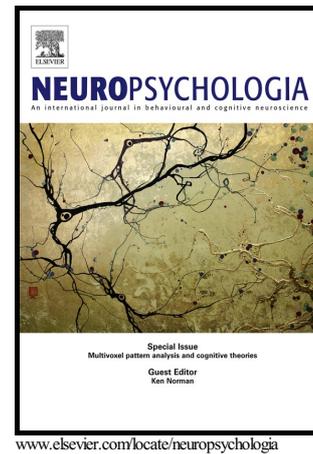


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Sex Differences in the Relationship between Planum Temporale Asymmetry and Corpus
Callosum Morphology in Chimpanzees (*Pan troglodytes*): A Combined MRI and DTI
Analysis

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Abstract

Increases brain size has been hypothesized to be inversely associated with the expression of behavioral and brain asymmetries within and between species. We tested this hypothesis by analyzing the relation between asymmetries in the planum temporale (PT) and different measures of the corpus callosum (CC) including surface area, streamline count as measured from diffusion tensor imaging, fractional anisotropy values and the ratio in the number of fibers to surface area in a sample of chimpanzees. We found that chimpanzees with larger PT asymmetries in absolute terms had smaller CC surface areas, fewer streamlines and a smaller ratio of fibers to surface area. These results were largely specific to male but not female chimpanzees. Our results partially support the hypothesis that brain asymmetries are linked to variation in corpus callosum morphology, although these associations may be sex-dependent.

Keywords: Corpus callosum; Planum temporale; Brain Asymmetry; Primates

Introduction

The corpus callosum (CC) is the major white matter tract connecting the left and right cerebral hemispheres (Pandya & Seltzer, 1986; Tomasch, 1954). The size of the CC, after adjustment for brain size, has been hypothesized to play a role in both within- and between-species variation in behavioral and brain asymmetries (Hanggi, Fovenyi, Liem, Meyer, & Jancke, 2014; Jancke & Steinmetz, 1996). Specifically, comparative studies have shown that the size of the CC did not keep pace with changes in total brain size during mammalian and, specifically primate evolution (Oliveras, Montiel, & Aboitiz,

2001; Rilling & Insel, 1999). That is to say, as brain size increased, the size of the CC did not keep pace and therefore animals with larger brains have relatively small CC surface areas. The consequence of a smaller CC surface area is that the interhemispheric transmission time between homotopically connected regions increases which places constraints on interhemispheric synchronization and transmission time (Aboitiz, Lopez, & Monitel, 2003; Ringo, Doty, Demeter, & Simard, 1994). Thus, over evolutionary time, there was selection for increased intra- rather than interhemispheric connectivity in primate brains (Hopkins & Cantalupo, 2008; Rilling & Insel, 1999). A similar argument has been made with respect to individual differences in brain asymmetry in relation to CC size within species, notably humans. For instance, Hanggi et al. have hypothesized that the ratio of inter- to intra-hemispheric connectivity is inversely associated with brain size in humans. Further, several studies have shown that individual differences in either anatomical or functional asymmetries are inversely correlated with adjusted corpus callosum size or fiber number (see Nowicka & Tacikowski, 2011 for review).

In the current study, we examined the relationship between individual variation in asymmetries in the planum temporale (PT) and variation in CC surface area in a sample of chimpanzees. The PT is the flat bank of tissue that lies posterior to Heschl's gyrus and overlaps with Wernicke's area, a region historically linked to speech comprehension, among other functions (Dorsaint-Pierre, et al., 2006; Galaburda, 1984; Galaburda, Corsiglia, Rosen, & Sherman, 1987; Galaburda & Sanides, 1980; Goulven & Tzourio-mazoyer, 2004; Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; Shapleske, Rossell, Woodruff, & David, 1999; Vadlamudi, et al., 2006; Xu, et al., 2006). Numerous studies in humans have shown that the PT, at least when measured using region of interest

approaches, is larger in the left compared to right hemisphere in typically developing individuals (Knaus, Bollich, Corey, Lemen, & Foundas, 2006; Shapleske, et al., 1999; Sommer, Aleman, Somers, Boks, & Kahn, 2008).

Studies in the past 15 to 20 years have shown that chimpanzees, like humans, also show a leftward asymmetry in the surface area of the PT when measured from post-mortem brains (Gannon, Holloway, Broadfield, & Braun, 1998; Gilissen, 2001), *in vivo* MRI scans (Hopkins & Nir, 2010) and cytoarchitecturally (Spociter, et al., 2010). Further, Hopkins, et al. (2012) have recently found in a sample of 20 post-mortem brains that surface area asymmetries in the PT were inversely associated with axon streamline counts in the corpus callosum. Thus, subjects with larger asymmetries had fewer fibers traversing the corpus callosum. Specifically, overall, more lateralized subjects had fewer fibers in the central midbody of the CC. Further, when separate analyses were performed in males and females, a significant negative association was found between absolute PT asymmetries and the isthmus in males while a significant positive association was found in females.

Rather than use post-mortem material, in this study, we examined the association between PT asymmetries and CC morphology using two different *in vivo* methods. First, as has been done in many studies with human and nonhuman primate subjects, we computed the surface area of the CC from T1-weighted MRI scans. We also calculated the total brain volume and computed the adjusted sizes of each CC region. These data were then regressed on directional and absolute PT asymmetries in a sample of > 200 chimpanzees. In addition, we also scanned a sample of 57 chimpanzees using diffusion tensor imaging (Phillips & Hopkins, 2012) and computed three measures of CC integrity

including (a) raw streamline counts (b) mean fractional anisotropy and (c) the ratio of number of streamline counts to surface area (i.e., fiber density) using similar to those used in previous studies with humans and chimpanzees (Hofer & Frahm, 2006; Hofer, Merbolt, Tammer, & Frahm, 2007; Phillips, Schaeffer, Barrett, & Hopkins, 2013; Phillips, Schaeffer, & Hopkins, 2013). Though the methods are difficult to compare, by quantifying streamline counts and their density from DTI, we sought to approximate the methods typically used in post-mortem material. That is, although only a crude approximation, computing streamline counts and their density were intended to assess whether a similar pattern of sex-specific asymmetries between PT asymmetry and CC streamline count from post-mortem brains would also be similarly found when using DTI.

Finally, we tested for the effect of handedness and sex on CC morphology and PT asymmetry. Though this was not the main focus of the study, these analyses seemed appropriate given the large and extant literature on this topic in the human neuropsychological literature (Aboitz, Scheibel, Fisher, & Zaidel, 1992; Ardekani, Figarsky, & Sidtis, 2013; Cherbuin, et al., 2013; Clarke & Zaidel, 1994; Dorion, et al., 2000; Driesen & Raz, 1995; Gurd, et al., 2013; Jancke & Steinmetz, 1996; Luders, et al., 2010; Welcome, et al., 2009; Westerhausen, et al., 2004). Based on the existing theories, if handedness and sex are linked to variation in the CC, then we hypothesized that left or ambidextrous chimpanzees would have larger CC surface areas, higher streamline counts and FA values than right-handed apes. Additionally, we hypothesized that, after adjustment for brain size, females would have larger CC surface areas, higher streamline counts and FA values than males.

Methods

Subjects

PT and CC surface area measurements were made on 223 captive chimpanzees including 131 females and 92 males. The chimpanzee ranged in age from 6 to 52 years of age (*Mean* = 25.72 years, *s.e.* = .719). The chimpanzees were housed at two research facilities including the Yerkes National Primate Research Center (YNPRC, *n* = 81) and The University of Texas MD Anderson Cancer Center (UTMDACC, *n* = 142). Within the entire sample, hand preference data were available on 213 chimpanzees including 52 left-handed (28 females, 24 males), 59 ambidextrous (35 females, 24 males) and 102 right-handed individuals (61 females, 41 males). Thus, assessing the effects of handedness and sex on both PT asymmetries and CC morphology were based on a slightly smaller sample of subjects. Handedness was determined based on data published in Hopkins, Gardner, Mingle, Reamer, and Schapiro (2013). Each chimpanzee was tested on 4 handedness tasks including measures of tool-use, simple reaching, coordinated bimanual actions and hand use for manual gestures. For each task, a handedness index (HI) was determined based on the frequency in left and right hand use following the formula [$HI = (R - L) / (R + L)$]. Positive values indicated right hand preferences and negative values indicated left hand biases. Based on the sign of the HI score, chimpanzees were classified as left or right preference and assigned a weighted value of 0 or 1. We then added the weighted scores across the 4 measures resulting in an overall handedness score ranging from 0 (always left) to 4 (always right). To simplify the analyses and to increase statistical power, we classified subjects with an overall hand preference score of 0 or 1 as left-handed, subjects with a score of 2 as ambidextrous and

chimpanzees with a score of 3 or 4 as right-handed. The sample of chimpanzees for the DTI analyses included 37 females and 21 males, all of whom were housed at the YNPRC. This sample ranged in age from 15 to 44 years ($Mean = 18.88$ years, $s.e. = 1.24$). Handedness data were available for the entire sample and included 10 left-handed, 17 ambidextrous and 31 right-handed individuals.

Magnetic Resonance Image Collection

All chimpanzees were scanned *in vivo* during one of their scheduled annual physical examinations. Magnetic resonance image (MRI) scans followed standard procedures at the YNPRC and UTMDACC and were designed to minimize stress. Thus, the animals were first sedated with ketamine (10 mg/kg) or telazol (3-5mg/kg) and were subsequently anaesthetized with propofol (40-60 mg/kg/h). They were then transported to the MRI scanning facility and placed in a supine position in the scanner with their head in a human-head coil. Upon completion of the MRI, chimpanzees were briefly singly-housed for 2-24 hours to permit close monitoring and safe recovery from the anesthesia prior to return to the home social group. All procedures were approved by the Institutional Animal Care and Use Committees at YNPRC and UTMDACC and also followed the guidelines of the Institute of Medicine on the use of chimpanzees in research.

For the structural MRI scans, 75 chimpanzees were imaged using a 3.0 Tesla scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania, USA). T1-weighted images were collected using a three-dimensional gradient echo sequence (pulse repetition = 2300 ms, echo time = 4.4 ms, number of signals

averaged = 3, matrix size = 320 x 320, with 0.6 x 0.6 x 0.6 resolution). The remaining chimpanzees were scanned using a 1.5T G.E. echo-speed Horizon LX MR scanner (GE Medical Systems, Milwaukee, WI). T1-weighted images were collected in the transverse plane using a gradient echo protocol (pulse repetition = 19.0 ms, echo time = 8.5 ms, number of signals averaged = 8, matrix size = 256 x 256, with 0.7 x 0.7 x 1.2 resolution).

For the DTI scans, the chimpanzees were imaged using a 3.0 Tesla scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania, USA). Two sets of whole brain diffusion-weighted data with a single-shot EPI sequence with a b value of 1000 s/mm² with 60 diffusion directions were acquired; plus one image without diffusion weighting (b value of 0 s/mm²). Data were acquired transaxially (FOV = 243 x 243) using 42 contiguous slices with no gap that covers the entire brain with resolution of 1.9 X 1.9 X 1.9 mm. Averages of two sets of diffusion-weighted data were collected per subject with phase-encoding directions of opposite polarity (left - right) to correct for susceptibility distortion. Initial preprocessing for images were performed using The Oxford Center for Functional Magnetic Resonance Imaging (FMRIB) software, FSL (www.fmrib.ox.ac.uk/fsl). Preprocessing included reorientation, removal of non-brain tissue, and correction for head motion and eddy current distortion (FDT). DTIFIT was performed for fitting of diffusion tensors at each voxel to create fractional anisotropy (FA) maps for each subject. The processed were then registered to the subjects individual T1-weighted MRI scan (see below).

Region of Interest Tracing

Planum temporale (PT)

The structural MRI scans were processed using the software program ANALYZE 11.0. The raw scans were initially realigned in the AC-PC axis and then outputted as a volume in 1 mm isotropic voxels in the axial, coronal and sagittal planes. The PT was traced primarily in the coronal plane using a 3D view that allowed simultaneous viewing of anatomical landmarks in the axial and sagittal planes. The exact methods and interrater reliability measurements have been described in detail elsewhere (Hopkins & Nir, 2010). Briefly, in the coronal plane, we identified the first slice in which the inferior limb of the insular sulcus was no longer visible (see Figure 1). This was the anterior border of the PT. On each coronal slice, using the line tool within ANALYZE, we measured the flat surface of the sylvian fissure (in mm) from the surface of the cortex to its most medial termination point. This was done all successive 1 mm images moving posteriorly until the termination of the sylvian fissure (i.e., it was no longer visible). If the sylvian fissure bifurcated into ascending and descending limbs, we followed the descending limb until its termination point. When completed, we summed the surface area across all slices within the left and right hemispheres to create a total surface area (mm²).

Corpus Callosum (CC)

We used a very straightforward method for determining the surface areas of the corpus callosum (Figure 2). The images were initially aligned along the AC-PC axis

in order to standardize the scans in the same orientation. In the sagittal plane, we found the image that corresponded to the longitudinal or interhemispheric fissure. Using the mouse-driven pointer, the entire CC was traced in the sagittal plane. When completed, we then used the grid tool in ANALYZE and selected a one row X 5 column split of the CC. This divided the entire CC region into 5 discrete regions and created object maps that approximated those previously used in chimpanzees and other species including the genu, anterior midbody, central midbody, isthmus and splenium, respectively. The surface area (in mm²) of each region was computed using the sample option tool in ANALYZE. The total CC surface (mm²) area was computed by summing the individual surface areas for each of the 5 CC regions. The object maps for each CC region were saved for later use with the DTI images. Note that in this study, we portioned the CC into 5 rather than 6 or 7 sections with the chimpanzee scans in this study (Clarke & Zaidel, 1994; Hofer, et al., 2007; Witelson, 1989). We used this approach because in a previous DTI study, Phillips and Hopkins (2012) found that 5 sets of distinct fibers accounted for a majority of homo- and heterotopic termination in anterior and posterior cortex in chimpanzees.

Image Registration and DTI Analysis

The main focus of the DTI analysis was to compute the streamline counts and mean fractional anisotropic (FA) values for each CC region. To accomplish this aim, we used the Fiber Assignment by Continuous Tracking (FACT) function within the DTI module in ANALYZE 11.0. The preprocessed and DTIFIT volumes were imported into the DTI function within the ANALYZE toolbox. The b-vector or

gradient direction files for the individual subjects were imported into the program and the images were subsequently manually thresholded to remove any signal from the background or outside of the brain. The “compute DTI maps” function was then selected within the DTI program leading to the creation of FA and other maps. To calculate the streamline count and FA values, we then selected the Fiber Tracking function in ANALYZE and loaded the CC object map that was drawn on the T1-weighted scan for each subject. We then selected the compute fibers option and recorded the number of fibers and the mean FA of the tracts for each CC region. The start and stop FA threshold values were set to .2, the angle stop threshold was 60 and the fiber length threshold was 1 mm. Recall that the voxel dimensions of the MRI and DTI scans were not the same; thus, before we applied the CC object maps to the DTI scans, we linearly registered the MRI and the accompanying object maps to the DTI scans thereby placing the two volumes and the CC object maps in the same stereotaxic space.

Data Analysis

PT directional asymmetries were computed following the formula $[AQ = ((R - L) / (R + L) * .5)]$ where R and L represent the surface areas of the right and left hemisphere, respectively. Negative AQ values indicated leftward biases and positive values represented rightward asymmetries. The absolute PT asymmetry (ABS_PT) was computed by taking the absolute value of the PT AQ score. The ABS_PT scores represented how lateralized the PT was for each individual chimpanzee independent of the direction of their PT asymmetry. Following the methods of Smith (2005), we adjusted

the surface area measures for each CC region for overall brain size. For this data transformation, the square root of the surface areas for the total CC as well as each of the 5 regions were divided by the cube root of the total brain volume. Brain volumes were based on the total gray and white matter for each hemisphere and excluded CSF as well as the cerebellum and brain stem regions. The streamline count and FA values for the overall CC and each CC region were computed directly from the output of the DTI module within ANALYZE 11.0. We also attempted to estimate the number of fibers per unit of surface area (FC:SA) in the CC by dividing the total streamline count for each region by the surface area of that region (e.g., Genu streamline count / Genu surface area). All the data were analyzed using inferential and non-parametric statistics depending on the scale of measurement of the dependent variable and whether the data met the assumption of normality and homogeneity of variance. Post hoc analyses, when necessary, were performed using Tukey's Honestly Significant Difference tests. Alpha was set to $p < .05$, two-tailed test.

Results

Planum Temporale

A one sample t -test of the AQ scores revealed a significant leftward asymmetry in the PT $t(222)=-9.59, p = .001$ as did a chi-square goodness of fit test based on the PT classification data $X^2=(2, N = 223)=147.91, p = .001$. The number of chimpanzees with a left-biased PT asymmetry was significantly higher than the number of individuals classified as right-based $X^2=(1, N = 202)=66.61, p = .001$ or having no bias $X^2=(1, N = 180)=105.80, p = .001$. The mean AQ scores and the distribution of PT asymmetries are

shown in Table 1. We next examined the effect of sex and handedness on PT asymmetry. Because the PT AQ data were not normally distributed, we used chi-square tests of independence to assess the independent effects of sex and handedness in the PT classification. No significant associations were found between either sex or handedness on the distribution of PT asymmetries.

We also examined the effect of handedness and sex on the ABS_PT scores using an analysis of variance. We found a significant two-way interaction between sex and handedness $F(2, 206)=4.26, p = .015$. Post hoc analysis indicated that there was no significant difference in ABS_PT scores among left-handed male ($Mean\ ABS_PT = .163$, $s.e. = .033$) and female ($Mean\ ABS_PT = .197$, $s.e. = .030$) chimpanzees. For ambidextrous chimpanzees, females had significantly higher ABS_PT scores ($Mean\ ABS_PT = .235$, $s.e. = .027$) than males ($Mean\ ABS_PT = .134$, $s.e. = .033$). In contrast, in right handed chimpanzees, males had significantly higher ABS_PT scores ($Mean\ ABS_PT = .220$, $s.e. = .024$) than females ($Mean\ ABS_PT = .168$, $s.e. = .020$). Thus, no sex or handedness effects were found in directional asymmetries in the PT but these factors did influence the magnitude of asymmetries.

Sex and Handedness Effects on CC Morphology

We next examined the effect of sex and handedness in CC morphology. For this analysis, we used a mixed model ANCOVA with CC region serving as the repeated measure while sex and handedness served as between group factors. Age at the time of the MRI scanning was the covariate. Neither sex nor handedness had a significant effect on overall or region specific CC morphology; however, the covariate, age, was

significant as a main effect $F(1, 196)=16.22, p = .001$ and as an interaction term with CC region $F(4, 784)=2.83, p = .022$. To further explore the relationship between age and the overall and region specific CC surface area, we performed a trend analysis for each region regressing the surface area CC adjusted size on age. We attempted to fit a linear and quadratic equation for each analysis. The results are shown in Table 2. We largely found significant positive associations between age and CC morphology with older subjects having larger CC surface areas; however for both the anterior and central midbody, we found significant quadratic associations found between and the CC surface area and age. In these regions, older and young subjects had relatively smaller CC surface areas compared to middle aged individuals.

PT Asymmetry and CC Morphology

In the next set of analyses, we examined the associations between PT AQ and ABS_PT scores and variation in the CC surface areas. We computed partial correlation coefficients, adjusting for age, between the PT AQ and ABS_PT scores and the overall and region specific variation in CC size. The results are show in Table 3. For the entire sample, small but significant associations were found between PT AQ scores and the genu and central midbody scores. Thus, subjects with more rightward asymmetries had larger CC regions. When the analyses were separated by sex, significant associations were found only in males. PT AQ scores were positively correlated with all CC regions except the splenium while the ABS_PT scores were negatively associated with all the CC regions except the splenium. Thus, male chimpanzees with more right PT asymmetries had larger CC surface areas. Conversely, males with larger absolute asymmetries had smaller CC surface areas. To test whether the partial correlation coefficients differed

significantly between males and females, we performed independent *z*-tests and these findings are also shown in Table 3. The associations between CC morphology, PT AQ and ABS_PT scores differed significantly between males and females for the overall surface area as well as the for the genu, anterior midbody, and central midbody.

Diffusion Tensor Imaging: Sex and Handedness Effects

As with the CC surface area data, we initially examined the influence of sex and handedness in variability in streamline counts, FA values and the FC:SA ratio in three separate mixed model analyses of variance. Sex and handedness were between group factors while the fiber, FA values and FC:SA ratio values for each CC region were the repeated measures in each analysis. No significant main effects or interactions were found for the FA values; however, for the streamline count $F(4, 200)=13.30, p = .001$ and FC:SA count ratio measures $F(4, 200)=7.65, p = .001$, significant main effects for CC region were found. The mean streamline count and FA:SC for each CC region are shown in Figures 3 and 4. Post hoc analysis of the streamline count data showed that the number of fibers in the splenium was significantly higher than all other regions. Further, the number of fibers in the anterior midbody was significantly higher than in the central midbody and isthmus. For the FC:SA measure, post hoc analysis indicated that the mean values for the genu were significantly lower than all other regions. Additionally, the mean FC:SA value for the anterior midbody was significantly larger than the splenium. None of the other means differed significantly from each other.

DTI and PT Asymmetry

Lastly, as we did with the surface area measures, we performed partial correlation coefficients (controlling for age) between PT AQ and ABS_PT scores and the streamline count, FA and FC:SA ratio measures for the overall sample and the male and female chimpanzees separately. The results are shown in Table 4. As with the surface area measure, to test whether the partial correlation coefficients differed significantly between males and females, we performed independent *z*-tests and these findings are also shown in Table 4. The associations between the DTI measures, PT AQ and ABS_PT scores differed significantly between males and females particularly for the streamline counts and the FC:SA ratio measures.

Discussion

Consistent with previous studies in post-mortem (Gannon, et al., 1998; Gilissen, 2001; Spocter, et al., 2010) and *in vivo* (Hopkins & Nir, 2010) scans, the results of this study showed that chimpanzees exhibit a population-level leftward asymmetry in the planum temporale. Neither sex nor handedness was associated with individual variation in directional asymmetries in the PT. The evidence of robust leftward bias in the PT suggests that this particular dimension of brain asymmetry has a strong evolutionary foundation in humans and chimpanzees (Hopkins, 2013). Previous studies suggest that population-level asymmetries in the surface area of the PT are not present in more distantly related Old World monkey primates (Gannon, Kheck, & Hof, 2008; Heilbronner & Holloway, 1988; Heilbronner & Holloway, 1989; Lyn, et al., 2011) and therefore this may be recently evolved trait.

In terms of the surface area, streamline counts, FA values or FC:SA ratio measures of the CC, we found no overall sex or handedness effects. The lack of significant effects for handedness differs from previous reports in chimpanzees (Hopkins & Phillips, 2010) and capuchin monkeys (Phillips, Sherwood, & Lilak, 2007). One potential explanation for this discrepancy in findings is because in this study, we characterized handedness based on their preference on 4 different tasks. In contrast, in the previous studies with chimpanzees, the apes were classified as left-, ambiguously- or right-handed based on *z*-scores applied to raw frequencies in hand use for a single measure (the TUBE task). Similarly, in the paper by Phillips, et al. (2007) handedness was characterized on the basis of their hand preference for the TUBE task. We chose to characterize hand preferences using data from multiple tasks in this study because this is the more common means of assessing handedness in humans and, thereby increasing the external validity of our work to previous and allowing better comparisons to previous reports of hand and sex effect on CC morphology in humans. Additionally, by characterizing handedness from multiple measures, we were able to define a group of chimpanzees that would truly be considered ambidextrous. Ambidexterity is defined as inconsistent hand preferences across multiple tasks, whereas ambiguously-handed subjects are those that do not show consistent hand preferences on the same task (Soper & Satz, 1989). The previous studies reporting associations between handedness and the TUBE task all had subjects that were ambiguously-handed whereas studies in human subjects typically have a cohort of ambidextrous individuals.

For the DTI data, we found significant main effects for CC region for both raw streamline counts and the FC:SA ratio; however, the patterns were different between

these two measures. The highest streamline counts were found in the splenium, genu and anterior midbody which largely correspond to the regions with the largest surface areas. Thus, it should not be surprising to find more fibers in regions with a larger surface area. However, for the FC:SA measure, the regions with the fewest fibers per unit surface area were the genu and splenium while the highest regions were the anterior midbody, central midbody and isthmus. In many ways, these data resemble the distribution and density of larger fiber diameter axons in the CC from human and nonhuman primates (see Figure 4). Specifically, larger diameter fibers have greater myelination and therefore increased speed of neural transmission compared to smaller, less myelinated axons. Studies have shown that there is a higher ratio of large to small diameter axons in the central regions of the CC compared to the genu and splenium in primates (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Hopkins, et al., 2012; Innocenti, Caminiti, & P.R., 2010; Pandya & Seltzer, 1986) and this presumably reflects the need for increased interhemispheric transfer times connecting primary sensory and motor cortex compared to association cortex. More recently, it has been reported that the distribution of large diameter axons are particularly prevalent in motor regions of the CC in humans and chimpanzees compared to macaques and that this has pronounced impacts on interhemispheric transfer time between species (Caminiti, Ghaziri, Galuske, Hof, & Innocenti, 2009).

When considering the overall association between PT asymmetry and corpus callosum morphology, we found small but significant positive correlations between the PT asymmetry and not the ABS_PT scores in relation to CC surface area, streamline count and FC:SA ratio scores. For the CC surface area and streamline count data, the

associations were significant for the genu and central midbody while for the FC:SA measure, the association was with the isthmus. For all three analyses, subjects with greater rightward asymmetries in the PT had higher CC values. Thus, our initial hypothesis of an association between directional PT asymmetries and CC morphology were supported, albeit the effects sizes were small. However, when considering the findings from the separate analyses of male and female data, the pattern of results and interpretation is quite different.

Specifically, a unique finding of this study was the sex specific associations between PT asymmetry and the CC surface area, streamline count and FC:SA ratio. Recall that no sex differences were found for CC morphology, streamline count, FA values or FC:SA ratio measures or in the PT asymmetry measures. However, when separate correlations were performed on males and females, the associations between PT and ABS_PT asymmetries were significant for a number of CC regions and measures but for the males only. In brief, more rightward PT asymmetries were associated with larger CC surface areas, streamline counts and FC:SA ratio measures. In contrast, significant negative associations were found between the ABS_PT measure and the CC surface areas, streamline counts and FC:SA measures. Thus, in males, both hypotheses regarding the predicted association between CC morphology and brain asymmetry were supported. The fact we found opposite correlations for the PT AQ and ABS_PT scores with the CC regions is due to the fact that the chimpanzees showed a significant leftward asymmetry in the PT. Thus, chimpanzees that didn't show a leftward asymmetry were closer to a value of zero for their AQ score rather than having a larger, positive AQ value. In short, if most of the distribution of a set of AQ scores lies below a value of zero, then being less

lateralized is equivalent to being less left lateralized. Because the sign is removed in the ABS_PT measure, it changes the direction of the correlation coefficient. This finding highlights an important consideration in assessing the relationship between behavioral or brain asymmetry and CC morphology. Notably, the distribution of the AQ scores for any brain measure will influence both the predicted findings and hypotheses. For measures of asymmetry that are not skewed leftward or rightward, the use absolute asymmetries scores will likely better predict variation in CC morphology. In contrast, for skewed measures, the directional biases may better predictors of CC morphology.

The findings that the association between CC morphology and PT asymmetry differs between males and females, of course, leads to the question of what biological mechanisms might underlie these effects. Sex hormones have been a central focus of studies of gender differences in behavioral and brain asymmetries as well as corpus callosum morphology in humans (Clements, et al., 2006; Hausmann, et al., 1998; Ide, Rodriguez, Zaidel, & Aboitiz, 1996; Ingallhalikar, et al., in press; Kimura, 1999; Luders & Toga, 2010; Moffat, Hampson, Wickett, Vernon, & Lee, 1997; Papadatou-Pastou, Martin, Munafò, & Jones, 2008; Rabi, Madhavi, Antonisamy, & Koshi, 2007; Sommer, et al., 2008; Wallentin, 2009). However, it is difficult to isolate the explicit role of steroids from experiential factors on laterality, particularly in humans (Rogers, 2014). In nonhuman animals, studies primarily in rats have reported sex differences in asymmetry as well as CC morphology and these differences be experimentally altered by manipulating pre- and post-natal hormones (Denenberg & Yutzey, 1985; Fitch, Berrebi, Cowell, Schrott, & Denenberg, 1990; Mack, Boehm, Berrebi, & Denenberg, 1995). However, the relevance of these studies to the findings reported here are not clear

because we did not find sex differences in either PT asymmetry or CC morphology per se but rather in the associations between these two brain measures. One possibility, though purely speculative, is that the organizational effects of testosterone early in life for males has a direct or indirect canalizing effect on the emergence of brain asymmetries and allows for less plasticity in nervous system development. Another possibility, as proposed by Geschwind and Galaburda (1985), is that testosterone early in life has an inhibitory effect on the growth rate of the left hemisphere and thereby induces a more robust asymmetry in the brain that results in increased intra- and reduced interhemispheric connectivity in males compared to females (Rosen, Sherman, & Galaburda, 1989). Notwithstanding the potential mechanisms, it is worth noting that the differences in correlation coefficients between the sexes were all moderate to large effects and were fairly consistent across the different methods used to characterize the corpus callosum (size, streamline count, FA values, and fiber density). Thus, the sex specific associations between PT asymmetry and CC morphology appear to be fairly robust, which is consistent with at least one other report in humans (Aboitz, et al., 1992). The results reported here are also consistent with the previous finding on the association between PT asymmetry and streamline counts within the CC in chimpanzee post-mortem brains (Hopkins, et al., 2012).

There are several limitations to this study. First, we focused on a single measure of neuroanatomical asymmetry in relation to variation in the composition of the corpus callosum. The extent to which the pattern of results reported here are evident for other measures of neuroanatomical or behavioral asymmetry is unclear. Second, we quantified streamline counts from different regions of the CC and correlated these with an

independent measure of the PT, as means of approximating the approach we have previously used with post-mortem materials. Arguably, a more direct approach would have been to use tractography of all fibers that directly connected the left and right PT via transcallosal projections through the corpus callosum. Third, although we estimated streamline counts and FA values in the CC based on ROIs drawn on the midsagittal slice, there are other more sophisticated approaches that could be employed to assess intra- and interhemispheric integrity in the chimpanzees. For instance, assessing white matter and functional connectivity between homologous regions anatomically defined in the left and right hemispheres may provide a more precise measurement of interhemispheric connectivity (Ingalhalikar, et al., in press; Li, et al., 2014).

Lastly, one curious and to some extent inexplicable finding in this study was the fact that the significant associations found between the PT asymmetry values and the CC surface area were largely evident across all regions (see Table 3) rather than confined solely to more posterior sections, which is presumably where fibers connecting the PT would reside. One possible explanation is that the leftward PT asymmetry, in males, is proxy to a larger set of leftward asymmetries for a variety of anatomical regions including those in more anterior portions of the brain. Assuming that greater rightward asymmetries in all regions are associated with larger CC surface areas, then it follows that asymmetries from any one specific region would be positively associated with CC surface areas for most of not all CC regions. Alternatively, it may be the case that surface area measures are simply not sensitive enough to detect smaller, more subtle associations in CC morphology while perhaps DTI measure of streamlines or post-mortem measures of fiber number or density might be better. In the case of this study,

the associations between PT asymmetry and CC streamline counts were more specific to the isthmus and splenium, which support this interpretation.

In summary, the data reported here show that PT asymmetries are associated with the surface area, streamline count, and fiber density of the corpus callosum in chimpanzees, particularly in males. These findings are consistent with the theory that larger brain asymmetries are associated with decreased interhemispheric connectivity. The extent to which these associations are evident for measures of brain asymmetries in other cortical regions and in other species remains to be tested in future studies. These data would prove useful in determining the extent to which the association between cortical asymmetries and interhemispheric connectivity represents a general principle in primate brain evolution or a unique adaptation in certain species, including humans (Hanggi, et al., 2014).

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Fig. 1: a. 3D rendering of chimpanzee brain. Red vertical lines indicate virtual slices from the posterior superior temporal gyrus. Images 1 to 6 represent coronal views of the tracing of the PT from more anterior to posterior images. Distance between successive slices is 4 mm. b. 3D rendering of the flat surface area of the PT after traced in the coronal plane.

Fig. 2: Midsagittal view of the chimpanzee brain with the 5 regions of the corpus callosum outlined and labeled on the image.

Fig. 3: Mean streamline counts (\pm s.e.) for male and female chimpanzees from the FACT analysis of the DTI scans.

Fig. 4: Mean FC:SA ratios (\pm s.e.) for male and female chimpanzees from the FACT analysis of the DTI scans and the surface area measurements from the T1-weighted scans.

Table 1

Descriptive Data on PT Asymmetries in Male and Female Chimpanzees

	#L	#A	#R	Mean AQ	s.e.
<i>Sex</i>					
Males	70	8	14	-.126	.024
Females	89	13	29	-.131	.020
<i>Total</i>	159	21	43	-.129	.013
<i>Handedness</i>					
Left	40	3	9	-.108	.031
Ambidextrous	44	9	6	-.162	.030
Right	68	8	25	-.121	.028
<i>Total</i>	152	20	40	-.129	.013

Table 2

Association between Age and CC Morphology

CC Region	Linear R	F	Quadratic R	F
Total	.281	18.01	.298	2.26
Genu	.256	14.68	.258	0.23
Anterior Midbody	.296	20.21	.323	3.92
Central Midbody	.236	12.40	.269	<u>3.69</u>
Isthmus	.141	4.25	.154	0.80
Splenium	.185	7.43	.202	1.48

Table 3

Partial Correlation Coefficients Between CC Surface Areas and PT AQ and ABS_PT Scores for the Overall Sample and Males and Females Separately

	Overall		Females		Males		PT AQ	ABS_PT
	AQ	ABS_PT	AQ	ABS_PT	AQ	ABS_PT	M vs F z-score	M vs F z-score
Total	.112	-.068	-.041	.075	.309*	-.264+	<u>-2.54</u>	2.43
Genu	.149+	-.111	-.036	.048	.341*	-.279+	<u>-2.75</u>	2.36
Anterior Midbody	.126	-.079	.044	.049	.247+	-.270+	-1.47	2.29
Central Midbody	.138+	-.038	-.007	.112	.321*	-.238+	-2.39	2.50
Isthmus	.111	-.084	.028	-.028	.228+	-.213+	-1.44	1.33
Splenium	-.015	.000	-.119	.079	.119	-.115	-1.68	1.37

+ $p < .05$, * $p < .01$. **Bolded** values without ($p < .05$) or with an **underline** ($p < .01$) indicate significant sex difference in the correlation coefficients.

Table 4

Partial Correlation Coefficients Between Streamline counts, FA and FC:SA Ratio DTI Measures for each CC Region and PT AQ and ABS_PT Scores for the Overall Sample and Males and Females Separately

	Overall		Females		Males		PT AQ		ABS_PT	
	AQ	ABS_PT	AQ	ABS_PT	AQ	ABS_PT	M vs F	z-score	M vs F	z-score
Streamline count										
Total	.112	-.068	.052	.063	.523+	-.610*	-1.81		<u>2.65</u>	
Genu	.149+	-.111	.074	-.071	.337	-.570*	-0.95		<u>1.98</u>	
Anterior Midbody	.126	-.079	.062	.080	.338	-.486+	-0.99		<u>2.10</u>	
Central Midbody	.138+	-.038	-.115	.218	.399	-.347	-1.85		<u>2.00</u>	
Isthmus	.111	-.084	.189	-.130	.535+	-.501+	-1.39		1.44	
Splenium	-.015	.000	.018	.144	.649*	-.510+	<u>-2.59</u>		<u>2.43</u>	
FA										
Total	-.053	.123	-.136	.238	.193	-.204	-1.15		1.54	
Genu	.049	.027	-.076	.142	.422	-.321	-1.81		1.63	
Anterior Midbody	-.082	.190	-.088	.224	-.018	.070	-0.24		0.61	
Central Midbody	-.110	.189	-.162	.295	.045	-.094	-0.72		1.37	
Isthmus	-.086	.137	-.223	.316	.332	-.406	<u>-1.95</u>		<u>2.60</u>	
Splenium	.020	-.042	.004	-.020	.071	-.119	-0.23		0.34	
FC:SA Ratio										

PT Asymmetry and CC Morphology

Total	.233	-.170	.115	-.016	.448+	-.415	-1.26	1.46
Genu	.159	-.231	.113	-.120	.282	-.496	-0.61	1.45
Anterior Midbody	.150	-.101	.095	.017	.256	-.302	-0.57	1.13
Central Midbody	.069	.007	-.078	.163	.300	-.144	-1.33	1.06
Isthmus	.292+	-.215	.175	-.117	.499+	-.381	-1.05	0.97
Splenium	.251	-.077	.140	.008	.452+	-.134	-1.19	0.49

+ $p < .05$, * $p < .01$. **Bolded** values without ($p < .05$) or with an **underline** ($p < .01$) indicate significant sex difference in the partial correlation coefficients.

Figure Captions

Figure 1: a. 3D rendering of chimpanzee brain. Red vertical lines indicate virtual slices from the posterior superior temporal gyrus. Images 1 to 6 represent coronal views of the tracing of the PT from more anterior to posterior images. Distance between successive slices is 4 mm. b. 3D rendering of the flat surface area of the PT after traced in the coronal plane.

Figure 2: Midsagittal view of the chimpanzee brain with the 5 regions of the corpus callosum outlined and labeled on the image.

Figure 3: Mean streamline counts (+/- s.e.) for male and female chimpanzees from the FACT analysis of the DTI scans.

Figure 4: Mean FC:SA ratios (+/- s.e.) for male and female chimpanzees from the FACT analysis of the DTI scans and the surface area measurements from the T1-weighted scans.

