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# Age-Related Differences in Corpus Callosum Area of Capuchin Monkeys

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## Abstract

Capuchin monkeys (*Cebus apella*) are New World primates with relatively large brains for their body size. The developmental trajectories of several brain regions – including cortical white matter, frontal lobe white matter, and basal ganglia nuclei – are similar to humans. Additionally, capuchins have independently evolved several behavioral and anatomical characteristics in common with humans and chimpanzees – including complex manipulative abilities, use of tools, and the use of precision grips – making them interesting species for studies of comparative brain morphology and organization. Here we report the first investigation into the development of the corpus callosum and its regional subdivisions in capuchins. Corpus callosum development was quantified using high-resolution structural MRI images from 39 socially reared subjects (male n = 22; female n = 18) ranging in age from 4 days (infancy) – 20 years (middle adulthood). The total area of the corpus callosum and the subdivisions of the genu, rostral midbody, medial midbody, caudal midbody, and splenium were traced from the midsagittal section. Total corpus callosum area displayed significant differences across this time span and was best explained by quadratic growth. Sustained linear growth was observed in the subdivisions of the genu, rostral midbody, and splenium; sustained quadratic growth was seen in the subdivision of the medial midbody. Differences in growth were not detected in the subdivision of the caudal midbody. Females had a larger raw area of the total CC and of the medial midbody and caudal midbody throughout the lifespan. Our results indicate that capuchins show continued white matter development beyond adolescence in regions related to cognitive and motor development.

### Keywords

brain development; *Cebus*; corpus callosum

## 1. Introduction

The corpus callosum (CC) is the major white matter tract in placental mammals that exchanges sensory, motor and higher-order cognitive information information between the two cerebral hemispheres. Information transfer occurs in a highly organized fashion, connecting both homotopic and heterotopic regions along a rostral-caudal gradient. The



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midsagittal area of the CC is frequently used as a sensitive marker of brain development (Clarke et al. 1989; Rajapakse et al. 1996; Pandya et al. 1971; LaMantia and Rakic 1990; Rakic and Yakovlev 1968), hemispheric lateralization (Witelson and Goldsmith 1991; Westerhausen et al. 2010), and connectivity and function (Luders et al. 2010) (Muetzel et al. 2008; Ringo et al. 1994; Wahl et al. 2007). Additionally, studies have shown a correlation between anatomical changes within the CC and certain neurological disorders (Hasan et al. 2005; Lyoo et al. 1997; Wang et al. 1992; Woodruff et al. 1995).

Several studies documenting brain development in humans have shown that the CC exhibits sustained growth through childhood and even beyond adolescence. The midsagittal area of the corpus callosum, particularly the posterior region, increases dramatically between 5 and 18 years (Giedd et al. 1999; Giedd et al. 1996a). While the area of these regions increases, the shape becomes more compact and boundaries become more distinct (Rajapakse et al. 1996). In humans, though the CC shows the most pronounced increases in size during childhood, it also continues to increase in size into early adulthood (~32 years) (Keshavan et al. 2002).

Understanding how nonhuman primate brain development compares to brain development of humans is important for translational research objectives. Perhaps surprisingly, quantitative data on neuroanatomical development of the corpus callosum in nonhuman primates is rather sparse, and there is a lack of information concerning early development. Chimpanzees (*Pan troglodytes*) show similar development of the CC as humans, with sustained growth in the total CC and subdivisions of the genu, posterior midbody, anterior midbody, isthmus and splenium occurring between 6 years and 54 years (Hopkins and Phillips 2010). Bonnet macaques (*Macaca radiata*) show age-related differences in CC:brain ratio across juvenile, adolescents, and adults with all subdivisions except the genu displaying this change (Pierre et al. 2008b). Rhesus monkeys (*Macaca mulatta*) also show significant increases in total callosal area between the ages of 10 months and 64 months (Knickmeyer et al. 2009); however growth in regional subdivisions of the CC was not reported. A recent study of development of the CC in the fetal and early postnatal period in *Papio* baboons (*Papio hamadryas anubis*) reported non-uniform increases in area. In particular, the splenium showed the most increase in midsagittal area by postnatal week 32, whereas the genu and anterior midbody showed the least midsagittal area increase by this time (Phillips and Kochunov 2011)

Comparative data on early developmental changes in the corpus callosum would enhance our understanding of the similarities and differences among species in the neural basis of behavioral development. Capuchin monkeys are New World primates that have been extensively studied for their social complexity, cognitive ability and manipulative propensities, including tool use (Fragaszy et al. 2004). Adult capuchins have a relatively large brain for their body size (Rilling and Insel 1999). The developmental trajectories of several brain regions – including cortical white matter, frontal lobe white matter, and basal ganglia nuclei – are similar to humans (Phillips et al. 2010; Phillips and Sherwood 2008). Capuchins also possess a proprioceptive cortical area 2 and a well-developed cortical area 5, which are associated with motor planning, visually guided reaching, grasping, and manipulation (Padberg et al. 2007). In this report, we extend our study of capuchin brain development to investigate age-related differences in the size of the corpus callosum and its regional subdivisions from a cross-sectional sample of 37 capuchin monkeys.

## 2. Experimental Procedures

### 2.1 Subjects

Magnetic resonance images were collected from 37 capuchin monkeys (*Cebus apella*; female $n = 16$, male $n = 21$), ranging in age from 4 days to 20 years. As the study was cross-sectional in design, each subject contributed one scan (data point). Data on corpus callosum area from 14 of these subjects were previously published (Phillips et al. 2007). All subjects were socially reared and were housed at the following institutions: Hiram College, Hiram OH; The College of Wooster, Wooster, OH; and The University of Pittsburgh, Pittsburgh, PA. The MRI scanning protocol was approved by the Institutional Animal Care and Use Committee at each institution.

### 2.2 Image Collection and Procedure

*In vivo* high-resolution structural MRI scans were obtained from each subject at the Neuroscience Imaging Center, University of Pittsburgh, Pittsburgh, PA. Once at the facility, subjects were initially immobilized with one of two drug cocktails: a) ketamine (7 mg/kg) injection IM, meditomidine (.06 mg/kg) injection IM and atropine (.05 mg/kg) injection SQ, or b) ketamine (25 mg/kg) injection IM, acetylpromazine (1 mg/kg) injection IM and atropine (.05 mg/kg) injection SC. An intravenous catheter was then placed in the saphenous vein and subjects given a bolus of propofol (2 – 5 mg/kg). A constant intravenous drip (250 – 350 μg/kg/min) maintained anaesthesia. Subjects were then placed into the scanner chamber and their heads were fitted inside a 16 cm or 12 cm head coil. Subjects remained anaesthetized throughout the MRI procedure and respiration rate, heart rate, and oxygen consumption were continually monitored. At the cessation of the scan, subjects receiving drug cocktail “a” received atipamazole (0.06mg/kg) injection IM. Scan duration was approximately 60 minutes.

Subjects were scanned on the same Siemens Allegra 3.0 Tesla scanner located at the Neuroscience Imaging Center. T1-weighted images were collected using a 3D gradient echo sequence (pulse repetition = 2300 ms, echo time = 4.4 ms, number of signals averaged = 3, matrix size = 320 × 320).

### 2.3 Image Quantification Method

Prior to morphometric analysis, data were converted into the ANALYZE 3D volume file format to facilitate re-slicing into orthogonal planes. Computer files for individual subjects were numerically coded prior to measurement to prevent observer bias. Each individual brain was realigned along the AC-PC and interhemispheric fissure. CC area measurements were performed by manual tracing on the midsagittal section according to the methodology originally described by Biegon et al. (Biegon et al. 1994) and later adapted to nonhuman primates by Sanchez et al. (Sanchez et al. 1998). In the Biegon et al. method, the anterior 20% of the CC was defined as the genu, the posterior 20% defined as the splenium, and the middle 60% defined as body. To adapt this to nonhuman primates, Sanchez et al. (1998), Phillips et al. (Phillips et al. 2007), and Pierre et al. (2008) further delineated the middle 60% into three equal sections: anterior midbody, medial midbody and caudal midbody. These subdivisions of the CC are believed to be based on differences in microstructure and functional connectivity with cortical areas (Aboitiz et al. 1992; Alexander et al. 2007; Hofer and Frahm 2006). The anterior region of the genu connects primarily higher-order cognitive regions of the frontal lobe; the anterior, medial and caudal midbody connect primarily sensorimotor regions; the posterior region of the splenium integrates visuospatial regions of the parietal, temporal, and occipital cortex. ANALYZE 10.0, an MRI analysis software program distributed by the Mayo Clinic, was used to divide and measure the corpus callosum. To subdivide the CC, the entire length of the CC was first manually traced, and

then divided into five equally spaced sections (see Figure 1) to determine area (in $mm^2$). The area of each individual subdivision was summed to derive an area measure for the total CC.

### 2.4 Data analysis

We analyzed growth of the CC using both the raw area measures of the total CC and its subdivisions, and the size of the total CC and its subdivisions after adjusting for brain size. To statistically adjust the CC data for total brain volume, we followed a recommendation by Smith (2005) wherein the square root of the CC area was divided by the cube root of total brain volume for each individual to bring all measures into the same geometric dimensionality. Additionally, we applied this adjustment to the various subdivisions of the CC. Analyses of total CC and CC subdivision areas were conducted using ANCOVA to determine the effects of sex and age. We used a series of ANCOVAs for several reasons. First, we wished to avoid the problem of multicollinearity on the total CC area (as total CC is a linear combination of the five CC subdivisions). Secondly, as testosterone modulates regional callosal architecture during development, differentially influencing subdivisions (Moffat et al. 1997), we conducted separate analyses on each raw subdivision measure. Age was treated as a fixed factor in these analyses, categorizing subjects as either "young" (≤ 3 years) or "adult" (> 3 years) based upon the age at which maximum total brain volume is attained (Phillips and Sherwood 2008). *F*- tests were then used to determine whether linear or quadratic growth models best fit the developmental change in these regions (Hasan et al. 2008; Phillips and Sherwood 2008; Pujol et al. 1993; Rauch and Jinkins 1994). SPSS 18.0 was used for conducting all analyses.

## 3. Results

### 3.1 Raw area CC measures

The raw area of the total CC was significantly influenced by sex. Females had a larger raw area of the total CC than males ($F$ (1, 33) = 4.96, $p$ = .033, partial $\eta^2$ = .13; Figure 2a). The subdivision of the caudal midbody was significantly influenced by sex, with females having larger raw area than males (caudal midbody: $F$ (1, 33) = 6.87, $p$ = .013, partial $\eta^2$ =.17). The medial midbody was significantly influenced by age (medial midbody: $F$ (1, 33) = 5.23, $p$ = .029, partial $\eta^2$ =.14), with adults having a larger raw area than young animals. There was no significant interaction of sex and age for any callosal subdivision (Figure 2b).

Total corpus callosum area displayed significant differences across this time span and was best explained by quadratic growth ($F$ (2, 36) = 3.89, $p$ = 0.029; $R^2$ = .18; see Figure 3). Sustained linear growth was observed in the subdivisions of the genu, rostral midbody, and splenium (genu: $F$ (1, 37) = 4.30, $p$ = 0.045; $R^2$ = .10; rostral midbody: $F$ (1, 37) = 5.55, $p$ = 0.024; $R^2$ = .13; splenium: $F$ (1, 37) = 3.63, $p$ = 0.065; $R^2$ = .18). Sustained quadratic growth was seen in the subdivision of the medial midbody ($F$ (2, 36) = 5.90, $p$ = 0.006; $R^2$ = .25). Differences in growth were not detected in the subdivision of the caudal midbody. Growth data for all subdivisions of the corpus callosum are displayed in Figures 4a – 3e.

We conducted an outlier analysis and found that the data point 0,20 was a definite outlier at > 3 SD below the mean CC. We reran the analysis to determine the best equation to explain changes in total CC area across age. Excluding this data point, the relationship remained best explained by quadratic growth. The data point at 0, 36 was marginal with respect to whether it could be considered an outlier (at 2.29 SD below the mean). Nonetheless, an analysis was conducted excluding both these cases. With the removal of these two subjects, the amount of variance accounted for in the relationship between total CC area and age remained best explained by a quadratic equation but was not significant [$F$ (2, 33) = 2.84, $p$

= .073, $R^2$ = .15]. The linear equation was significant [$F$ (1, 34) = 4.64, $p$ = .038, $R^2$ = .12] but accounted for less variance in the relationship.

### 3.2 CC relative area measures

Sex and age were significant factors influencing the CC:brain ratio. Females had a larger CC:brain ratio than males ($F$ (1, 33) = 11.99, $p$ = .002, partial $\eta^2$ = .27); adults had a larger CC:brain ratio than young animals ($F$ (1, 33) = 7.16, $p$ = .011, partial $\eta^2$ = .18). All subdivisions - the genu, rostral midbody, medial midbody, caudal midbody, and splenium – showed significant sex differences (genu: $F$ (1, 33) = 5.50, $p$ = .025, partial $\eta^2$ = .14; rostral midbody: $F$ (1, 33) = 9.03, $p$ = .005, partial $\eta^2$ = .22; medial midbody: $F$ (1, 33) = 9.52, $p$ = .004, partial $\eta^2$ = .22; caudal midbody: $F$ (1, 33) = 13.46, $p$ = .001, partial $\eta^2$ = .29; splenium: $F$ (1, 33) = 5.72, $p$ = .023, partial $\eta^2$ = .15). In all cases females had larger ratios of the CC subdivision than males.

The subdivisions of the rostral midbody, medial midbody and splenium were influenced by age (rostral midbody: $F$ (1, 33) = 4.43, $p$ = .043, partial $\eta^2$ = .12; medial midbody: $F$ (1, 33) = 8.06, $p$ = .008, partial $\eta^2$ = .20; splenium: $F$ (1, 33) = 6.85, $p$ = .013, partial $\eta^2$ = .17). Adult had larger ratios of the CC subdivision than young animals.

## 4. Discussion

Capuchins showed age-related change in the area of the total CC and in all subdivisions except the caudal midbody. Importantly, the areas of the genu and splenium displayed age-related change over the lifespan investigated in this sample. These regions of the CC connect areas of higher cognitive functioning and visuospatial processing, respectively. Capuchins display similarity in the development of these callosal subdivisions to humans and chimpanzees, where these regions also continue to mature well into adulthood (Hopkins and Phillips 2010; Hasan et al. 2008). Capuchins reach sexual maturity at 5 years; these data indicate continued development of the corpus callosum past adolescence. Other brain regions also show continued development past sexual maturity in capuchins, including cortical white matter, frontal lobe white matter, and basal ganglia nuclei (Phillips and Sherwood 2008; Phillips et al. 2010). Interestingly, a recent study of CC age-related changes in bonnet macaques did not report developmental changes in the genu (Pierre et al. 2008a).

Sex differences in the raw area measures were found in this sample, with female capuchins having larger raw total CC area than males, and a larger medial midbody and caudal midbody throughout the lifespan. This result, using a larger data set, is consistent with our previous work reporting sexual dimorphism of the total cross-sectional area of the CC in capuchin monkeys (Phillips et al. 2007; Phillips and Sherwood 2008) and in chimpanzees (Phillips et al. 2009) but not bonnet macaques (Pierre et al. 2008b). Previously, we have also reported significant associations between CC morphology, sex and handedness (Phillips et al. 2007), with left-handed individuals having a larger relative overall CC area than right-handed individuals. Callosal relationships to hand preference were not analyzed in the present study as we did not have handedness data on most of these additional subjects. Such additional data to further verify such relationships in capuchins are needed.

We did not detect sex differences in the growth curves of the CC in capuchins. Chimpanzees display sex differences in the development of the CC, in total CC area and in the subdivisions of the anterior midbody, posterior midbody and isthmus (Hopkins and Phillips 2010). Whether or not sex differences are present in the development of the human CC is controversial, as reports are inconsistent (Allen et al. 1991; Giedd et al. 1996a; Giedd et al. 1996b; Giedd et al. 1999; Rajapakse et al. 1996; Lenroot et al. 2007; Hasan et al. 2008). However, different methodologies, including varying sample sizes, ages, and means of

quantifying the CC, may explain these discrepancies. In fact, when controlling for these variables, human males and females display significant differences in the maturation of the CC and CC subdivisions (Luders et al. 2010). These sex differences vary as a function of callosal region and developmental stage. Postnatal structural changes in the human CC are likely due to myelination, pruning, and axonal redirection (Galaburda et al. 1990; Luo and O'Leary 2005).

While the use of MRI to document patterns of global developmental changes in neural structures can illustrate important patterns, such as those reported here, studies of the development of cortical microstructure will provide addition information about age-dependent changes in neuronal morphology, myelination, synapse density, and the expression of signaling molecules and receptor subunits. For example, the temporal profile of the maturation of pyramidal neurons in marmoset visual cortex and dorsolateral cortex has been studied extensively (Burman et al. 2007; Bourne and Rosa 2006) using immunohistochemistry against non-phosphorylated neurofilament protein. These researchers demonstrated that pyramidal neurons in the caudal portion of the frontal lobe matures at a slower rate than the visual areas. Specifically, pyramidal neuron maturation occurred earlier in the somatosensory and motor areas, progressing rostrally in the prefrontal cortex.

Although the corpus callosum is the largest commissural tract in placental mammals, the anterior and posterior commissures also provide interhemispheric connectivity. While it was not possible to provide accurate data on age-related changes of either the anterior or posterior commissure in the present study due to limitations of voxel size of the MRI scans, such data would likely provide important details relevant to understanding brain evolution in primates. For example, in owl monkeys and marmosets the connections of the rostrotemporal auditory area pass almost exclusively through the anterior commissure (Fitzpatrick and Imig 1980; Reser et al. 2009).

Humans show pronounced postnatal growth of the CC in the anterior and posterior regions; the growth is age-related and occurs in a rostrocaudal wave (Thompson et al. 2000). Earlier development shows more pronounced growth in anterior regions whereas later growth is more pronounced in the posterior regions (Luders et al. 2010; Giedd et al. 1999; Giedd et al. 1996a; Rajapakse et al. 1996; Brun et al. 2008). The maturation observed in regions of the CC parallels the growth in percentage of white matter (Hasan et al. 2008; Sowell et al. 2003). Additionally, there is an increasing accumulation of data supporting the hypothesis that maturation of white matter (and subcortical brain structures) is related to the development of cognitive and motor abilities in children (Pangelinan et al. 2011). Increases in total white matter volume, including increases in volume of tracts of the corpus CC, due to myelination improve the speed and synchronization of neural transmission – two key features in cognitive and motor development (Paus et al. 1999; Tirapu-Ustarroz et al. 2011). Cognitive and motor skills may be fundamentally interrelated. Thus, the development of the CC in capuchins is likely correlated with the emergence of species-specific skills and behavior. Although studies of integrated relationship between brain development, cognitive ability and motor ability in capuchins are still needed, behavioral data suggest that such coordination may occur. For young capuchins, developing the skilled manipulative actions required for becoming a proficient forager may be one of the most demanding and important challenges. Young foragers are rather inefficient and unskilled, yet persistent in their manipulation of objects. It takes up to at least 3 years for a young capuchin to develop the cognitive and motor skills used in processing food efficiently – including precision handling and tool use (Fragaszy et al. 2004). An example of how growth in the tracts of the CC might be associated with the development of skilled foraging concerns the complex foraging skill of prey capture. The increase in posterior region of the CC, the splenium, which connects information between parietal and temporal lobes and is associated with visuospatial skills,

may be linked to skills such as prey capture (Hellner-Burris et al. 2010), Phillips, unpublished results). Ongoing longitudinal research in our laboratory is exploring these questions, and has the potential to provide a more accurate means of tracking the development of the CC in capuchins and integrating brain development with development of cognitive and motor abilities.

In summary, we found that capuchin monkeys are similar to humans and chimpanzees in displaying growth in the anterior and posterior regions of the CC from birth through adulthood. Combined with previous data showing that capuchins display similar developmental trajectories to humans for the volume of the cortical white matter, frontal lobe white matter, and basal ganglia nuclei (Phillips and Sherwood 2008; Phillips et al. 2010), our results are likely to have significant translational implications. Identifying appropriate primate species that model the typical developmental trajectory of the human brain is an essential step before determining the mechanisms by which this course is altered in neurodevelopmental disorders.

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## List of the Abbreviations

| | |
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| **CC** | corpus callosum |
| **MRI** | magnetic resonance imaging |
| **IM** | intramuscular |
| **SC** | subcutaneous |
| **ANCOVA** | analysis of covariance |

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## Highlights

- The development of the corpus callosum (CC) in capuchin monkeys is described.
- High-resolution anatomical MRI scans were used to visualize and measure the CC.
- Total CC area and subdivision areas showed sustained linear or quadratic growth.
- Capuchins show similarities to humans with prolonged white matter development.

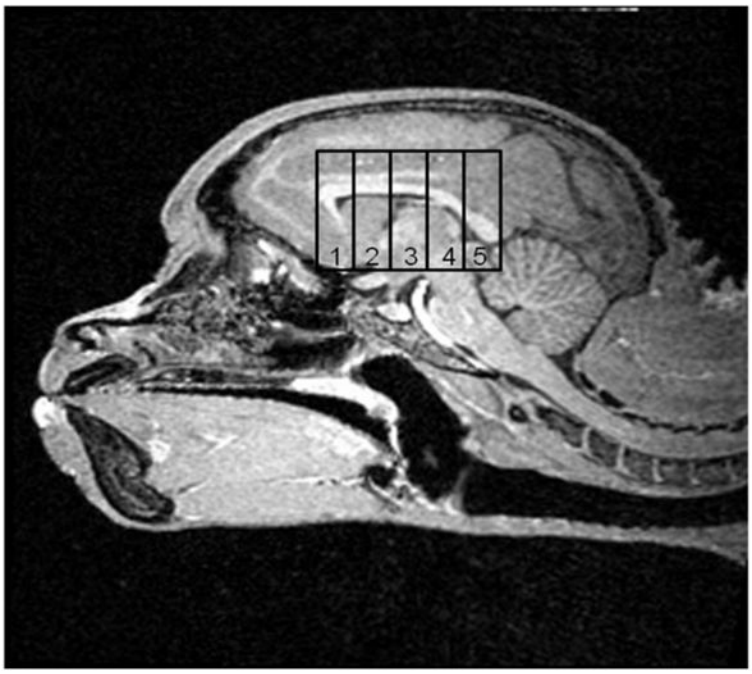



**Figure 1.**
Anatomical subdivision of the capuchin corpus callosum from MRI midsagittal view. The total midsagittal area was divided into five equally spaced subdivisions: 1 = genu, 2 = rostral midbody, 3 = medial midbody, 4 = caudal midbody, and 5 = splenium.

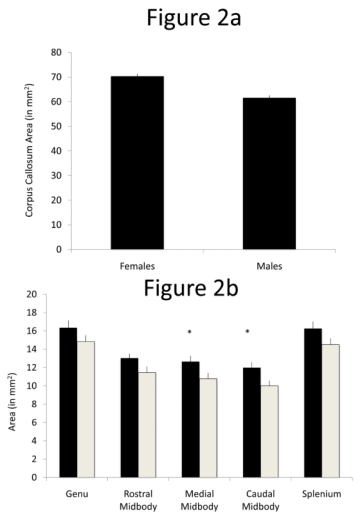



**Figure 2.**

Figures 2a and 2b. (a) Differences in total corpus callosum area in female and male capuchins (M + SE). (b). Differences in area of corpus callosum subdivisions in female and male capuchins (M + SE). Females are represented by black bars; males represented by cream bars.

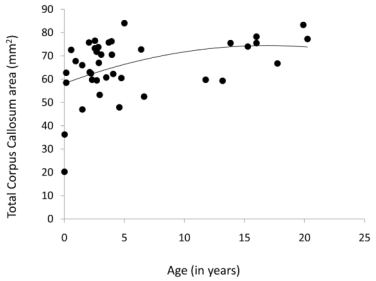
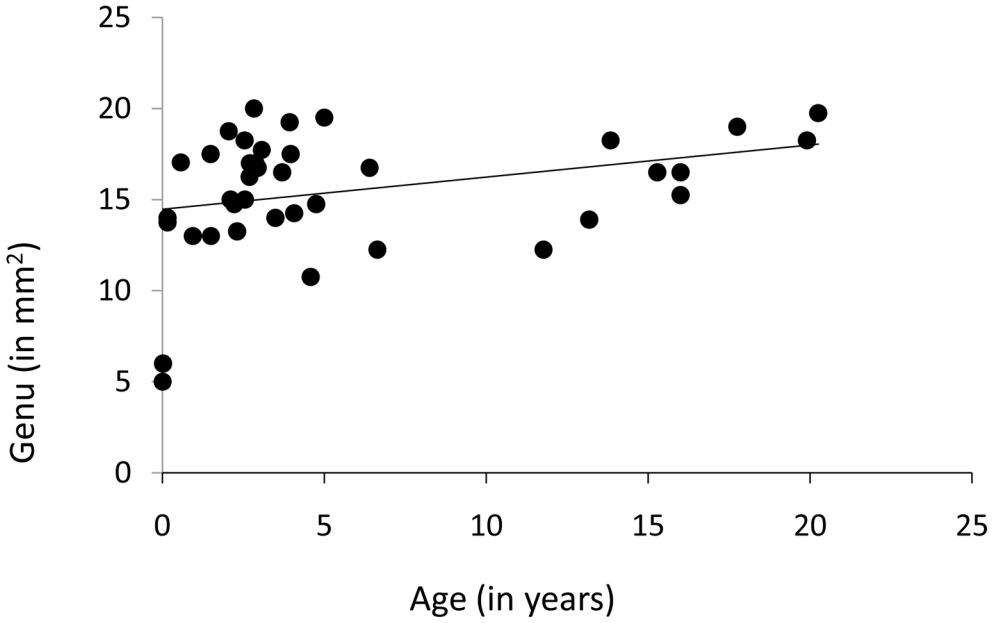
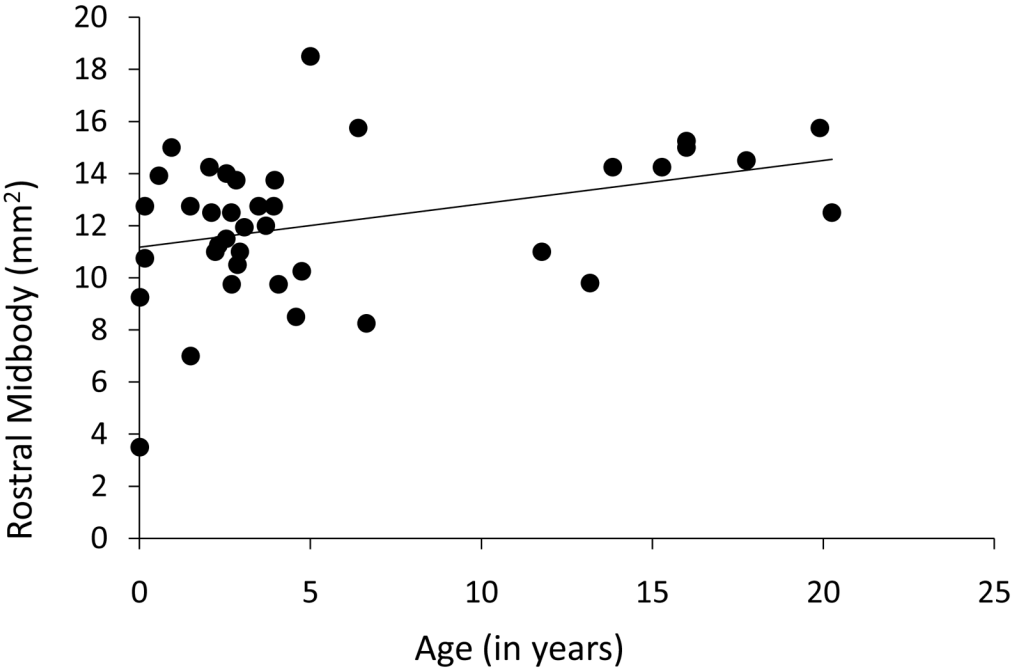



**Figure 3.**
Growth trajectory of the total midsagittal CC area (in $mm^2$) in a sample of 37 capuchin monkeys ranging in age from 4 days – 27 years.

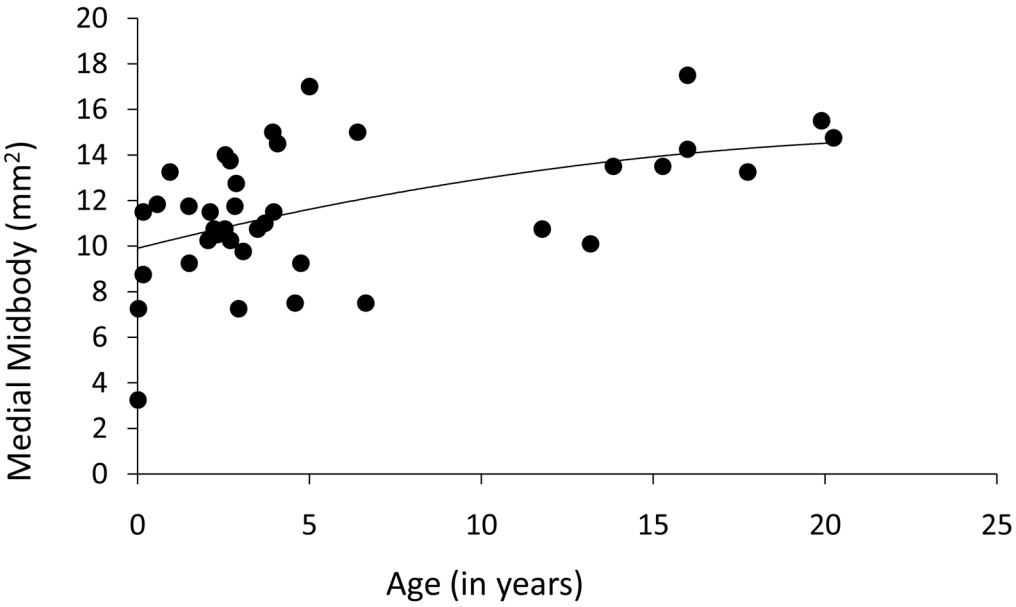
# Figure 4a



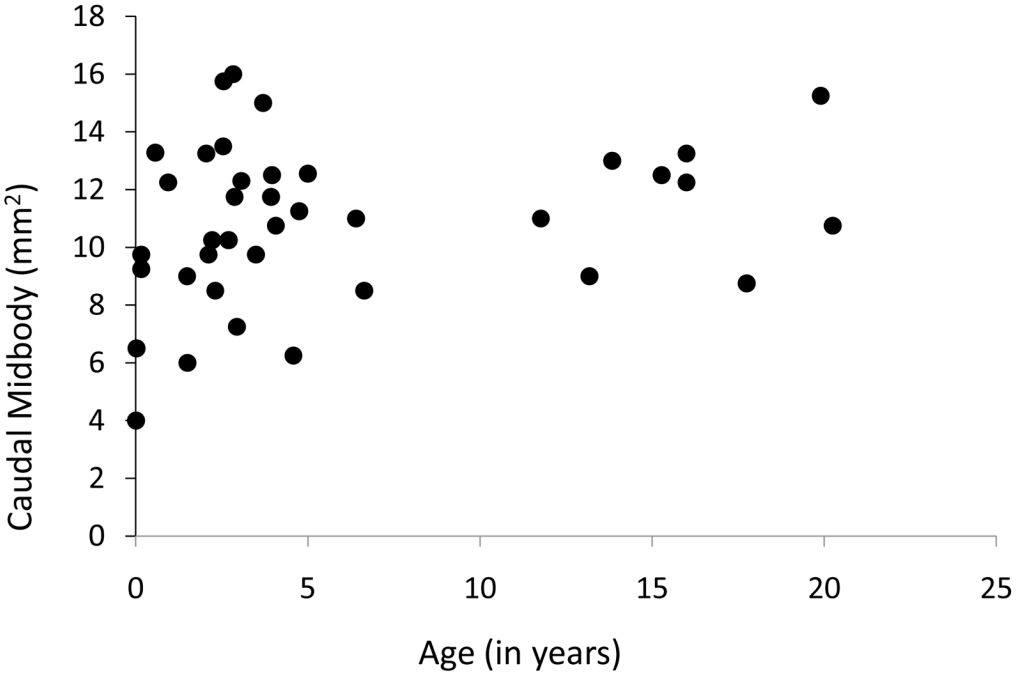

# Figure 4b



# Figure 4c




# Figure 4d



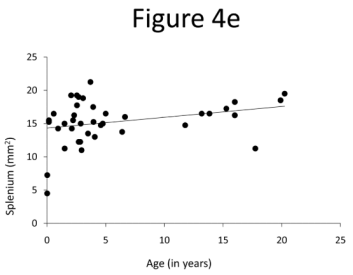



**Figure 4.**

Figures 4a–e. Growth trajectories of CC subdivisions in a sample of capuchin monkeys from 4 days – 27 years: (a) genu, (b) rostral midbody, (c) medial midbody, (d) caudal midbody, and (e) splenium.