, rather than 1.5T for Payne et al.) to allow for a more accurate amygdala parcellation-particularly given the lack of white matter contrast at younger ages. A third factor is more speculative. The present experiment was conducted with rhesus macaques living in large troops in outdoor corrals that had a complex, species-typical social structure and were reared by their mothers. In contrast, the primates studied by

Payne et al. (2010) were nursery-reared by humans with more limited access to species-typical social stimuli. Although the animals in the Knickmeyer study were maternally reared, they were artificially weaned at a relatively young age and then housed in small social groups. It is plausible that differences in the environment shape social processing demands (Lambert et al., 2016; Lederbogen et al., 2011; Urakawa et al., 2013) and may have affected the trajectory of amygdala growth. This hypothesis is supported by a body of literature describing the impact of maternal deprivation on amygdala development and connectivity in human and nonhuman primates (de Campo et al., 2017; Gee et al., 2013; Olsavsky et al., 2013; Sabatini et al., 2007).

Human amygdala MRI studies.

How closely do the findings in the monkey parallel human amygdala protracted volumetric growth? (Giedd et al., 1996) were among the first to use MRI to study brain development in children (4–8 years of age), reporting that the left amygdala in males increases with age, in contrast to a stable temporal lobe volume. Our group later replicated the finding in males of increasing amygdala volume with age from 8–18 years in a small cross-sectional study (Schumann et al., 2004). Several larger studies of amygdala development in typically-developing boys and girls have since confirmed these findings of protracted growth in the human amygdala (Goddings et al., 2014; Herting et al., 2014; Hu, Pruessner, Coupe, & Collins, 2013; Wierenga et al., 2014). Physical sexual maturity during the pubescent period, rather than age alone, may be an important factor in predicting amygdala volumetric growth (Bramen et al., 2011; Herting & Sowell, 2017). An analysis from the Brain Development Cooperative Group identified a sexual dimorphism in the growth trajectory of the amygdala from 7–20 years of age, such that males continue to show an increase in amygdala volume in late puberty, whereas females plateau earlier (Goddings et al., 2014). The effects of puberty are not limited to the amygdala, however, as pubertal development is significantly related to structural volume in other subcortical regions and the hippocampus. A recent, rigorous study of multiple independent datasets from the same group report that the amygdala continues to grow through early adulthood, with no significant differences in trajectories of age development between sexes (Herting et al., 2018). Similarly, we found that male monkeys have an 8% larger amygdala volume than female monkeys, yet no difference in trajectory of growth. In contrast to the protracted volumetric growth trajectory of the human amygdala, numerous human MRI studies have found a stable or decreasing total brain and isocortical gray matter volume as well as an increasing white matter volume through adolescence (Giedd, Raznahan, Mills, & Lenroot, 2012; Mills et al., 2016), similar to our findings in the nonhuman primate reported here. Although imaging data were collected at 3 years of age during the transition from pre-pubertal 1-year old juveniles though sexually mature 5 year old adults, the period of puberty varies in individual rhesus macaques (Stephens & Wallen, 2013; Zehr, Van Meter, & Wallen, 2005) and was not formally evaluated though hormonal assays. The onset of puberty in outdoor-housed female rhesus macaques typically occurs around 2.5 years of age, as indexed by menarche, through the first ovulation may take place in the breeding season at 2.5 years of age or the following breeding season at 3.5 years of age (Wilson & Gordon, 1989; Wilson, Gordon, Blank, & Collins, 1984; Wilson, Gordon, & Collins, 1986). The onset of puberty in outdoor-housed rhesus macaque males occurs around 3.5 years of age, as indexed by increased testosterone levels and testicular volumes (Herman,

Zehr, & Wallen, 2006). Thus, the 3-year imaging time point may have captured the onset of puberty for a subset of females in the study, but unlikely captured the onset of puberty for male subjects*, which is a limitation of the study and an important factor for future consideration*.

Cellular changes underlying amygdala volumetric growth.

Protracted postnatal volumetric growth of the amygdala observed in MRI may be due to a combination of cellular factors including expansion of neuropil, maturation of white matter tracts, increases in oligodendrocyte numbers, and continuous neuronal maturation (Avino et al., 2018; Chareyron et al., 2012; deCampo & Fudge, 2012; Fudge et al., 2012). In a recent stereological study of the postmortem human amygdala, we found that the number of neurons in the amygdala in humans increases from 2–50 years of age (Avino et al., 2018). Specifically, the number of neurons in the human basal nucleus increases by 30% from youth to adulthood, an identical finding also reported in rhesus macaques (Chareyron et al., 2012). We speculate that this increase may be due to a pool of immature neurons in the paralaminar nucleus located in the ventral portion of the amygdala. Immature neurons from the paralaminar nucleus may migrate into the basal nucleus to become mature neurons (deCampo & Fudge, 2012; Fudge, 2004). In addition, we have reported that dendritic arborization of human amygdala neurons continues well into adulthood (Weir, Bauman, Jacobs, & Schumann, 2018), further expanding amygdala volume.

Functional Implications.

For humans, and many species of nonhuman primates, living in social groups is an adaptive advantage (Silk, 2007) that likely requires a sophisticated “social brain” network (Dunbar, 2009). The primate amygdala plays a key role in processing social information (Adolphs, 2009), thus it is not surprising that social interaction with peers and social network size are related to amygdala volume (Bickart et al., 2011; Lewis & Barton, 2006). Our present finding of protracted amygdala growth in rhesus monkeys raised in a complex social environment suggests that structures such as the amygdala that modulate socioemotional behavior may continue to grow well into adulthood with the development of more complex social behavior. Moreover, the trajectory of species-typical amygdala development provides a framework for other nonhuman primate models examining the role of the amygdala in anxious temperament (Kalin et al., 2016), early life adversity (Coplan et al., 2014; Howell et al., 2014) and social processing (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007; Hoffman, Gothard, Schmid, & Logothetis, 2007; Mosher, Zimmerman, & Gothard, 2014; Zhang, Noble, Winslow, Pine, & Nelson, 2012). These studies in nonhuman primate models are critical, given that the amygdala, perhaps more than any other brain region, has been implicated in many human neurodevelopmental and psychiatric disorders (Schumann et al., 2011). For example, in autism spectrum disorder, alterations in amygdala growth are found throughout development (Nordahl et al., 2012; Nordahl & Schumann, 2019; Schumann, Barnes, Lord, & Courchesne, 2009) (Nordahl et al., 2012; Nordahl & Schumann, 2019; Schumann et al., 2009). Whereas the amygdala appears to continue to grow in both size and neuron number in typically-developing individuals throughout adolescence, the amygdala in people with autism slows to where a difference in volume may not be detected in adults, perhaps due to a lack of increase, or even loss, of neurons (Avino et al., 2018). Similar to

ASD, adults with schizophrenia also show a decreased number of neurons in the amygdala (Kreczmanski et al., 2007), although medications may have an impact on amygdala structure (Berretta, Pantazopoulos, & Lange, 2007). An extensive literature indicates that early exposure to adversity, excessive stress, or maltreatment alters the structural development of the amygdala and corresponds to aberrant amygdala-mediated socioemotional behaviors in adolescence and adulthood (Bremner, 2005; Dannlowski et al., 2013; Fareri & Tottenham, 2016; Hanson et al., 2015; Howell et al., 2014; Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016; Merz, Tottenham, & Noble, 2018).

Conclusion.

For the past 15 years, we and others have speculated that the primate amygdala undergoes a unique protracted growth trajectory. This study now provides concrete evidence of this phenomenon by directly comparing longitudinal growth rates of amygdala volume to other brain regions in rhesus macaques reared in a naturalistic social environment from youth to early adulthood. This study provides an important point of reference for nonhuman primate models of neurodevelopmental and psychiatric disorders. Although the underlying neurobiology has yet to be clearly identified, recent studies of human and nonhuman primates suggests extensive cellular plasticity. This prolonged period of amygdala plasticity is likely designed to benefit from environmental experience. However, it may also render the amygdala vulnerable to alterations in the developmental trajectory. A better understanding of the characteristics of this unique developmental trajectory may provide important insights into many of the psychiatric disorders in which the amygdala is implicated.

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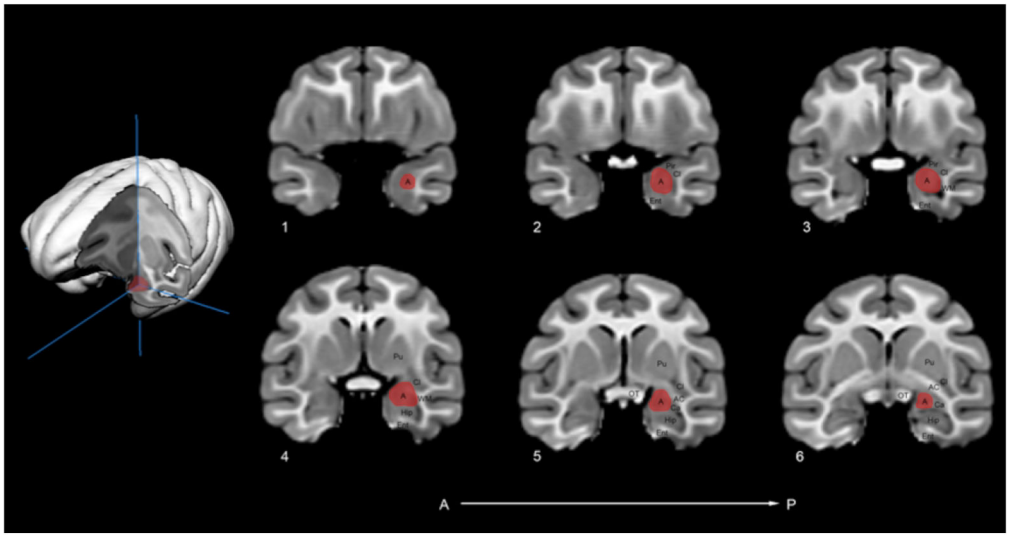

Figure 1.

Anatomical segmentation of the macaque monkey amygdala on MRI. Left: 3D rendering of 5-year brain image with fronto-lateral cut-away that displays the amygdala in red. Right: Coronal section 1 to 6 show rostral to caudal progression of the amygdala. A: amygdala, AC: anterior commissure, Ca: caudate nucleus, Cl: claustrum, Ent: entorhinal cortex, Hip: hippocampus, Pir: piriform cortex, Pu: putamen, OT: optic tract, WM: white matter

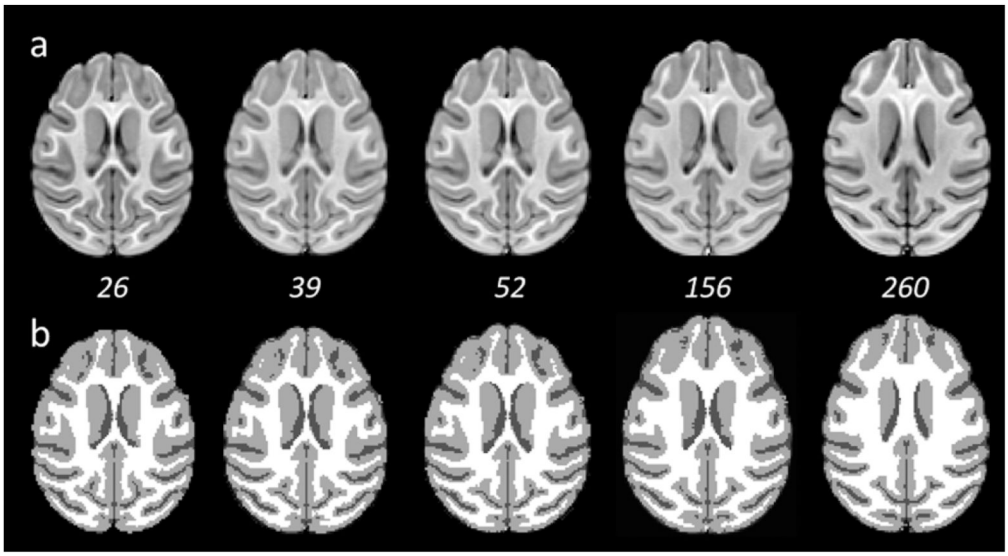

Figure 2.

Axial slice through age-specific template images (a) and tissue segmentations (b) at the level of the corpus callosum for 26, 39, 52, 156, and 260 weeks of age. Voxels were labeled as white matter (white), gray matter (light grey), or CSF (dark gray). Deep gray structures and non-cerebral regions, including amygdala and hippocampus, were subtracted from the gray matter segmentations prior to calculating volumes.

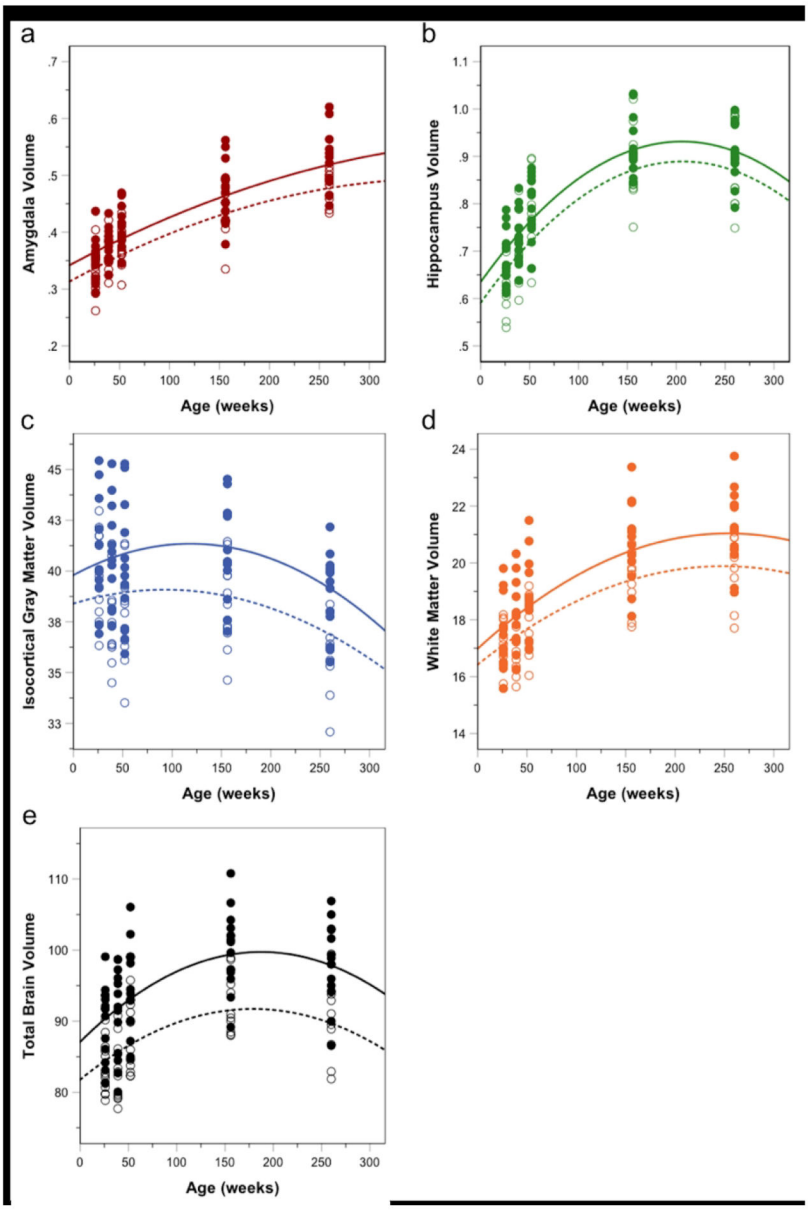

Figure 3.

Male (closed circle, solid line) and female (open circle, dashed line) growth trajectories for absolute bilateral volumes (cm^3) of (a) amygdala, (b) hippocampus, (c) isocortical gray matter, (d) cerebral white matter, and (e) total brain volume (gray plus white matter and CSF). Separate longitudinal models were calculated for each sex.

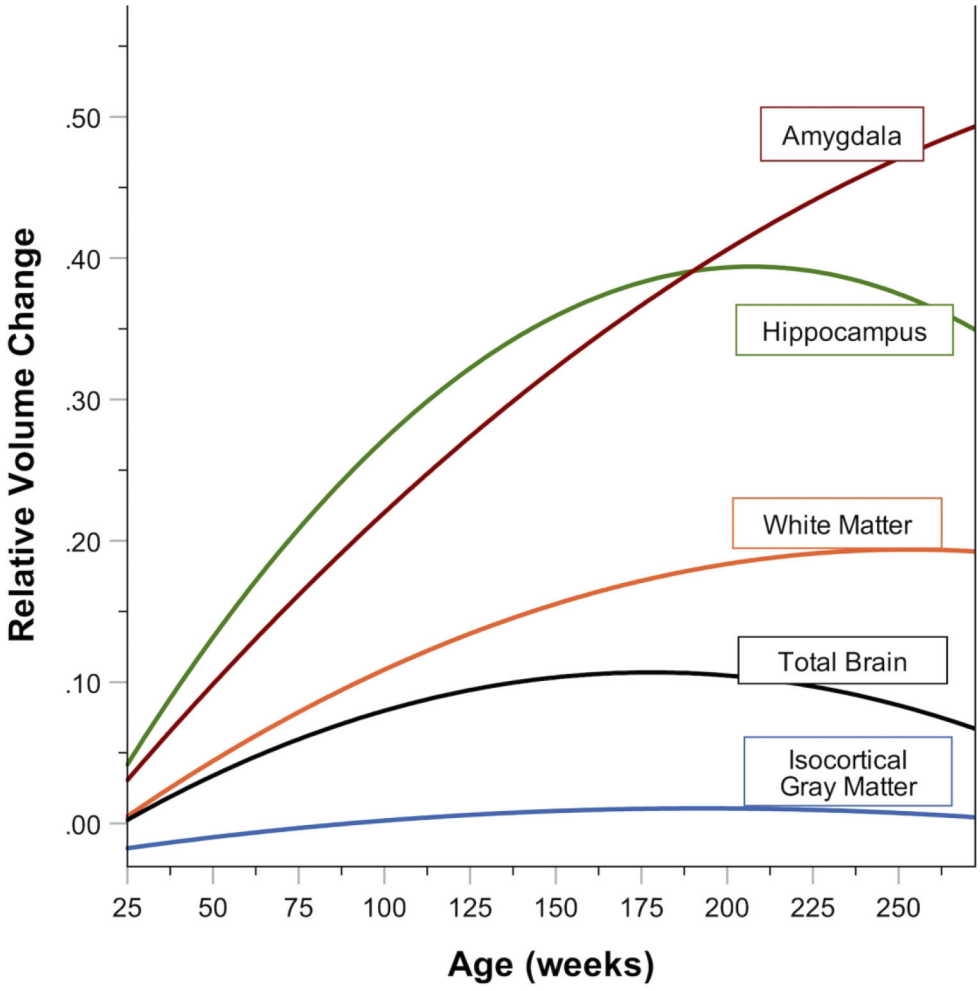

Figure 4.

Relative growth trajectories for amygdala (red), hippocampus (green), isocortical gray matter (blue), cortical white matter (orange), and total brain volume (dashed black). Vertical dashed line marks 26 weeks as the earliest data point and the reference point for relative change. The amygdala continues to have a relative gain through 5 years (260 weeks) of age. In contrast, hippocampal and white matter volumes plateau approaching 5 years. Gray matter shows a markedly different trajectory with net decline between 6 months and 5 years.

Table 1.

Cohort characteristics. Twenty-four (13 males, 11 females) rhesus monkeys (Macaca mullata) participated in the longitudinal neuroimaging studies. The infants were reared by their mothers and raised in complex social groups in outdoor, half-acre enclosures that house 75 to 120 animals.

Sex	Social Rank	Enclosure	Matriline
Female	High	1	3
Female	Mid	2	9
Female	Low	3	20
Female	Mid	3	7
Female	Low	4	14
Female	Mid	5	4
Female	Mid	5	13
Female	High	7	15
Female	Low	7	10
Female	Low	7	10
Female	Mid	7	5
Male	High	1	3
Male	High	1	3
Male	High	2	17
Male	Low	2	21
Male	Mid	2	9
Male	Mid	2	9
Male	Mid	2	9
Male	Low	4	22
Male	High	5	19
Male	Low	5	1
Male	Low	5	16
Male	High	6	6
Male	High	7	18

Table 2.

Absolute Mean Volumes and Standard Deviations (cm^3) for ROIs.

	26 weeks	39 weeks	52 weeks	156 weeks	260 weeks
Female					
Amygdala	0.33 (0.04)	0.35 (0.03)	0.37 (0.03)	0.44 −0.05	0.48 −0.03
Hippocampus	0.62 (0.05)	0.70 (0.07)	0.77 (0.08)	0.88 −0.08	0.89 −0.09
Isocortical Gray Matter	39.57 (2.25)	37.56 (2.22)	37.99 (2.37)	38.34 −2.14	36.35 −2.22
Cortical White Matter	17.03 (0.93)	16.81 (0.79)	17.89 (1.01)	19.52 −0.98	20.01 −1.16
Total Brain	84.14 (4.17)	84.04 (6.17)	87.82 (4.73)	92.73 −4.23	90.86 −5.63
Male					
Amygdala	0.35 (0.03)	0.38 (0.03)	0.40 (0.04)	0.47 −0.05	0.52 −0.05
Hippocampus	0.68 0.06)	0.73 (0.06)	0.80 (0.06)	0.92 −0.06	0.91 −0.06
Isocortical Gray Matter	41.04 (2.58)	40.63 (2.56)	40.07 (3.10)	40.76 −2.56	38.60 −2.11
Cortical White Matter	17.52 (1.22)	18.04 (1.29)	18.80 (1.38)	20.64 −1.43	21.29 −1.38
Total Brain	89.42 (5.51)	90.33 (5.82)	94.64 (6.40)	100.27 −5.50	98.25 −5.88

Table 3.

Bilateral Growth Models

	Age	Age^2	Intercept
Female			
Amygdala	0.97(0.20)***	−0.0013(0.0006)*	313.25(11.16)***
Hippocampus	2.89(0.48)***	−0.007(0.002)***	591.02(27.81)***
Isocortical Gray Matter	14.66(8.37)	−0.079(0.026)**	38,399.13(757.59)***
Cortical White Matter	27.85(3.32)***	−0.056(0.01)***	16,424.67(327.68)***
Total Brain	111.21(18.48)***	−0.31(0.058)***	81,790.38(1,506.13)***
Male			
Amygdala	0.94(0.17)***	−0.001(0.0005)	342.67(12.59)***
Hippocampus	2.88(0.32)***	−0.007(0.001)***	634.53(18.83)***
Isocortical Gray Matter	26.06(6.41)***	−0.11(0.02)***	39.817(719.35)***
Cortical White Matter	31.97(2.58)***	−0.063(0.008)***	16,983(377.39)***
Total Brain	134.94(17.86)***	−0.36(0.056)***	87,103.46(1,675.10)***

Footnotes:

Model equation: $Volume=a*(age)+b*(age)^2+Intercept$. Age is measured in weeks. All units are in mm^3. Parameter Estimates (Standard Error) are significant at

* $p<0.05$,

** $p<0.01$, or

*** $p<0.001$.

Table 4.

Relative to 26 Weeks Mean Change in Volumes and Standard Deviations for ROIs.

	39 weeks	52 weeks	156 weeks	260 weeks
Female				
Amygdala	8% (11%)	15% (10%)	36% (14%)	50% (14%)
Hippocampus	11% (9%)	24% (13%)	42% (13%)	43% (18%)
Isocortical Gray Matter	−4% (3%)	−4% (2%)	−3% (2%)	−8% (3%)
Cortical White Matter	−1% (2%)	5% (2%)	15% (2%)	17% (3%)
Total brain	0% (3%)	4% (2%)	9% (4%)	7% (4%)
Male				
Amygdala	7% (8%)	15% (6%)	33% (9%)	49% (11%)
Hippocampus	7% (5%)	17% (11%)	35% (16%)	34% (16%)
Isocortical Gray Matter	−1% (2%)	−0.02 (4%)	−1% (3%)	−6% (3%)
Cortical White Matter	3% (2%)	7% (2%)	18% (3%)	22% (4%)
Total brain	1% (2%)	6% (3%)	12% (4%)	9% (7%)