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### Publication Details

Brain Research

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### Repository Citation

Phillips, K. A., Sobieski, C. A., Gilbert, V. R., Chiappini-Williamson, C., Sherwood, C. C., Strick, P. L. (2010). The development of the basal ganglia in Capuchin monkeys (*Cebus apella*). *Brain Research*, 1329, 82-88. doi: 10.1016/j.brainres.2010.03.017

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Published in final edited form as:

Brain Res. 2010 May 6; 1329: 82–88. doi:10.1016/j.brainres.2010.03.017.

## The Development of the Basal Ganglia in Capuchin Monkeys (*Cebus apella*)

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### Abstract

The basal ganglia are subcortical structures involved in the planning, initiation and regulation of movement as well as a variety of non-motor, cognitive and affective functions. Capuchin monkeys share several important characteristics of development with humans, including a prolonged infancy and juvenile period, a long lifespan, and complex manipulative abilities. This makes capuchins important comparative models for understanding age-related neuroanatomical changes in these structures. Here we report developmental volumetric data on the three subdivisions of the basal ganglia, the caudate, putamen and globus pallidus in brown capuchin monkeys (*Cebus apella*). Based on a cross-sectional sample, we describe brain development in 28 brown capuchin monkeys (male  $n = 17$ , female  $n = 11$ ; age range = 2 months – 20 years) using high-resolution structural MRI. We found that the raw volumes of the putamen and caudate varied significantly with age, decreasing in volume from birth through early adulthood. Notably, developmental changes did not differ between sexes. Because these observed developmental patterns are similar to humans, our results suggest that capuchin monkeys may be useful animal models for investigating neurodevelopmental disorders of the basal ganglia.

### Keywords

brain development; basal ganglia; *Cebus*

### 1. Introduction

The basal ganglia are subcortical nuclei originally thought to be involved solely in the control of movement, based on their extensive projections to the primary and supplementary motor cortex via the ventral anterior and ventral lateral nuclei of the thalamus. This view has been challenged as the cortical targets of basal ganglia output have been found to include

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regions that include premotor and prefrontal cortex, inferotemporal cortex, and posterior parietal cortex (Clower et al., 2005; Middleton and Strick, 1996, 2002). Thus, outputs of these structures are not only involved in the planning, initiation and regulation of movement but also in a variety of non-motor, cognitive functions such as working memory, visual perception and attention switching (Akkal et al., 2007; Middleton and Strick, 1996).

Besides their involvement in motor-based disorders including Parkinson's disease and Huntington's chorea, the basal ganglia have been implicated in a variety of non-motor, neurodevelopmental disorders including obsessive-compulsive disorder, schizophrenia, and ADHD (Attention Deficit Hyperactivity Disorder). Because the basal ganglia arbitrates and selects among potential action plans generated by the cortex (Redgrave et al., 1999), dysfunction of these structures results in excessive involuntary movement (as in chorea), excessive involuntary thought (as in obsessive-compulsive disorder), or failure in selective attention (as in ADHD). As the basal ganglia are believed to be affected in neurodevelopmental disorders such as autism, schizophrenia (Mamah et al. 2007), and ADHD (Silk et al., 2009; Qiu et al., 2009), understanding the normal development of these brain structures provides a necessary frame of reference.

Several structural imaging studies have charted the developmental trajectory of subcortical regions of the human brain, including the basal ganglia (Giedd et al., 1996; Giedd et al., 1999; Reiss et al., 1996; Sowell et al., 1999; Sowell et al., 2003). In humans, the caudate nucleus, putamen, and globus pallidus have been shown to decrease in volume between 4 and 18 years of age (Jernigan et al., 1991, Giedd et al., 1996). Furthermore, using voxel-based morphometry, Sowell et al (1999) reported reductions in gray matter density in the striatum in post-adolescence. Sex differences have been reported in the development of these nuclei as well, with males showing significant decreases in the volume of the caudate nucleus and putamen after controlling for total cerebral volume, whereas females do not (Giedd et al., 1996). This sexual dimorphism in development may be related to the organizational effects of hormones, environmental influences, or a combination of both. For example, studies of individuals with Turner's Syndrome suggest involvement of the X chromosome and the sex hormones estrogen and progesterone in the development and aging of the striatum (Cutter et al., 2006; Murphy et al., 1993). Males with ADHD show volumetric and shape differences in the basal ganglia whereas females with ADHD do not. Additionally, boys with ADHD show smaller left basal ganglia volumes of the caudate nucleus and putamen, and smaller right basal ganglia volumes in the putamen and globus pallidus (Qiu et al 2009).

As nonhuman primates share several important characteristics of development with humans, including a prolonged infancy and juvenile period, long lifespan, and complex social behavior, they are ideal models for investigating developmental psychopathology (Nelson and Winslow, 2008) and are likely to further our understanding of neurodevelopmental disorders, psychiatric conditions and disease (Dawson et al., 2000). Capuchin monkeys have independently evolved several behavioral and anatomical characteristics in common with humans and chimpanzees – including complex manipulative abilities, the use of tools in the wild (Phillips 1998, Fragaszy et al. 2004) and the use of precision grips (Costello and Fragaszy 1988, Spinozzi et al. 2004). In addition, capuchins possess multiple premotor areas in the frontal lobe (Dum and Strick, 2005), as well as a proprioceptive cortical area 2 and a well-developed cortical area 5, which is associated with motor planning, visually guided reaching, grasping, and manipulation (Padberg et al., 2007). While numerous studies have investigated the behavioral development of such dextrous actions in capuchins, very limited data are available on the concomitant development of neural structures associated with these actions. Our previous study of normative brain development in capuchin monkeys indicated that this species undergoes significant postnatal growth of the neocortex. In particular,

neocortical development is characterized by rapid growth of white matter volume during the first few years of life, especially in the frontal lobes (Phillips and Sherwood, 2008). As the basal ganglia function in both complex cognitive and motor acts, understanding the development of these nuclei in a primate known for its dextrous abilities may provide an ideal comparative model for disorders of basal ganglia development and function.

## 2. Results

### Raw volumes

Analyses were conducted using MANCOVA to determine the effect of sex and hemisphere on the development of these brain regions while controlling for age. SPSS 16.0 was used to perform all statistical analyses. The covariate age significantly influenced the combined dependent variable (DV), Wilks'  $\Lambda = .49$ ,  $F(3, 19) = 4.82$ ,  $P = .012$ , multivariate partial  $\eta^2 = .50$ . Univariate ANOVA results indicated the raw volumes of the putamen ( $F(1, 24) = 4.71$ ,  $P = .04$ ,  $\eta^2 = .16$ ) and caudate ( $F(1, 24) = 4.64$ ,  $P = .043$ ,  $\eta^2 = .24$ ), were significantly affected by the covariate age. The globus pallidus did not show any age-related changes in raw volume. There were no effects of the variables sex or hemisphere.

We used  $F$  tests to determine whether linear or quadratic models best fit the developmental change in these regions (Phillips and Sherwood 2008; Pujol et al. 1993; Rauch and Jinkins 1994). A quadratic trajectory best explained the developmental change observed in the putamen (linear component,  $R^2 = .20$ ,  $F(1, 27) = 6.43$ ,  $P = .018$ ; quadratic component,  $R^2 = .27$ ,  $F(2, 27) = 4.56$ ,  $P = .02$ ). Developmental changes in the caudate were similarly explained by linear and quadratic trajectories (linear component,  $R^2 = .27$ ,  $F(1, 27) = 9.52$ ,  $P = .005$ ; quadratic component,  $R^2 = .27$ ,  $F(2, 27) = 4.58$ ,  $P = .02$ ). These best-fit parameters were used to generate the growth curves illustrated in Figures 2a (putamen) and 2b (caudate). Notably, the globus pallidus did not display significant age-related changes in raw volume (Figure 2c).

As the putamen and caudate showed significant age-related change, we next examined age-related changes in these structures just during the period from birth to sexual maturity (5 years) to determine whether developmental changes during this time period correspond to developmental patterns of humans. The putamen showed significant change, both as change in raw volume and as percentage of total brain volume (raw volume: quadratic component,  $R^2 = .47$ ,  $F(2, 14) = 5.82$ ,  $P = .02$ ; percentage of total brain volume: cubic component,  $R^2 = .52$ ,  $F(3, 12) = 4.32$ ,  $P = .03$ ). The caudate did not display significant change during this period and was best explained by a linear trajectory ( $R^2 = .2$ ,  $F(1, 15) = 3.88$ ,  $P = .07$ ).

### Relative volumes

We also conducted similar analyses for the basal ganglia nuclei as a percentage of total brain volume. The covariate age significantly influenced the combined DV, Pillai's Trace'  $\Lambda = .48$ ,  $F(3, 19) = 5.82$ ,  $P = .005$ , multivariate partial  $\eta^2 = .50$ . Univariate ANOVA results indicated the relative volume of the putamen ( $F(1, 24) = 5.81$ ,  $P = .03$ ,  $\eta^2 = .16$ ) and caudate ( $F(1, 24) = 4.99$ ,  $P = .04$ ,  $\eta^2 = .17$ ) were significantly affected by the covariate age. The relative volume of the globus pallidus did not display age-related change. There were no effects of the variables sex or hemisphere. The developmental change observed in the relative volumes of the putamen and caudate were best explained by linear models (relative volume of putamen: linear component,  $R^2 = .13$ ,  $F(1, 27) = 3.11$ ,  $P = .065$ ; quadratic component,  $R^2 = .18$ ,  $F(2, 27) = 7.60$ ,  $P = .003$ ; relative volume of caudate: linear component,  $R^2 = .13$ ,  $F(1, 27) = 3.99$ ,  $P = .056$ ). Growth curves were generated using the best-fit parameters and are illustrated in Figures 3a (putamen) and 3b (caudate). Data for the globus pallidus are presented for comparison (Figure 3c).

### 3. Discussion

Our data indicate that the putamen and caudate in capuchin monkeys show significant age-related change and that these changes are similar to the development of these basal ganglia nuclei in humans.

In the putamen, both the raw volume and the percentage of the total brain volume decrease from birth through early adulthood, followed by a slight increase in volume during later adulthood. The developmental changes seen in the putamen differ from humans during later adulthood in that, in humans, the putamen continues to decline with aging (Gunning-Dixon et al., 1998). The caudate in our capuchin monkey sample declined in volume throughout development. These observed changes in the caudate are consistent with reports of age-related changes seen in these structures in both humans and rhesus monkeys (Giedd et al., 1996; Jernigan et al., 1991, Lacreuse et al., 2005; Matochick et al., 2000; Raz et al., 2003). In contrast, no age-related changes were detected in the globus pallidus – which is somewhat inconsistent with studies of humans. In particular, Gunning-Dixon and colleagues (1998) reported that human males, but not females, display a significant age-related decline in globus pallidus volume. While it may appear then that the development of the globus pallidus in capuchin monkeys is similar to human females, this conclusion could be biased by the uneven sampling of male and female adults in this study.

The relative volumes of these basal ganglia nuclei in capuchins are similar to relative volumes for rhesus monkeys (*Macaca mulatta*, Knickmeyer et al., 2010). Both capuchin and rhesus monkeys show greater relative volumes of these nuclei than do humans, where the mean relative volumes for adults are caudate: 0.77; putamen: 0.82; globus pallidus: 0.21 (N. Raz, personal communication). The proportions of basal ganglia are much lower in humans due to the expansion of neocortex.

Despite the significant developmental change we observed, two limitations of this study are important to note. First, the sample consisted predominantly of animals from birth – 6 years (around the time of sexual maturity). Our data then best provide information as to early life-span development of these structures. In that context, the developmental change seen in the putamen corresponds well with developmental change seen in this structure in humans. Secondly, while our imaging protocol provided high-resolution brain images, for three adult subjects we were unable to reliably trace the globus pallidus. Thus, the removal of these data points from analyses may have reduced our ability to discern aging-related changes in the globus pallidus.

We did not detect sex differences in the development of any of these basal ganglia subdivisions. Whether humans show such differences is unclear. Although Giedd et al. (1996) reported sex differences in the growth trajectories of the basal ganglia in humans, with only males showing declines in putamen volume during the late adolescent period, others have not (Sowell et al., 2002). However, the present sample was unbalanced with respect to age and sex, as most of the younger animals were male while most of the older animals were female. Thus, whether or not capuchin monkeys display sex differences in the development of these structures remains unclear.

Maturation of these structures is an important factor in cognitive and motor development due to their interconnections to frontal areas including the primary motor cortex, supplementary motor area, and prefrontal cortex (Doyon et al., 2009; Leh et al., 2007; Lehericy et al., 2004). An examination of the developmental changes observed in relation to our previous data on frontal lobe white matter (Phillips & Sherwood, 2008) from birth through 5 years (early adulthood) in capuchin monkeys indicates that the volume of the putamen declines in size concurrently with sharp increases in the volume of frontal lobe

white matter. This is a similar pattern to that observed in humans. The development of frontostriatal circuitry in humans, as measured histologically and via brain imaging, shows that synaptic pruning and myelination of prefrontal fibers occur during this time period (Huttenlocher, 1979; Paus et al., 2001; Sowell et al., 1999; Yakovlev and Lecours, 1967). Accordingly, cognitive control, including memory and attention-related processes, develop slowly throughout the late juvenile and adolescent period (Giedd et al., 2008). Abnormal frontostriatal structure and function has been linked with neurodevelopmental disorders such as ADHD (Casey et al., 2007; Castellanos et al., 1996). While an integrated study of cognitive and motor skill development in relation to basal ganglia structures and frontostriatal connections is lacking (in both humans and capuchin monkeys), such longitudinal data would further inform our understanding of normative brain development and developmental neuropathology.

The pattern of overall brain development in this species appears similar to humans, particularly in the frontal lobe (Phillips and Sherwood, 2008) and in the basal ganglia subdivisions of the putamen and caudate nucleus, making capuchin monkeys a key species for such comparative investigation. A thorough understanding of capuchin brain development from birth through old age is essential for understanding the emergence of complex cognitive and motor skills in this intelligent primate species.

## 4. Experimental procedure

### Subjects

*In vivo* magnetic resonance images were collected from 28 capuchin monkeys (*Cebus apella*; male  $n = 17$ , female  $n = 11$ ) ranging in age from 2 months – 20 years. Of the total subjects, 12 were adults ( $\geq 5$  years; male  $n = 4$ , female  $n = 8$ ) and 16 were juveniles (between 2 months – 5 years; male  $n = 13$ , female  $n = 3$ ). Subjects were housed at Hiram College (Hiram, Ohio), Northeastern Ohio Universities College of Medicine (Rootstown, Ohio), the College of Wooster (Wooster, Ohio), or the University of Pittsburgh (Pittsburgh, Pennsylvania). The MRI scanning protocol was approved by the Institutional Animal Care and Use Committee at each institution.

### MRI Acquisition Procedure

Capuchins were transported to the Brain Imaging Research Center in Pittsburgh, Pennsylvania for the MRI procedure. Once at the facility, subjects were initially immobilized with one of two drug cocktails: a) ketamine (7 mg/kg) injection IM, medetomidine (.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 SQ. An intravenous catheter was then placed in the saphenous vein. Subjects were given a bolus of propofol (2 – 5 mg/kg) intravenously; a constant intravenous drip (250 – 350  $\mu\text{g}/\text{kg}/\text{min}$ ) maintained anaesthesia. Subjects were 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.

All subjects were scanned on the same Siemens 3T Allegra Scanner. Sagittal T1-weighted 3D MPRAGE MR images were acquired through the entire brain using a TR = 1,500 ms and TE = 3.04 ms with no echo-train. Scan acquisition time was approximately 30 min. For each monkey the number of signals averaged three. Slices were obtained as 0.5-mm thick contiguous slices with a matrix size of  $256 \times 256$  and a field of view of  $128 \text{ mm} \times 128 \text{ mm}$ , resulting in a final voxel size of  $0.5 \text{ mm} \times 0.5 \text{ mm} \times 0.5 \text{ mm}$ . Between 100 and 120

contiguous slices were obtained for each subject. Prior to morphometric analysis, data were converted into the ANALYZE 3D volume file format to facilitate reslicing into orthogonal planes. Computer files for individual monkeys were numerically coded prior to measurement to prevent observer bias.

### Image Quantification Method

The archived MRI data were transferred to a PC running Analyze 8.0 (Mayo Foundation for Medical Education and Research, Lenexa, Kansas) software and ImageJ 1.26t (<http://rsb.info.nih.gov/ij/>) for post-image processing. Images were spatially realigned into standard anatomical orientation with the transaxial plane parallel to the anterior commissure – posterior commissure line and perpendicular to the interhemispheric fissure. All volumetric and surface area measures were conducted on the raw image series, with no warping or registration to a template.

Measures of putamen, globus pallidus, and caudate nucleus were performed using ImageJ from horizontal sections, using a rhesus monkey atlas for guidance (Saleem & Logothetis, 2007; Figure 1). The putamen was measured in every other section beginning where there was clear separation of the putamen from surrounding structures and continuing until the structure could no longer be seen next to the caudate nucleus. The caudate nucleus was measured beginning at the point of complete separation of the caudate head from the putamen as the anterior horn of the lateral ventricle enters, picking up the body as the atrium of the lateral ventricle enters and continuing until the structure could no longer be seen next to the body of the lateral ventricle. The nucleus accumbens does not appear separated from the putamen whereas the caudate nucleus does; therefore the ventral border was determined to be where the caudate completely separated from the putamen (according to Saleem and Logothetis, 2007). Measurement of the globus pallidus was started as soon as the structure appeared along the medial border of the posterior edge of the putamen and continued until it could no longer be seen at the medial border of the anterior edge of the putamen. All basal ganglia nuclei included were measured in both the left and the right hemispheres separately. There were three subjects from whom measurement of the globus pallidus proved unreliable; thus these data were excluded from analyses. Inter-rater agreement (between KAP and CCW) was 92%.

Total brain volume measures were completed in Analyze, using the Cavalieri method for estimation of volume. For Cavalieri estimates of volume, most within-subject variance in a structure can be captured in 8 to 10 systematic-random sections regardless of the irregularity of the structure (Mouton, 2002). Increasing the number of sections sampled only leads to minor increases in the precision of the estimate. Thus, the Cavalieri method is an efficient tool for measuring volume without bias. To determine total brain volume, we measured every 8th slice from the parasagittal series. This yielded, on average, 12.1 slices that were measured per individual to calculate total brain volume. In each slice, voxels representing gray matter, white matter, and ventricular space were identified and separated from the skull using manual segmentation. The entirety of the cerebral hemispheres, cerebellum, midbrain, brainstem, and ventricles were included in the measurement of brain volume, following protocols described in a previous study of nonhuman primate brains (Sherwood et al., 2004). The volume corresponding to these voxels was calculated for each slice and multiplied by the interslice distance to obtain the whole brain volume. Total brain volume was measured so that the raw volume measures of the basal ganglia could be adjusted to relative volume measures.

## Acknowledgments

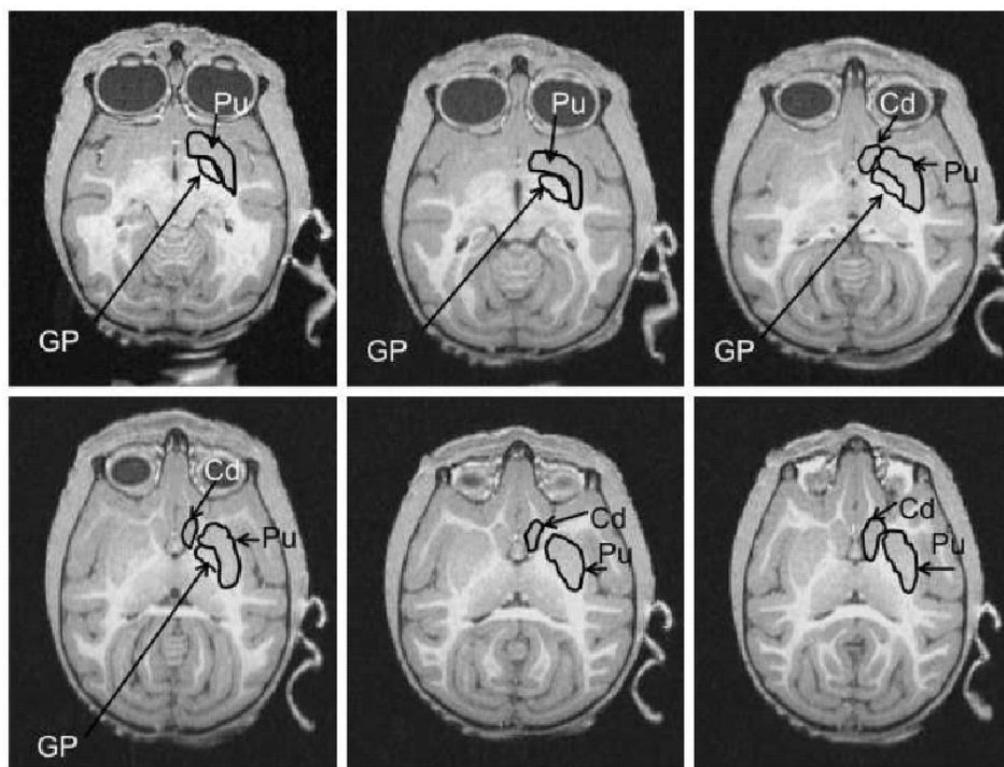
This work was supported by the National Science Foundation [BCS-0515484 (CCS), BCS-0549117 (CCS), BCS-0827531 (CCS), DGE-0801634 (CCS)], National Institutes of Health [NS42867 (CCS); NS24328; (PLS) MH056661 (PLS)], Wenner-Gren Foundation for Anthropological Research (CCS), James S. McDonnell Foundation [22002078 (CCS)], and Office of Research and Development, Medical Research Service, Department of Veterans Affairs (PLS).

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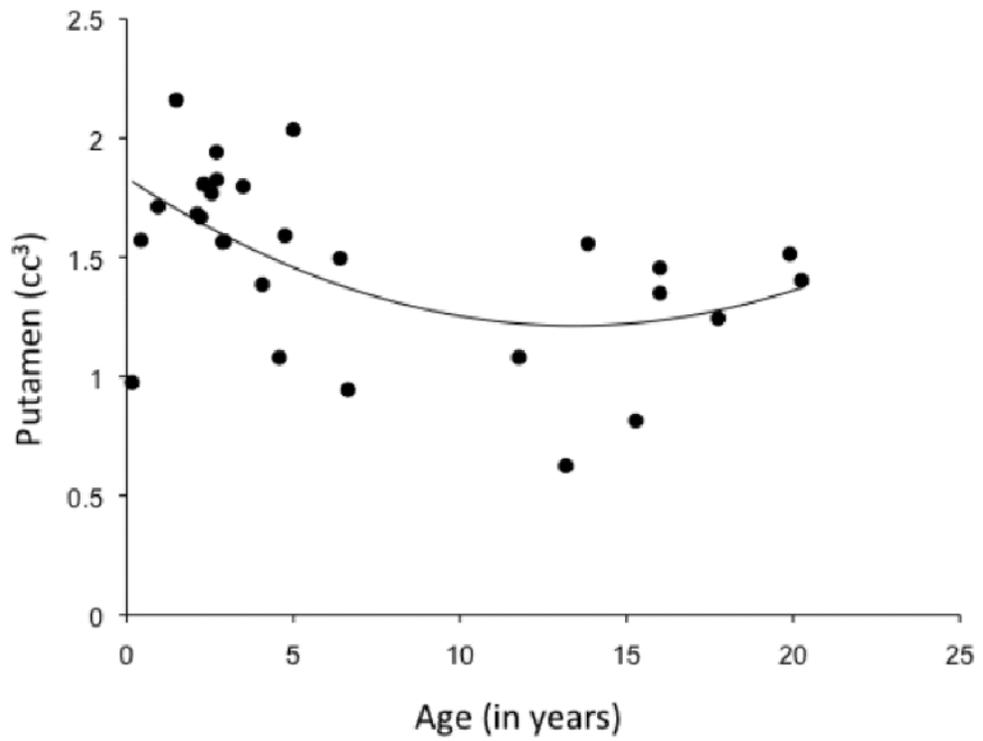
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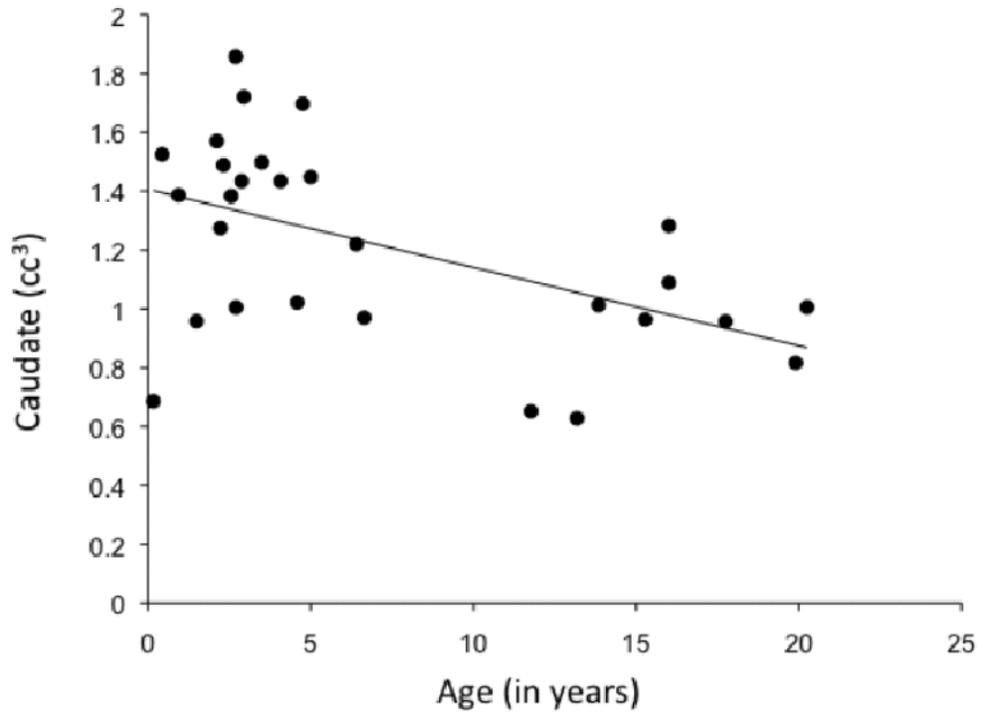


**Figure 1.** Serial sections from capuchin monkey MRI showing basal ganglia. Pu = putamen; GP = globus pallidus; Cd = caudate nucleus.

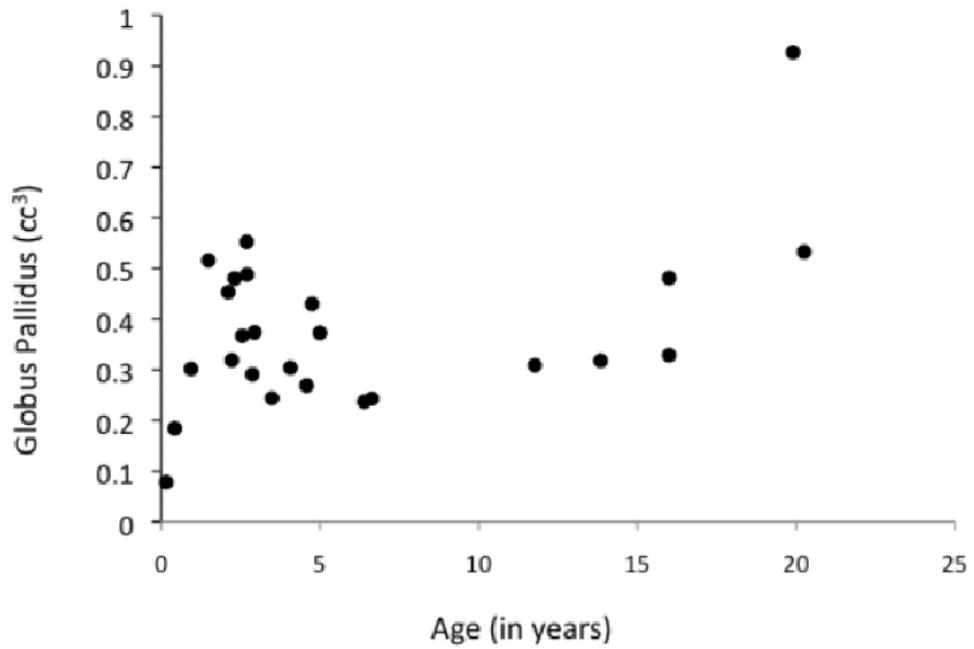
# Figure 2a



# Figure 2b



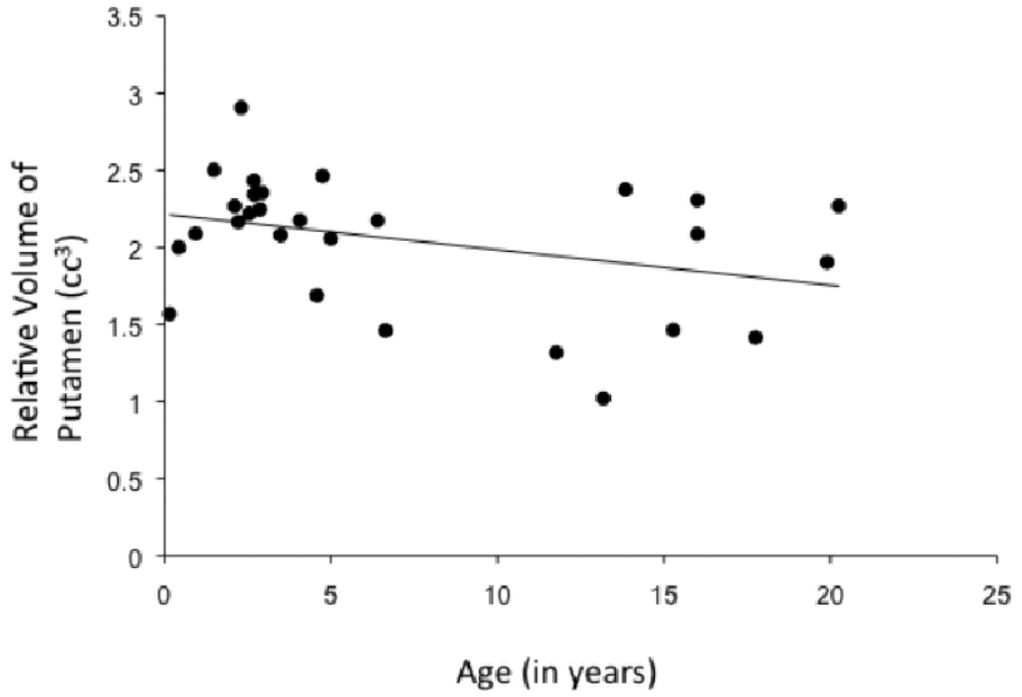
# Figure 2c



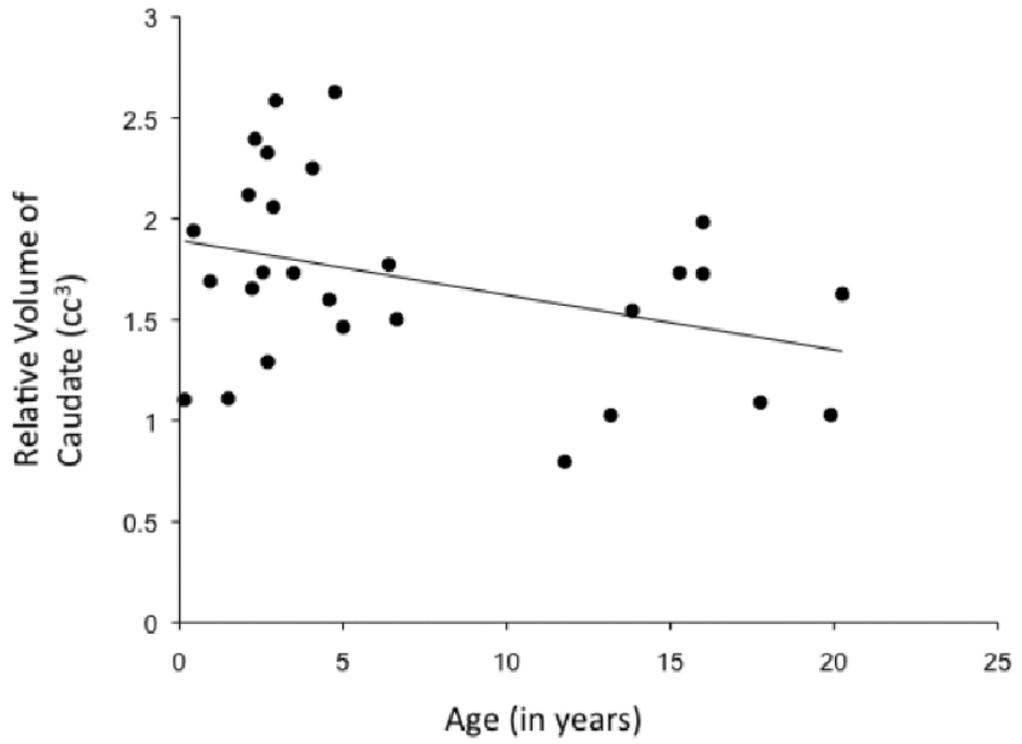
**Figure 2.**

Scatterplots representing age effects for the raw volumes of the basal ganglia: a) putamen, b) caudate nucleus, and c) globus pallidus.

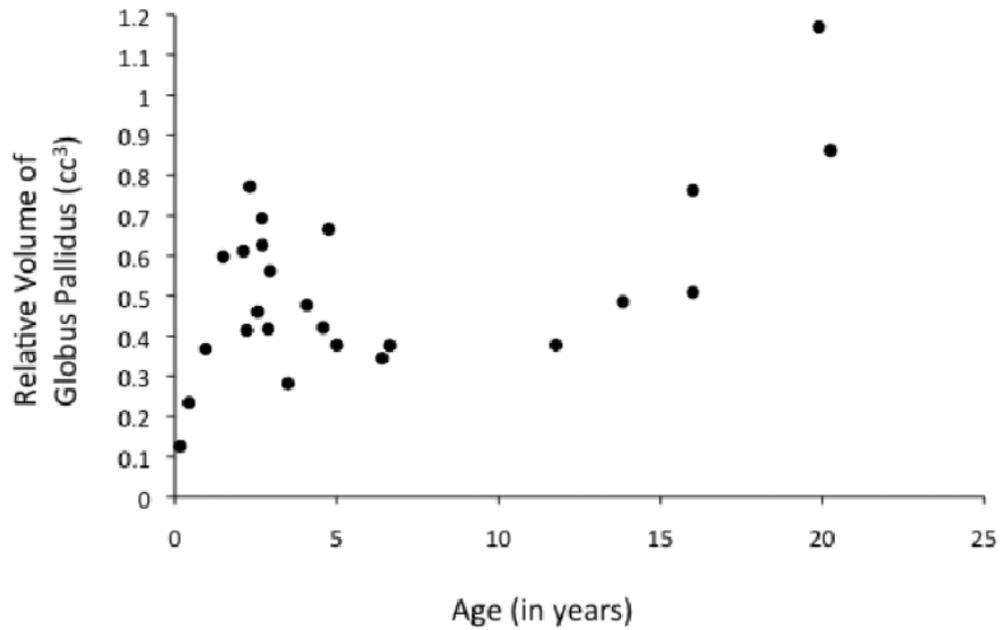
# Figure 3a



# Figure 3b



# Figure 3c



**Figure 3.** Scatterplots representing age effects for the volume of the basal ganglia as a percentage of total brain volume: a) putamen, b) caudate nucleus, and c) globus pallidus.