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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.

1. Introduction

The corpus callosum (CC) is the major white matter tract connecting the left and right cerebral hemispheres(Pandya and 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, and Jancke, 2014; Jancke and 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 et al., 2001; Rilling and 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 et al., 2003; Ringo et al., 1994). Thus, over evolutionary time, there was selection for increased intra- rather than interhemispheric connectivity in primate brains (Hopkins and Cantalupo, 2008; Rilling and 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 and 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 et al., 1987; Galaburda and Sanides, 1980; Goulven and Tzourio-mazoyer, 2004; Josse, Mazoyer, Crivello and Tzourio-Mazoyer, 2003; Shapleske et al., 1999; Vadlamudi et al., 2006; Xu et al., 2006). Numerous studies in

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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 et al., 2006; Shapleske et al., 1999; Sommer et al., 2008).

Studies in the past 15–20 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 et al., 1998; Gilissen, 2001), *in vivo* MRI scans (Hopkins and Nir, 2010) and cytoarchitectonically (Spocter 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 and 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 and Frahm, 2006; Hofer et al., 2007; Phillips et al., 2013a, 2013b). 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 (Aboitiz et al., 1992b; Ardekani et al., 2013; Cherbuin et al., 2013; Clarke and Zaidel, 1994; Dorion et al., 2000; Driesen and Raz, 1995; Gurd et al., 2013; Jancke and 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 then right-handed apes. Additionally, we hypothesized that, after adjustment for brain size, females would large CC surface areas, higher streamline counts and FA values than males.

2. Methods

2.1. 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 females). 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 et al. (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.

2.2. 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 (3–5 mg/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 h 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 T 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=320×320, with $.6\times0.6\times0.6$ resolution). The remaining chimpanzees were scanned using a 1.5 T 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=256×256, with $.7\times0.7\times1.2$ resolution).

For the DTI scans, the chimpanzees were imaged using a 3.0 T 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/mm^2 with 60 diffusion directions were acquired; plus one