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Maturation of the Hippocampal Formation and Amygdala in *Macaca mulatta*: A Volumetric Magnetic Resonance Imaging Study

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Abstract

Malformations of the hippocampal formation and amygdala have been implicated in several neurodevelopmental disorders; yet relatively little is known about their normal structural development. The purpose of this study was to characterize the early developmental trajectories of the hippocampus and amygdala in the rhesus macaques (*Macaca mulatta*) using noninvasive MRI techniques. T1-weighted structural scans of 22 infant and juvenile monkeys (11 male, 11 female) were obtained between 1 week and approximately 2 yrs of age. Ten animals (five males, five females) were scanned multiple times and 12 monkeys (six males, six females) were scanned once between 1 and 4 weeks of age. Both structures exhibited significant age-related changes throughout the first 2 yrs of life that were not explained by overall brain development. The hippocampal formation increased 117.05% in males and 110.86% in females. No sex differences were evident, but the left hemisphere was significantly larger than the right. The amygdala increased 86.49% in males and 72.94% in females with males exhibiting a larger right than left amygdala. For both structures, the most substantial volumetric increases were seen within the first month, but the hippocampal formation appeared to develop more slowly than the amygdala with the rate of hippocampal maturation stabilizing around 11 months and that of amygdala maturation stabilizing around 8 months. Differences in volumetric developmental trajectories of the hippocampal formation and amygdala largely mirror differences in the timing of the functional development of these structures. The current results emphasize the importance of including early postnatal ages when assessing developmental trajectories of neuroanatomical structures and reinforces the utility of nonhuman primates in the assessment of normal developmental patterns.

Keywords

emotion; medial temporal lobe; memory; nonhuman primate; structural MRI

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Additional Supporting Information may be found in the online version of this article.

Introduction

The hippocampal formation and amygdala are neuroanatomical structures that specifically contribute to memory and emotional regulation throughout development in both human and nonhuman primates (Bachevalier and Beauregard, 1993; Rudy et al., 1993; Overman et al., 1996; Lewis, 1997; Málková et al., 2000; Overman and Bachevalier, 2001; Bachevalier and Vargha-Khadem, 2005; Alvarado and Bachevalier, 2000, 2008; Payne and Bachevalier, 2009). Malformation or dysfunction of these structures is often associated with severe and permanent cognitive and socioemotional impairments related to several neurodevelopmental disorders such as autism, schizophrenia, Down and Williams syndromes, and mental retardation (Bauman and Kemper, 1985; Uecker et al., 1993; Dierssen et al., 1996; Raymond et al., 1996; Leverenz and Raskind, 1998; Harrison, 1999; Saitoh et al., 2001; Lipska and Weinberger, 2002; Machado and Bachevalier, 2003). Mapping the emergence of complex behavioral repertoires onto the developmental trajectories of these structures could begin to identify critical periods when these structures are particularly susceptible to perturbations and, in turn, provide valuable insight into the neural substrates of human neuropathology (Machado and Bachevalier, 2003).

Noninvasive neuroimaging techniques provide an excellent tool for studying the development of brain structures in primates. Volumetric changes and white/gray matter differentiation are observable with imaging techniques and are thought to reflect postnatal processes of competitive elimination, myelination and dendritic arborization (see for review Lenroot and Giedd, 2006). Although current imaging techniques do not possess the resolution of morphological studies, they offer the opportunity to study large sample sizes across an extended developmental period. In this way, noninvasive imaging can identify critical periods of maturation as well as sexual and individual differences that are not amenable with morphological or connectional techniques. Further, comparing volumetric trajectories to functional trajectories for a given structure may help identify potential age ranges that could subsequently be investigated using targeted and more precise neurohistochemical, lesion or transient inactivation techniques.

Several developmental neuroimaging studies have been recently conducted in humans (see for review Lenroot and Giedd, 2006) and are providing important insights into the maturation of several structures within the human brain. Volumetric changes in both the hippocampal formation and amygdala have been previously reported in cross-sectional human neuroimaging studies (Caviness et al., 1999; Casey et al., 2000; Saitoh et al., 2001; Giedd et al., 2006; Lenroot and Giedd, 2006; Thompson et al., 2009). When accounting for total cerebral volumes, females demonstrated a disproportionately larger hippocampus than males in a group of 7- to 11-yr-old subjects (Filipek et al., 1994; Caviness et al., 1996). In contrast, Giedd et al. (1996, 1997) reported that, between 4 and 18 yrs of age, males had larger hippocampi than females, but these differences disappeared when total cerebral volumes were taken into account. These investigators further demonstrated that females, but not males, exhibited significant age related changes in hippocampal volume (right hemisphere only). The lack of volumetric change in the male hippocampus was further supported by Schumann et al. (2004), and the hemispheric differences are supported by repeated observations that the right hippocampus is larger than the left in adults (Weis et al., 1992; Jack et al., 2000), children (Giedd et al., 1996; Pfluger et al., 1999; Utsunomiya et al., 1999), and neonates (Thompson et al., 2009). One investigation reported a 13% hippocampal volume increases between 1 and 2 yrs of age (collapsed across sexes) that disappeared when measurements were corrected for gross maturational changes of the brain (Knickmeyer et al., 2008).

The existence of sexual dimorphism in amygdala volume has also been investigated (Filipek et al., 1994; Caviness et al., 1996; Giedd et al., 1996, 1997). In contrast to the hippocampus, early investigations indicated that females, as compared to males, had a proportionately smaller amygdala (Filipek et al., 1994; Caviness et al., 1996); however, other investigations have not supported this finding (Giedd et al., 1996, 1997). Interestingly, Giedd et al. (1996, 1997) showed that only males exhibited significant age-related changes in amygdala volume (left hemisphere only) between 4 and 18 yrs of age. Age-related differences in male amygdala volume were also observed in a group of normally developing participants between 7.5 and 18.5 yrs old (Schumann et al., 2004).

Such inconsistency has prompted investigators to evaluate developmental trajectories or patterns by scanning the same individuals longitudinally (Giedd et al., 2006; Lenroot et al., 2007). Given that morphological differences between males and females, such as androgen receptor concentrations, may result in sexually dimorphic maturational time-courses, assessing group differences at a given time-point may not fully capture putative dimorphisms. Hence, the use of developmental trajectories to ascertain the existence of a sexual dimorphism for a given structure or neural region becomes more pertinent.

To date, only the total cerebral volume has been assessed in this manner (Giedd et al., 2006; Lenroot et al., 2007). No age-related changes in total cerebral volume were found in either sex between the ages of 4 and 22 yrs, although male brains were approximately 9% larger than female brains. However, total cerebral volume peaked earlier in females than males (11.5 yrs vs. 14.5 yrs respectively; Geidd et al., 2006). Using younger subjects, significant increases in total cerebral volume have been shown in the first and second years of life (increases of 101 and 15%, respectively; Knickmeyer et al., 2008). Thus, it is crucial to consider these youngest ages when characterizing developmental trajectories.

The importance of including the earliest ages is further supported by neuroimaging investigations in nonhuman primates. Franklin et al. (2000) reported a gender difference in rhesus monkey total brain volume between 1.5 and 7.2 yrs old (roughly corresponding to 6- to 30-yr-old in humans). Similar to humans, total cerebral volume was approximately 20% larger in male monkeys relative to females, but no age-related changes were observed during this age range. However, a recent longitudinal study revealed a significant increase in total cerebral volume between 1 week and 4 yrs of age (Málková et al., 2006). Given the neuroanatomical and behavioral homologies between humans and some nonhuman primate species, the rhesus monkey provides an excellent animal model to characterize the maturation of specific brain structures and major white matter pathways from birth to adulthood. In particular, developmental neuroimaging investigations of rhesus macaques could identify periods of significant volumetric change that can be targeted using invasive techniques to determine the neuroanatomical mechanisms responsible for the volumetric changes.

Although assessments of developmental trajectories in the human brain have begun, this approach has not been employed to analyze the maturation of the hippocampal formation or amygdala in monkeys. There is currently no description of nonhuman primate hippocampal development using MRI, and the only investigation of the nonhuman primate amygdala (Franklin et al., 2000) showed that neither males nor females exhibited age-related changes in the surface area of a single image through the amygdala between 8 months and 7.2 yrs. Thus, the purpose of the current investigation was to examine the volumetric development of the cerebrum, hippocampal formation and amygdala in macaque monkeys from 1 week old to approximately 2 yrs old using noninvasive MRI techniques. Given the reported gender differences in human and nonhuman primate neurodevelopment, this study

considered maturation of the male and female brain separately. Preliminary findings have already been presented in abstract form (Machado et al., 2003, Payne et al., 2005).

Method

All procedures were approved by the Animal Care and Use Committee of the University of Texas Health Science Center, Houston and carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize the number of animals used, as well as any pain and suffering.

Subjects

Eleven male and eleven female rhesus monkeys (*Macaca mulatta*) participated in this study. All infant monkeys were raised in an enriched nursery environment as described previously (Goursaud and Bachevalier, 2007). Briefly, animals were individually housed in size-appropriate wire cages that allowed physical contact with animals in neighboring cage(s), as well as visual, auditory, and olfactory contact with all other infants in the nursery. Each infant was provided a synthetic plush surrogate and cotton towels for contact comfort. The infants were provided daily social interaction with age- and sex-matched peers as well as daily interaction with human caregivers. The animals described here were also involved in multiple experiments of memory, emotional reactivity, social behavior, and reward assessment concurrently with this study.

Ten animals (five male, five female) were assessed in a longitudinal fashion, and thus received multiple imaging sessions (range: 2–9 scans for males and 6–8 for females) between 1 week and 2 yrs old. Twelve monkeys (six male, six female) received a single scan between 1 and 4 weeks old. Poor image quality resulted in the exclusion of some of the scans from volumetric assessment of the hippocampus and amygdala. Therefore, 76 scans (34 scans of 11 males; 42 scans of 11 females) were used to assess total cerebral volume development. Of these, 66 scans (29 scans of 7 males; 37 scans of 7 females) were used to assess the volumetric maturation of the hippocampal formation and amygdala. The ten animals scanned longitudinally were included in the analysis of all regions. See Table 1 for an account of the number of scans acquired in a given age range.

MRI Acquisition

Animals between 1 week and 8 months old were removed from their cages, wrapped in a blanket, and sedated with isoflurane inhalation (1–2% to effect) using an induction box. The sedated animal was then intubated with an endotracheal tube to allow for constant isoflurane anesthesia during the entire scanning session. Animals older than 8 months were first immobilized in their living quarters using ketamine hydrochloride (10 mg/kg), then intubated and anesthetized in the same manner as the infants. All animals were transported to the MRI facility, secured in a nonferromagnetic stereotaxic frame (Crist Instruments, Damascus, MD), placed in a GE Signa 1.5 Tesla Echo Speed scanner (GE Medical Systems, Milwaukee, WI) and leveled/centered with respect to the bore of the magnet. For animals less than 1-month-old, images were acquired using a 3" circular surface coil (GE Medical Systems). All other scans were acquired using a 5" circular surface coil. Two MRI series were acquired in the coronal plane. A 3D T1-weighted fast spoiled gradient (FSPGR)-echo sequence (TE $\approx$ 2.0 μ s, TR $\approx$ 10.0 μ s, 25° flip angle, number of excitations (NEX) = 5, contiguous 1 mm-thick images, 12 cm FOV, 256 $\times$ 256 matrix) included the entire anterior/posterior brain axis and was used to measure the structural development of the cerebrum. A 3D Fast Spin-Echo-Inversion Recovery (FSE-IR) series (TE = 20 μ s, TR = 4,500/250 μ s, ETL = 6, BW = 32 kHz, NEX = 2, contiguous 1.5 mm-thick images, 12 cm FOV, 256 $\times$ 256 matrix) began 4–5 mm anterior to the genu of the corpus callosum and terminated 4–5 mm

posterior to the splenium of the corpus callosum. Relative to T1-weighted FSPGR images, FSE-IR images provide superior contrast between gray and white matter, especially at the youngest ages when white matter is still poorly myelinated. Therefore, FSE-IR images were used to measure the volumetric development of the hippocampal formation and amygdala (Fig. 2).

Volumetric Measurements

Four trained observers used the ImageJ® software (<http://rsb.info.nih.gov/ij/>) to measure the volume of the total cerebrum, hippocampal formation and amygdala (Cronbach's alpha; $P < 0.01$ for all inter- and intraobserver reliabilities). Surface area measurements (in mm²) of the left and right cerebral hemispheres (including ventricles if present) were recorded separately for coronal images spaced 5 mm apart (relative to the anterior commissure) extending from the frontal to the occipital pole. Images containing the hippocampal formation (dentate gyrus (DG), CA1, CA2, CA3, CA4, subicular complex, alveus and fimbria; Figs. 2D,F) or amygdala (all nuclei; Figs. 2A–C) were identified. Surface area measurements were recorded for the left and right hemispheres separately using the boundaries described later. Selection of the boundaries of the hippocampus and amygdala were performed with reference to histological sections from rhesus macaques aged 3 weeks, 1 yr, and 2 yrs (J. Bachevalier, unpublished atlases). Once all surface area measurements were collected, the volume of the total cerebrum, hippocampal formation, or amygdala was calculated for the left and right hemispheres separately (in mm³) using Cavalieri's principle (Gundersen and Jensen, 1987). The surface areas of each structure across all images were summed and multiplied by the distance between the images (i.e., 5 mm for total cerebrum, 1.5 mm for the hippocampal formation and amygdala) to obtain a volume.

Total Cerebrum Boundaries

Total cerebrum volume included the telencephalon, diencephalon, and the midbrain above the superior aspect of the pons (Fig. 1). When the brainstem was visible, the ventral border of the measurement was either the notch superior to the pons or entry points of the cerebellar peduncles (Fig. 1C). No portion of the cerebellum, optic chiasm, brainstem, or midbrain below the superior aspect of the pons was included in the total cerebral volume measurement.

Amygdala Boundaries

The anterior pole of the amygdala was found approximately at the level where the optic nerves begin to fuse to form the optic chiasm (Fig. 2A). This coronal image was selected as the most anterior section of the amygdala. The most posterior portion of the amygdala was just above the anterior hippocampus and was reliably identified on the coronal image where the optic tracts began to be separated by the median eminence and infundibular stalk (Fig. 2B). Measurements were collected on these most anterior and posterior coronal images as well as on all coronal images in between them. There were three images through the amygdala until approximately 1 yr of age, after which four images contained measurable amygdala. For all images, the superior border of the amygdala was not always easily dissociable from the nucleus basalis of Meynert dorsally and the tail of the putamen more laterally. To overcome this problem, a horizontal line that began medially at the limen insulae and extended to the white matter laterally delineated the dorsal border of the amygdala. Thus, rostrally, the dorsal portions of the anterior amygdala area and the anterior cortical nucleus and, more caudally, the central and medial nucleus were excluded. The lateral boundary was the temporal lobe white matter separating the amygdala from the claustrum dorsally and the cortex of the fundus of the superior temporal sulcus laterally. The inferior boundary was the temporal lobe white matter separating the amygdala from the entorhinal cortex (EC) on the anterior slices and from the hippocampus on the most

posterior slices. The medial border of the amygdala followed the medial border of the amygdaloid cortical nuclei.

Hippocampal Formation Boundaries

The anterior border of the hippocampal formation was the image following that of the most posterior border of the amygdala and was usually the first image posterior to the optic chiasm. This coronal image typically showed the optic tracts splitting away from the optic chiasm and moving to a more lateral position (Fig. 2D). In this image, the hippocampal formation is located ventral to the amygdala, and often the tail of the lateral ventricle is visible on the lateral and superior aspects of the hippocampal formation. The most posterior measurement for the hippocampal formation was made on the image that clearly showed the crus of the fornix emerging from the hippocampal formation (Fig. 2F). On this image, the gyrus fasciolaris and the fornix were excluded from the measurements. On all images between these two extremes, the boundaries of the hippocampal formation were defined ventrally and medially by the white matter separating the hippocampus from the parahippocampal gyrus. Laterally and dorsally, the borders of the hippocampus followed the temporal horn of the lateral ventricle. Thus, the volume of the hippocampus included the CA fields, dentate gyrus, subicular complex, alveus, and fimbria, but excluded the entorhinal, perirhinal, and parahippocampal cortices. There were nine images through the hippocampus at all ages.

Data Analysis

Hierarchical multilevel regression, which accounts for irregular intervals between measurements and correlated within-subject variance (Singer and Willett, 2003), was used to assess the influence of age on the volumetric development of the total cerebrum, hippocampal formation, and amygdala. For the hippocampal formation and amygdala, the predictor of hemispheric volume was centered separately for males and females to reduce nonessential colinearity. The presence of linear and curvilinear (quadratic and cubic) patterns was assessed for a given structure with the following model: $\text{Volume}_{ij} = \text{intercept} + d_i + d_{\text{TCV}} + B_1(\text{Age}) + B_2(\text{Age})^2 + B_3(\text{Age})^3 + e_{ij}$; where d_i represents the normally distributed random effect modeling within-subject dependence; d_{TCV} represents the normally distributed random effect modeling the contribution of the total cerebral volume; e_{ij} represents the normally distributed residual error; and the B_1 , B_2 , and B_3 coefficients indicate how volume changes with age. A preliminary evaluation of the data indicated an exponential relationship between volume and age, and was therefore assessed with the following model: $\text{Volume}_{ij} = d_i + \text{intercept}(\text{Age})^{B_1} + B_{\text{TCV}}(\text{TCV}) + e_{ij}$. In all cases, the intercept and B terms were modeled as fixed effects, but were allowed to vary by sex, producing two distinct growth curves. F tests and log-likelihood ratios were used to determine whether a linear, quadratic, cubic, or exponential relationship best described the data. Fixed effects (intercepts and slopes) were used to generate fitted values used for graphing purposes. Patterns of hippocampal and amygdala development were assessed both with and without adjustment for total cerebral volume. Hemispheres were analyzed both separately and together.

Results

Scatterplots representing the raw data for all volumetric analyses are illustrated in Figure 3, and modeled developmental trajectories are presented in Figures 3–5. A summary of regression parameters is shown in a table provided in the Supporting Information. The observations of developmental rates for each region are also illustrated as volume percent-change in Table 2. For comparison purposes, the age ranges mirror those used by Málková et al. (2006). Initial analyses revealed a significant Age $\times$ Sex interaction for total cerebral

volume [$F(1,76) = 5.961, P = 0.017$], indicating that males and females should be analyzed separately. Therefore, the intercept and B terms were allowed to vary by sex for all subsequent analyses.

Total Cerebral Volume

Significant age-related changes in total cerebral volume were best characterized by a power function in both males [$F(1, 33.810) = 329.941, P < 0.001$] and females [$F(1, 41.760) = 232.393, P < 0.001$]. Of note, the observed age-related changes in total cerebral volume also exhibited a strong cubic relationship in both sexes [males $F(1, 28.053) = 45.129, P < 0.001$; females $F(1, 36.313) = 44.352, P < 0.001$; Supporting Information Table]. Both functions were fully characterized (see Supporting Information Table). Because of the superior fit to the data, only the power function is represented graphically (Fig. 4) and described later.

Random effects modeling revealed a significant Age $\times$ Sex $\times$ Hemisphere interaction [$F(3, 134.6) = 2.804, P = 0.042$], further indicating that hemispheric volumes should be analyzed separately for males and females (Supporting Information Table, Fig. 4). Neither males nor females exhibited hemispheric difference [males $F(1, 56.856) = 0.811, P = 0.372$; females $F(1, 73.255) = 1.262, P = 0.265$]. There was a tendency for the cerebral volume to be greater in males than females in both hemispheres [left hemisphere $F(1, 56.935) = 3.770, P = 0.057$; right hemisphere $F(1, 61.384) = 3.355, P = 0.072$].

Total cerebral volume increased substantially between 1 week and 2 yrs of age (males, 69.06%; females, 61.96%). The tangent line slopes for the modeled trajectories were calculated at 1-week intervals to assess the rate of volumetric change (Fig. 7, top panels). The most rapid volumetric increases were seen between 1 and 2 weeks of age, followed by a somewhat slower, although considerable, growth rate that continued throughout the first year. The rate of volumetric increase did not appear to stabilize (i.e., minimal changes in rate of volumetric increases are observed for five successive weeks) until approximately 11.5 months of age.

Hippocampal Formation

To assess sex differences in the development of the hippocampal formation, overall differences in male and female brain size should be considered (Arndt et al., 1991; Mathalon et al., 1993). Thus, the total cerebral volume was modeled as a random effect. This did not account for any additional variance in the models ($Z = 1.539, P = 0.124$) and did not affect the results (see Supporting Information Table); therefore, only the unadjusted models are presented later.

The age-related changes associated with the development of the hippocampal formation were best characterized by a power function in both males [$F(1,28.801) = 90.245, P < 0.001$] and females [$F(1,36.824) = 155.590, P < 0.001$]. In contrast to cerebral volume, the development of the hippocampal formation varied by hemisphere, with the left larger than the right [$F(1, 114.552) = 4.439, P = 0.037$], but neither hemisphere varied by sex [left hemisphere $F(1, 16.239) = 0.106, P = 0.749$; right hemisphere $F(1, 16.549) = 0.309, P = 0.586$; Fig. 5]. Hippocampal volume in both males and females more than doubled (117.05% and 110.86%, respectively) from 1 week to 2 yrs of age. Although the modeled trajectories indicated consistent growth (see Table 2), the most dramatic change in the rate of volumetric increases was observed between 1 and 2 weeks of age (Fig. 7, middle panels). The growth of the hippocampal formation largely mirrors overall cerebral maturation in that the stabilization of the rate of volumetric increases beginning around 11 months of age (vs. approximately 11.5 months for total cerebral volume).

Amygdala

Similar to analyses of the hippocampal formation, adjusting for total cerebral volume did not account for any additional variance ($Z = 1.411$, $P = 0.156$) and did not alter the general findings. Accordingly, only the unadjusted models are presented. Amygdala volumes demonstrated significant age-related volumetric changes best characterized by a power function for both males [$F(1, 58.000) = 81.579$, $P < 0.001$] and females [$F(1, 36.246) = 49.000$, $P < 0.001$]. For males, the right hemisphere was larger than the left throughout the first 2 yrs of development [$F(1, 58.000) = 5.959$, $P = 0.018$]. No such difference was found in the females [$F(1, 64.003) = 2.327$, $P = 0.132$; Fig. 6]. However, it is important to note that neither hemisphere exhibited sex differences [left: $F(1, 9.659) = 0.020$, $P = 0.890$; right: $F(1, 10.114) = 0.196$, $P = 0.667$].

From 1 week to 2 yrs of age, amygdala volume increased by 86.49% in males and 72.94% in females. Again, the tangent line slopes of the modeled trajectories reveal that the most dramatic volumetric increase (Fig. 7, bottom panels) occurred within the first 2 weeks of life. The rate of amygdala maturation appears to stabilize earlier (around 8 months of age) than the total cerebrum or hippocampal formation (around 11.5 and 11 months of age, respectively).

Discussion

This is the first characterization of hippocampal and amygdala developmental trajectories in rhesus macaques using MRI. The inclusion of the earliest age points in the present investigation revealed that both structures exhibit significant age-related increases in volume throughout the first 2 yrs of life. Although the hippocampal formation did not differ between males and females, both sexes exhibited hemispheric asymmetries (left > right). Volumetric increases in the hippocampal formation proceeded rapidly from 1 week to approximately 11 months of age but more slowly until the second year of life. By contrast, the amygdala hemispheric difference (right > left) was only evident in the males and the largest volumetric increases were within the first 2 weeks, but leveled off earlier, around 8 months.

Before discussing these developmental trajectories, it is important to explore an important caveat inherent to any developmental study. Brain maturation is the result of complex interactions between genetic factors and environmental conditions and any changes in these factors may significantly affect the normal maturation of the brain. Thus, although infant monkeys from our study came from the same genetic pool and had similar experience from birth to adulthood, it remains possible that the rearing conditions they received may have altered the maturation of brain structures as demonstrated by others (Sanchez et al., 1998). However, the rearing conditions provided to our animals were far richer than those used by Sanchez et al. (1998) and have been shown to be optimal for the rearing of nonhuman primates in a laboratory environment (Ruppenthal et al., 1991; Sackett et al., 2002; Goursaud and Bachevalier, 2006). Thus, animals in the present studies developed behavioral and cognitive skills very similar to those found in adult monkeys born and raised in seminaturalistic environment. Specifically, they performed comparably in a concurrent discrimination learning task designed to measure procedural learning mediated by the temporal-striatal interactions (Bachevalier, 1990), in a visual paired-comparison task assessing recognition memory (Zeamer et al., 2007, 2008), and in a reinforcer devaluation task that measures flexible decision making (Machado and Bachevalier, 2007) which is known to depend on the interactions between the amygdala and the orbital frontal cortex (Izquierdo and Murray, 2004).

Development of Total Cerebral Volume

The observed developmental trajectories for the total cerebral volume were consistent with and extend those reported previously for rhesus macaques and humans. In both species, total cerebral maturation was best described by a cubic relationship (Málková et al., 2006; Lenroot et al., 2007). Although a cubic relationship was also observed in the current investigation (see Supporting Information Table), the maturational changes were best characterized by a power function that was not assessed in either of the previous reports. The inclusion of neonatal measurements in the monkey studies (Málková et al., 2006; and this study) was most likely responsible for the significant increase in total cerebral volume. Although Lenroot et al. (2007) did not observe significant age-related changes in human cerebral volume from 4 to 22 yrs, the same increase may be present in humans since Knickmeyer et al. (2008) noted a significant increase in total cerebral volume in the first 2 yrs of life.

The concordance of gross cerebral volume maturation between rhesus macaques and humans further emphasizes the appropriateness of using this primate species to provide information about normal development of other neural structures in humans. The one apparent inconsistency between imaging studies of nonhuman primates and humans is that the total cerebral volume of normally developing human males is consistently larger than females (Giedd et al., 1999; Lenroot et al., 2006), a dimorphism not apparent in rhesus macaques. However, the observed statistical trends of rhesus males to have larger cerebral volumes than females (see Fig. 4) indicate that the discrepancy in the assessment of sexual dimorphisms is likely a function of sample size and not an inherent species difference.

Development of Hippocampal Volume

The data provide the first description of hippocampal maturation in nonhuman primates using noninvasive MRI techniques. A previous assessment of hippocampal volume in two groups of older macaques (mean ages: 11.17 yrs and 26.33 yrs) reported hemispheric volumes that are largely consistent with the data obtained at 2 yrs (Shamy et al., 2006). However, the presence of sexual dimorphism in the hippocampal formation, a finding inconsistently reported in the human literature (Filipek et al., 1994; Caviness et al., 1996; Giedd et al., 1996, 1997; Schumann et al., 2004), was not apparent in the current study. Although both species exhibit hemispheric differences in hippocampal volume during maturation, the differences are in opposite directions. The right hippocampus is consistently larger than the left in humans (Weis et al., 1989; Watson et al., 1992; Giedd et al., 1996; Pfluger et al., 1999; Utsunomiya et al., 1999; Jack et al., 2000; Thompson et al., 2009), but the left hippocampus appears to be larger than the right in the rhesus macaque. Despite this difference, it is important to note that the estimated change in rhesus hippocampal volume from 3 to 6 months is approximately 12% in males and 14% in females and is consistent with the 13% increase (collapsed across sexes) reported between 1 and 2 yrs of age in humans (Knickmeyer et al., 2008; note that 1–2 yrs of age in humans roughly corresponds to 3–6 months of age in rhesus monkeys).

Neuroimaging studies in monkeys could provide critical information about the relationships between MRI volumetric changes and morphological changes during development. The majority of the neurons in the primate hippocampal formation are generated prenatally (Nowakowski and Rakic, 1981; Eckenhoff and Rakic, 1988; Arnold and Trojanowski, 1996), but a substantial number of dentate gyrus granule cells continue to be generated postnatally (Nowakowski and Rakic, 1981; Rakic and Nowakowski, 1981; Eckenhoff and Rakic, 1988; Lavenex et al., 2007) and into adulthood (Gould et al., 1999; Kornack and Rakic, 1999). The pattern of cell proliferation within the rhesus dentate gyrus (Lavenex et al., 2007) is similar to the pattern observed in humans (Seress, 1992, 1998; Seress et al.,

2001). These age-related changes are attributable to dendritic arborization, synaptogenesis, and myelination of the granule cells (Duffy and Rakic, 1983; Eckenhoff and Rakic, 1991; Seress, 1992). Likewise, cells of the CA1 and CA3 fields do not appear “adult-like” until between 6 months and 1 yr of age, which roughly corresponds to when volumetric changes leveled off (i.e., around 11 months; Khazipov et al., 2001; Seress, 2001; Altemus et al., 2005; Lavenex et al., 2007). Although there appears to be agreement between the maturational changes observed histologically and the current developmental trajectories, more direct comparisons are needed to fully elucidate the specific neuronal mechanisms driving the gross changes captured by imaging techniques.

Development of Amygdala Volume

As with the hippocampal formation, age-related changes in rhesus amygdala volume have not been previously reported. The only developmental neuroimaging study in monkeys reported no surface area changes between 8 months and 7.2 yrs of age (Franklin et al., 2000). This lack of age-related changes in the amygdala is explained by the fact that the most robust maturational changes for the amygdala occur before the age of 8 months. No sexual or hemispheric differences in amygdala volume have been previously reported in rhesus macaques although inconsistent gender differences have been found in humans. In this study, both males and females exhibited age-related changes in amygdala volume, and only males displayed a hemispheric difference with the right hemisphere larger than the left. This hemispheric difference for the amygdala is opposite to that observed in the hippocampus (see above), indicating that the hemispheric differences in the two structures are not linked simply to one temporal lobe being smaller than the other. Finally, the maturation of the amygdala appears to level off slightly earlier (8 months) than the maturation of the hippocampus (11 months). Thus, given that volumetric changes within the hippocampus seem to be associated with morphometric changes within the same developmental period, it is expected that similar processes are driving the volumetric changes in the amygdala. However, there are currently no morphological data available to support this proposal.

Sexual Dimorphism Through Development

Although the current investigation provides valuable information about the previously uncharacterized early maturation of the hippocampus and amygdala in nonhuman primates, the complete development of these animals is not represented. A generally accepted age for the onset of sexual maturity in rhesus monkeys is 4 yrs for males and 2.5–3.5 yrs for females (Terasawa et al., 1983; Wilson et al., 1984; Mann et al., 1998). Thus, the monkeys in this study have not yet gone through a pubertal stage. This is a factor of interest when comparing the results of the current study with previous findings reported in humans. Giedd et al. (2006) and Lenroot et al. (2007) have suggested that localized differences in androgen receptor concentration may manifest as sexually dimorphic developmental trajectories. Thus, hormonal fluctuations during puberty may have differential effects on the maturation of the hippocampal formation and amygdala. Longitudinal scans across these age ranges are needed to assess this possibility. This study was designed to maximize the limited subject resources by staggering the ages of scan acquisition to span the entire timeline. Although the mixed design hierarchical regression analysis accounts for variability in scanning ages, additional scans at each age point are also needed to make direct quantitative comparisons between ages.

Brain–Behavior Relationships

One critical goal of developmental studies of brain structures is their potential to provide information on the development of cognitive functions and behavior. The current longitudinal MRI-based morphometry study suggests differential developmental trajectories

for the amygdala relative to the hippocampus that may contribute to differences in the functional maturation of these structures. Thus, it seems logical to propose that, within the first year of life in monkeys, amygdala function develops slightly earlier than hippocampal function.

In addition, the dramatic volumetric increases observed during the first 2 yrs of life indicate that this period in neurodevelopment is highly susceptible to perturbations. Disruption of normal developmental processes during this time may have long-lasting or permanent effects on brain structure and function. Previous studies have demonstrated that neonatal damage to the amygdala and the hippocampus yielded dramatic and permanent changes in behavioral and cognitive functions (Bachevalier et al., 1999a,b; Alvarado et al., 2002; Bauman et al., 2004, 2008). In addition, many human neuropsychological disorders, such as autism, schizophrenia, Down and Williams syndromes, and mental retardation, are characterized by behavioral abnormalities consistent with malfunctions of the hippocampal formation and/or the amygdala (Uecker et al., 1993; Dierssen et al., 1996; Raymond et al., 1996; Leverenz and Raskind, 1998; Harrison, 1999; Saitoh et al., 2001; Machado and Bachevalier, 2003; Bauman and Kemper, 1985, 2005). However, structural brain imaging of patient populations have not consistently identified specific brain anomalies (Weis et al., 1990; Bailey et al., 1993; Csernansky et al., 1998; Courchesne et al., 2001; Schumann et al., 2004; Hazlett et al., 2005). One factor that may contribute to this inconsistency is the reliance on group differences at an arbitrary age. A better understanding of developmental trajectories is crucial to reliably identify putative structural aberrations in patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Series of coronal MR images at three anterior-posterior levels through the cerebrum (A–C) taken at 1 month, 6 months, and 1 yr of age.

FIGURE 2. Series of coronal MR images at three anterior-posterior levels through the amygdala (A–C) and hippocampal formation (D–F) taken at 1 month, 6 months, and 1 yr of age.

FIGURE 3.

Scatterplots of actual volumetric measurements in cubic millimeters for total cerebrum (A: males; B: females), total hippocampal formation (C: males; D: females) and total amygdala (E: males; F: females) as a function of age. Lines between data points represent longitudinal measurements on the same animal for males (solid) and females (dashed).

FIGURE 4.

Modeled developmental trajectories for total cerebral volume of males (A, solid line) and females (B, dashed line). Individual volumes are represented by squares (males) and circles (females). Modeled developmental trajectories for left (thick, thatched lines; filled symbols) and right (thin, solid lines; open symbols) cerebral hemispheres (C, males; D, females).

FIGURE 5. Modeled developmental trajectories for left (thick, dashed lines) and right (thin, solid lines) hippocampal formation volume in males (A) and females (B). Actual volume measurements are represented by filled (left hemisphere) and open (right hemisphere) symbols.

FIGURE 6. Modeled developmental trajectories for left (thick, dashed lines) and right (thin, solid lines) amygdala volume in males (A) and females (B). Actual volume measurements are represented by filled (left hemisphere) and open (right hemisphere) symbols.

FIGURE 7.

Tangent line slope values of modeled developmental trajectories for cerebral volume in males (A) and females (B), hemispheric hippocampal formation volume (C, males; D, females) and hemispheric amygdala volume (E, males; F, females). Small, filled symbols represent the left hemisphere and large, open symbols represent the right hemisphere. For each structure, the arrow indicates the age at which differences between two adjacent data points did not substantially differ, and thus represents the approximate age at which growth of the structure leveled off.

TABLE 1

Number of Scans Across Ages

	Total cerebrum		Hippocampal formation		Amygdala	
	Male	Female	Male	Female	Male	Female
1 week–1 month	9 (9)	9 (8)	4 (4)	4 (3)	4 (4)	4 (3)
1–2 months	2 (2)	3 (3)	2 (2)	3 (3)	2 (2)	3 (3)
2–4 months	2 (2)	7 (5)	2 (2)	7 (5)	2 (2)	7 (5)
4–6 months	4 (2)	4 (3)	4 (2)	4 (3)	4 (2)	4 (3)
6–8 months	4 (3)	2 (2)	4 (3)	2 (2)	4 (3)	2 (2)
8–12 months	6 (5)	7 (5)	6 (5)	7 (5)	6 (5)	7 (5)
12–16 months	4 (4)	3 (3)	4 (4)	3 (3)	4 (4)	3 (3)
16–20 months	2 (2)	4 (4)	2 (2)	4 (4)	2 (2)	4 (4)
20–24 months	0	1 (1)	0	1 (1)	0	1 (1)
24–28 months	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)	2 (2)

Number in parentheses denotes the number of animals scanned in a given age range.

TABLE 2

Estimates for Percentage of Volumetric Change

Anatomical structure	Model	Sex	1 week-1 month	1-2 months	2-3 months	3-4 months	4-5 months	5-8 months	8-12 months	1-2 years
Total cerebrum	power	M	15.93	7.69	4.42	3.11	2.41	5.13	4.42	8.70
		F	14.16	6.84	3.95	2.79	2.15	4.59	3.95	7.76
	cubic	M	7.97	8.60	6.69	5.21	4.02	7.05	1.60	7.12
		F	6.57	7.17	5.67	4.47	3.48	6.17	1.52	6.20
Left hemisphere	power	M	16.12	7.76	4.47	3.15	2.43	5.20	4.47	8.80
		F	14.12	6.85	3.95	2.79	2.16	4.60	3.96	7.77
	cubic	M	8.13	8.76	6.80	5.29	4.08	7.13	1.58	6.84
		F	6.56	7.18	5.67	4.47	3.48	6.18	1.53	5.95
Right hemisphere	power	M	15.72	7.57	4.36	3.08	2.38	5.07	4.36	8.59
		F	14.16	6.84	3.95	2.79	2.15	4.59	3.95	7.76
	cubic	M	7.81	8.44	6.58	5.13	3.97	6.96	1.63	7.42
		F	6.59	7.21	5.69	4.47	3.49	6.17	1.49	6.27
Hippocampal formation										
Left hemisphere	power	M	19.33	9.24	5.31	3.74	2.89	6.18	5.31	10.50
		F	28.24	13.24	7.55	5.30	4.08	8.80	7.55	15.08
Right hemisphere	power	M	19.32	9.23	5.30	3.73	2.88	6.17	5.30	10.49
		F	29.99	14.01	7.97	5.59	4.31	9.30	7.97	15.96
Amygdala										
Left hemisphere	power	M	20.13	9.60	5.51	3.88	3.00	6.42	5.51	10.91
		F	23.10	10.95	6.27	4.41	3.40	7.30	6.27	12.45
Right hemisphere	power	M	17.14	8.23	4.74	3.34	2.58	5.51	4.74	9.34
		F	23.83	11.28	6.45	4.54	3.51	7.52	6.45	12.83

Percent volumetric change = $[(X_2 - X_1)/X_1] \times 100$; where X_1 is modeled volume at first age in specified range, and X_2 is modeled volume at second age in specified range.