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Cite this article: Spocter MA, Sherwood CC, Schapiro SJ, Hopkins WD. 2020 Reproducibility of leftward planum temporale asymmetries in two genetically isolated populations of chimpanzees (*Pan troglodytes*). *Proc. R. Soc. B* **287**: 20201320.
http://dx.doi.org/10.1098/rspb.2020.1320

Received: 9 June 2020
Accepted: 17 August 2020

Subject Category:
Neuroscience and cognition

Subject Areas:
neuroscience, evolution

Keywords:
asymmetry, reproducibility, chimpanzee, planum temporale, heritability

Author for correspondence:
Muhammad A. Spocter
e-mail: muhammad.spocter@dmu.edu

Electronic supplementary material is available online at https://doi.org/10.6084/m9.figshare.c.5104058.

THE ROYAL SOCIETY PUBLISHING

Reproducibility of leftward planum temporale asymmetries in two genetically isolated populations of chimpanzees (*Pan troglodytes*)

Muhammad A. Spocter[1,2], Chet C. Sherwood[3], Steven J. Schapiro[4,5] and William D. Hopkins[4]

[1]Department of Anatomy, Des Moines University, 3200 Grand Avenue, Des Moines, IA 50312, USA
[2]School of Anatomical Sciences, University of Witwatersrand, Johannesburg 2094, South Africa
[3]Department of Anthropology and Center for the Advanced Study of Human Paleobiology, The George Washington University, Washington, DC 20052, USA
[4]Department of Comparative Medicine, UT MD Anderson Cancer Center Bastrop, TX 78602, USA
[5]Department of Experimental Medicine, University of Copenhagen, Copenhagen, Denmark

MAS, 0000-0003-1174-7444; CCS, 0000-0001-6711-449X; SJS, 0000-0001-5406-1739; WDH, 0000-0003-3480-1853

Once considered a hallmark of human uniqueness, brain asymmetry has emerged as a feature shared with several other species, including chimpanzees, one of our closest living relatives. Most notable has been the discovery of asymmetries in homologues of cortical language areas in apes, particularly in the planum temporale (PT), considered a central node of the human language network. Several lines of evidence indicate a role for genetic mechanisms in the emergence of PT asymmetry; however, the genetic determinants of cerebral asymmetries have remained elusive. Studies in humans suggest that there is heritability of brain asymmetries of the PT, but this has not been explored to any extent in chimpanzees. Furthermore, the potential influence of non-genetic factors has raised questions about the reproducibility of earlier observations of PT asymmetry reported in chimpanzees. As such, the present study was aimed at examining both the heritability of phenotypic asymmetries in PT morphology, as well as their reproducibility. Using magnetic resonance imaging, we evaluated morphological asymmetries of PT surface area (mm^2) and mean depth (mm) in captive chimpanzees ($n = 291$) derived from two genetically isolated populations. Our results confirm that chimpanzees exhibit a significant population-level leftward asymmetry for PT surface area, as well as significant heritability in the surface area and mean depth of the PT. These results conclusively demonstrate the existence of a leftward bias in PT asymmetry in chimpanzees and suggest that genetic mechanisms play a key role in the emergence of anatomical asymmetry in this region.

1. Introduction

Ever since the seminal publication of Charles Darwin's *Origin of Species* [1], several lines of comparative evidence have demonstrated the close kinship shared between humans and chimpanzees. The genetic similarities of chimpanzees to humans [2] and the relative shortness of our evolutionary separation [3] indicate that many features of the modern human phenotype have evolutionary roots that pre-date our divergence from the last common ancestor [4]. In this regard, brain asymmetries, particularly those within language-associated areas, have been suggested as a key difference between humans and our nearest ancestors and living relatives [5–7]. While earlier studies seemed to reinforce the assertion of human uniqueness in terms of brain asymmetry [5,8–11], this assumption has been challenged by discoveries of population-level behavioural and neuroanatomical asymmetries in other species (e.g. [12,13]), including

structural asymmetries in primate brains for homologues of areas implicated in human language and speech production among primates (e.g. [14–16]).

One key brain region is the planum temporale (PT) – the bank of cerebral cortex that lies posterior to Heschl's gyrus and considered an integral component of the language network [17–22]. The leftward asymmetry of the PT is the most pronounced and consistently reported asymmetry in the human brain [22,23], and has received considerable attention in relation to language dominance [24–26]. In particular, the surface area of the PT is on average larger in the left hemisphere, which is significant in that it overlaps with Wernicke's area, a key brain region involved in auditory and lexical processing which is associated with functional cerebral lateralization for language. In humans, deviations from normal PT asymmetry are associated with severe deficits in language comprehension and production [25,27–30]. In addition, comparisons of sulcal depth in regions surrounding the PT have also proven useful as markers of neurological dysfunction as well as species-specific morphology, prompting further exploration of PT asymmetry and its functional implications [31–33].

Population-level leftward asymmetry of the PT has been documented in olive baboons, suggesting the emergence of this leftward bias in primates by at least 30–40 Ma [34]. Chimpanzees are also known to have significant leftward asymmetries of the PT, both cytoarchitecturally [35] and morphologically [36–38], and there is some evidence that PT asymmetries are associated with handedness [39].

In humans, asymmetry in the PT as well as surrounding sulci emerges early in development [40–45], indicating a potential role for genetic mechanisms in the emergence of PT asymmetry. However, very few individual genes have so far been implicated in any aspect of lateralization of the human brain [46–49], and the genetic determinants of cerebral asymmetries are unknown and remain elusive [19,50,51]. Studies in humans suggest that there is heritability of brain asymmetries, notably within the PT [52–54], but this issue has not been explored in a wide range of nonhuman primates [55–58] or, to any extent, in our closest living relatives, the chimpanzees.

To this end, we examined the repeatability and heritability of asymmetries in the PT of common chimpanzees. Specifically, *in vivo* and postmortem magnetic resonance imaging (MRI) scans were obtained from two captive chimpanzee populations that are genetically isolated from each other (i.e. the two populations are geographically isolated from one another and there is no gene flow between the two groups), but for whom there are well-documented pedigrees dating back to the founder animals [59]. By measuring PT surface area (mm^2) and the mean sulcal depth (mm) in these two populations, we had a unique opportunity to evaluate the consistency with which PT phenotypic asymmetries could be observed across a variety of non-genetic factors including MRI scanner magnet strength, sex, handedness and rearing history. For example, some have suggested that population-level behavioural asymmetries in nonhuman primates, including chimpanzees, may be influenced by their early handling by right-handed humans [60]. In rodents, there is good evidence that early handling can induce population-level behavioural asymmetries [61]. Within our sample, we had chimpanzee subjects with differing early social rearing experiences with human carers, and this allowed us to test this hypothesis as it relates to PT asymmetries. If early handling experiences by humans influence PT asymmetries, then we hypothesized that apes with more extensive caregiver contact would differ from chimpanzees with less history of human handling. Furthermore, through the use of heritability analyses we explored the proportion of variance in PT asymmetry in chimpanzees associated with genetic factors. We hypothesized that if population-level PT asymmetries are reproducible across chimpanzee populations and under genetic control, then significant leftward biases and heritability would be evident in the surface area and/or sulcal depth of the PT in both cohorts.

2. Material and methods

(a) Subjects

The PT was measured from *in vivo* ($n = 229$) and postmortem ($n = 62$) magnetic resonance images in a sample of 291 chimpanzees (*Pan troglodytes*) housed at two research facilities in North America. One sample included 155 individuals from the National Center for Chimpanzee Care (NCCC), which is part of the University of Texas MD Anderson Cancer Center. The remaining 136 chimpanzees were housed at the Yerkes National Primate Research Center (YNPRC) of Emory University. The entire sample ranged in age from 3 to 52 years at the time of MRI scanning (mean = 27.6, s.d. = 11.0) and included 165 females and 126 males, respectively. Within the entire sample, there were 135 mother-reared (MR), 92 nursery-reared (NR) and 64 wild-caught (WC) chimpanzees.

(b) MRI scanning

Both *in vivo* and postmortem MRI scan data were used in this study [62]. Seventy-seven chimpanzees were scanned using a 3.0 Tesla scanner (Siemens Trio, Siemens Medical Solutions USA, Malvern, Pennsylvania, USA) at YNPRC. 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). Additionally, 139 NCCC and 13 YNPRC chimpanzees were scanned using a 1.5 Tesla Phillips machine (The Netherlands). 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, and a 256 × 256 matrix). Postmortem T2-scans were obtained from 62 chimpanzees that had died from natural causes or were euthanized for humane reasons. For the postmortem scanning, either 4.7 or 7T magnets were used, and T2-weighted images were collected in the transverse plane using a gradient echo protocol (pulse repetition = 22.0 s, echo time = 78.0 ms, number of signals averaged = 8–12, and a 256 × 192 matrix reconstructed to 256 × 256).

(c) Sulci extraction and measurement

The sequence of post-image processing steps performed on the images is shown in figure 1*a–h* and have been described in detail elsewhere [62–64]. The pipeline of processing used to extract the sulci from the raw T1-weighted image derives from a pipeline initially dedicated to the human brain and freely distributed as a BrainVISA (BV) toolbox (http://brainvisa.info) [65]. The pipeline process of extracting the sulci from the cortex involved a number of steps [65] (figure 1*a–h*). The first step was to correct for spatial inhomogeneities in the signal intensity, providing a spatially smooth bias field with a stable distribution of tissue intensities (figure 1*b*). Next, the analysis of the signal histogram and mathematical morphology were performed using an automatic analysis of the voxel intensities for the entire brain to obtain a binary mask of the brain (figure 1*c*). The mask was then split into the left and right hemispheres and the cerebellum (figure 1*d*).

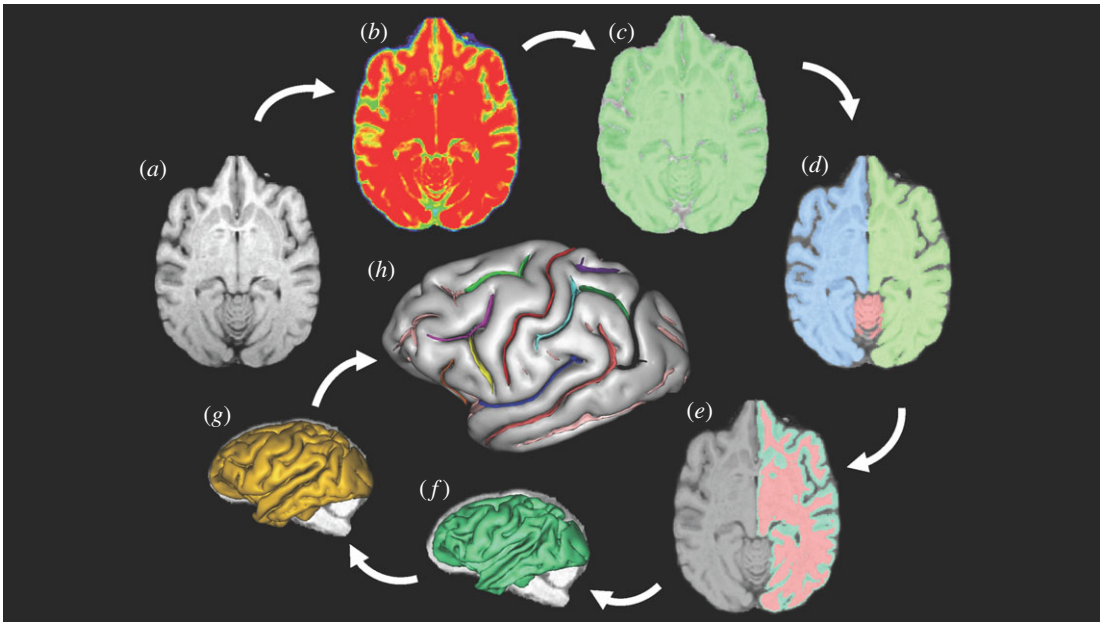

Figure 1. An outline of the image processing pipeline as implemented in BrainVisa. (Online version in colour.)

A negative mould of the white matter was computed from the split-brain mask. The outside boundary of this mould results from a 5 mm morphological closing of the masked hemisphere, filling up the folds. The grey/white interface is the inside boundary that preserves deformations and assures the spherical topology of the mould (figure 1*e*). Finally, the mould was skeletonized to detect cortical folding, while topological constraints guaranteed the resulting surfaces would have no holes [65,66] (figure 1*f*,*g*). The folds making up the sylvian fissure in each hemisphere were selected manually (figure 1*h*) by the user, using a three-dimensional visualization. The sensitivity of the extraction of sulci can be influenced by factors such as the scanner magnet strength; thus, in all analyses, we used scanner magnet as a covariate in order to statistically control for this variable.

As noted above, the sylvian fissure was extracted during the pipeline procedure and manually labelled. To quantify the surface area (mm^2) and mean depth of the PT (mm), we used the sulci editing function in BV. Specifically, the T1 scan and three-dimensional sulci display were opened simultaneously in the viewer window with the cursor visible in both windows (figure 2). On the T1 scan, the image was manipulated and rotated so that it was perfectly aligned in the *x*-, *y*- and *z*-axes, at the exact point at which the inferior limb of the insula was no longer visible in the anterior–posterior plane. When clicking with the mouse on this exact location, it would simultaneously display the anterior border of the PT in the sagittal plane. Using the scissors tool, we then section the sylvian fissure from its most medial to lateral point on the surface, which separated the sylvian fissure into that portion belonging to the PT and the remaining anterior region (figure 2). Using the labelling tool in BV, we then labelled the PT region and saved the image file for subsequent quantification of the PT surface area (mm^2) and mean depth (mm) for each hemisphere.

(d) Heritability analyses

Consistent with our and others' previous work, to estimate heritability we used the software package SOLAR [67]. SOLAR uses a variance component approach to estimate the polygenic component of variance when considering the entire pedigree [64,68–71]. We used SOLAR to determine heritability in the average surface area and average depth for each sulcus by adding the left and right hemisphere values and dividing by two. For all heritability analyses, scanner strength (1.5T, 3T and 4.7T/7T), sex, age, rearing group and colony served as covariates in the analyses. To examine lateralization, an asymmetry quotient (AQ) was calculated using the equation $|(\text{right}-\text{left})/[(\text{right}+\text{left})/2]|$. Positive values indicate a right greater than left asymmetry and negative values indicate a left greater than right asymmetry. We also classified subjects as left-lateralized (≤ -0.025), right-lateralized (≥ 0.025) or having no bias (more than -0.0249 and less than 0.0249) using cutpoints based on their AQ values.

3. Results

(a) Descriptive data on planum temporale asymmetry

Consistent with previous reports, using one sample *t*-tests on the AQ values, we found significant population-level leftward asymmetries for PT surface area ($t_{290} = -9.083$, $p < 0.001$) and mean sulcal depth ($t_{290} = -5.521$, $p < 0.001$) in the total sample, and these results were significant when analysed separately within the three samples of chimpanzees that were scanned at different magnet strengths. Detailed results from these analyses are provided in the electronic supplementary material, table S1.

For descriptive purposes, we also report the percentage of chimpanzees that were classified as having a left, right or no bias (based on the AQ cut points) in PT surface area and mean depth asymmetry (figure 3*a*,*b* and electronic supplementary material, table S3). For each measure, the percentage of chimpanzees classified left, right and no bias in PT asymmetry is shown across scanner magnet strength, rearing history, sex and chimpanzee colony. These data corroborate the consistency in leftward biases within each scanner magnet cohort. Chi-square tests of independence revealed that significantly more chimpanzees were classified as left-lateralized compared to right and no bias for both PT surface area $\chi^2(2,\ n = 291) = 159.28,\ p < 0.001$ and mean sulcal depth $\chi^2(2,\ n = 291) = 63.27,\ p < 0.001$ and, like the mean AQ values, the distribution of lateralization was consistent across the brains scanned at different magnet strengths (figure 3).

We also tested for consistency in PT asymmetries between chimpanzee populations, sexes and rearing groups using a multivariate analysis of covariance. The AQ values for the

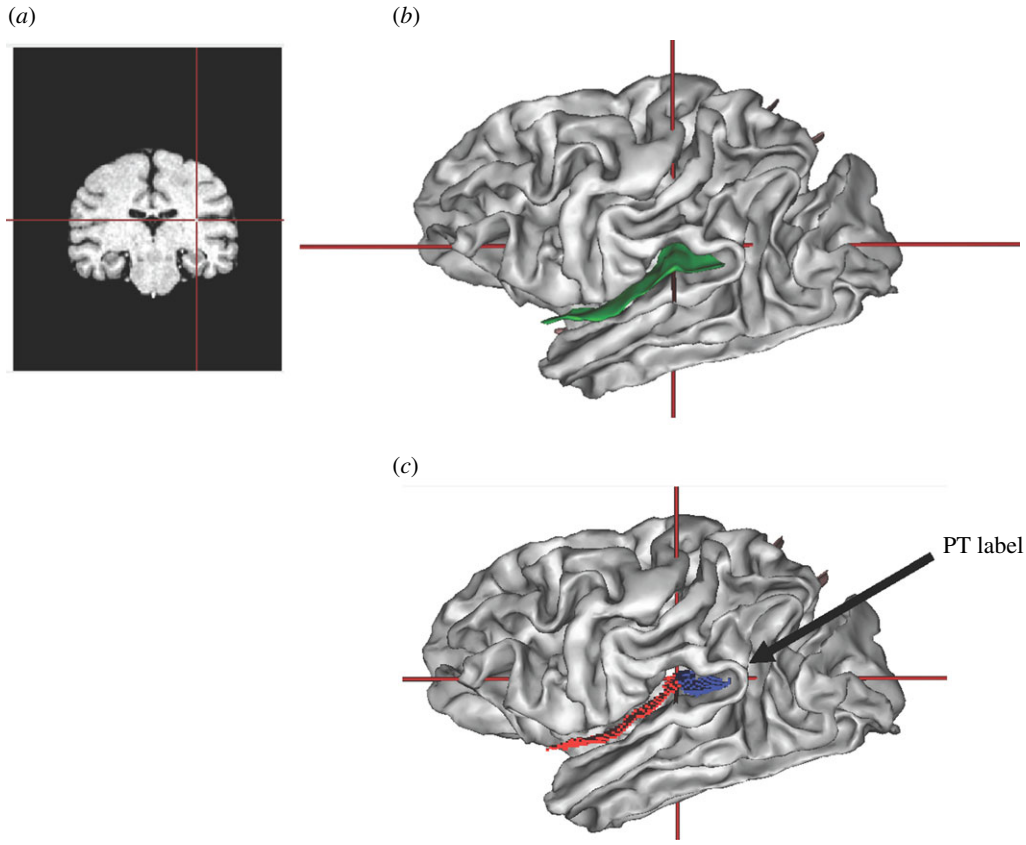

Figure 2. (*a*) Coronal view of T1 can and (*b*) lateral view of the three-dimensional brain with the Sylvian fissure outlined in green. Note that the cross bars in each image reflect the location of the point of closure of the inferior limb of the insula, which served as the anterior border to define the PT. (*c*) Lateral view of the three-dimensional brain showing the division of the Sylvian fissure into the anterior (red) and posterior (blue) regions after using the scissors to bifurcate the fold. (Online version in colour.)

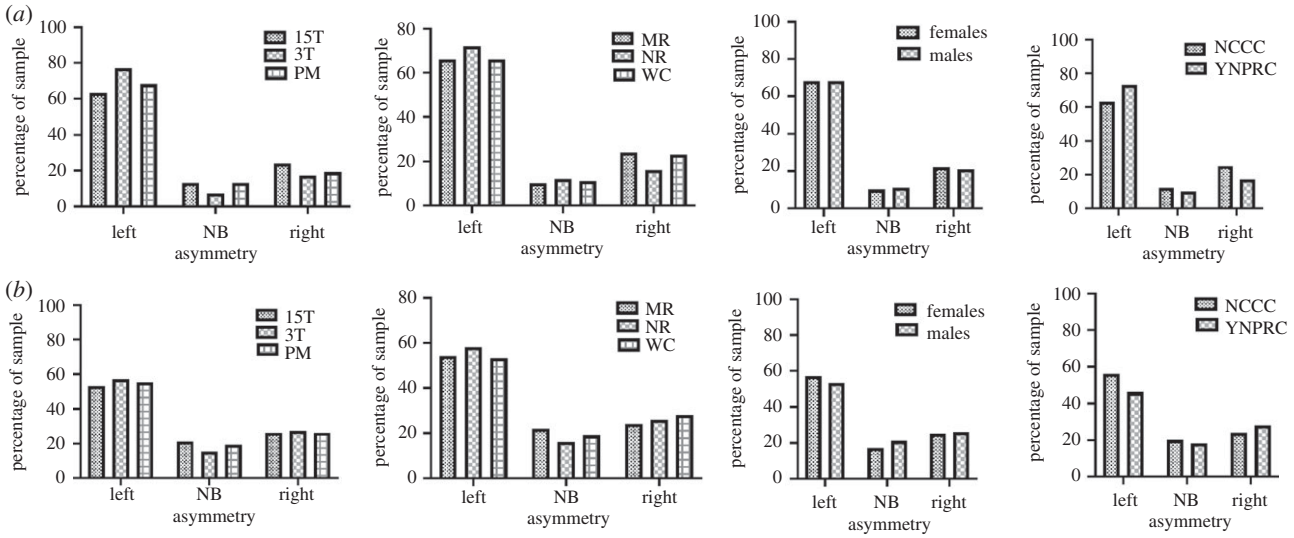

Figure 3. Per cent of chimpanzees classified as having a left, right or no bias in PT surface area (*a*) and mean depth (*b*) asymmetry. For each row, from left to right, the percentage of chimpanzees classified left, right and no bias in PT asymmetry is shown across scanner magnets and protocol, rearing history, sex and chimpanzee colony.

surface area and mean depth were the dependent measures, while sex (male, female), rearing group (MR, NR, WC) and colony (NCCC, YNPRC) were between-group factors. Scanner magnet and age were covariates. We found no overall significant main effects or interactions for this analysis (see electronic supplementary material, table S1). The AQ for the surface area and mean depth scores for the NCCC and YNPRC chimpanzees, was generally consistent across the two colonies, sexes and rearing groups (figure 3).

(b) Heritability analyses

Heritability in the left and right hemisphere PT surface areas and mean depths were determined for the entire sample.

Scanner magnet strength, sex, age and colony were used as covariates. We found significant heritability in the mean hemisphere PT surface area ($h^2 = 0.22$; $p < 0.05$) as well as the mean sulcal depth of the PT (h^2 range = 0.42; $p < 0.05$). Detailed results from these analyses are provided in the electronic supplementary material, table S2. Additionally, we found a small, but significant, heritability for the AQ surface area ($h^2 = 0.13$; $p < 0.05$), but not the mean depth AQ ($h^2 = 0.03$; $p > 0.05$). We also estimated heritability within the NCCC and YNPRC colonies separately to examine consistency in heritability between the two populations. Within the NCCC population, significant heritability was found for both mean PT surface area and mean depth. By contrast, for the YNPRC population we failed to find significant heritability in mean PT surface area, although the mean depth, was significantly heritable. Thus, heritability in the mean depth of the PT was consistently significant between the NCCC and YNPRC chimpanzee populations. By contrast, heritability in surface area was not found to consistently be significant between the NCCC and YNPRC populations. Lastly, we performed genetic correlations between the left and right hemisphere surface area and mean depth values for the entire chimpanzee sample. A significant genetic correlation was found for mean depth (rhoG = 0.975, s.e. = 0.189 $p < 0.001$), but not for surface area, though the estimate approached conventional levels of statistical significance (rhoG = 0.755, s.e. = 0.212, $p < 0.054$).

4. Discussion

Our findings indicate that chimpanzees exhibit a robust and consistent pattern of population-level leftward asymmetry for the PT, which was evident across MRI scanner magnets, sexes, and colonies, and among chimpanzees that experienced different early social rearing experiences. Lastly, we found a small but significant heritability in the AQ scores for the PT mean depth but not the surface area. These findings should be interpreted with caution in light of the inconsistency in findings between the measures and the relative small effect size. Arguably, perhaps molecular biological methods might produce more compelling evidence for genetic factors influencing directional asymmetries than quantitative genetic approaches.

(a) Genetic factors

In human twin studies, PT morphological asymmetry has been shown to display heritability, an observation supported by human developmental studies [40,45,72], which have highlighted the early establishment of PT asymmetry *in utero*, suggesting genetic factors play a central role. More recent genome-wide analyses (GWAS) have confirmed the influence of genetic factors, with observations of significant heritability (14%) in PT asymmetry reported for the general population [73]. Although an earlier meta-analysis of PT asymmetry failed to detect any associations with gene loci [19], recent studies point towards significant associations between changes in loci of the *BOK* and *DTYMK* genes and PT asymmetry [73]. We believe there are three important aspects of the findings on heritability in the PT asymmetry values in the chimpanzee sample. First, the small, but significant, heritability we found in chimpanzee PT surface area approximates the 14% of heritability reported in a heterogenous sample of human subjects, suggesting similar contributions of genetic factors between the two species [73]. Second, Hopkins *et al*. [59] has previously found that overall tool use skill is significantly heritable in chimpanzees, and performance asymmetries in tool use skill are small, but significantly, heritable ($h^2 = 0.17$), a value that is also comparable to the heritability estimate reported here for the PT. Third, the genetic correlation between the mean PT depth of the left and right hemispheres was significant and higher than for the surface area measures. The AQ values for surface area were significantly heritable, but this was not the case for the mean depth. It should be acknowledged that the higher genetic correlation between the two hemisphere values, the less likely it is that a specific gene may code for left–right asymmetry. Genetic correlations evaluate shared genetic variance between traits and higher values indicate that a common gene or sets of genes underlie the same phenotypes. Thus, if the left and right hemisphere genetic correlations are high, it suggests that the same gene(s) underlies their expression. If brain asymmetries reflect specific left or right hemisphere genetic regulation, then more lateralized brain regions would presumably have weaker interhemispheric correlations. This interpretation is supported by the results reported here, but whether this pattern could be expanded to additional brain regions remains unclear [58].

(b) Environmental factors

We found very little evidence that experiential, methodological or biological factors (i.e. sex) influenced PT directional asymmetries in either surface area or mean depth. Indeed, there is remarkable consistency in findings between these two chimpanzee populations, as well as between sexes, rearing groups and independent of the scanning procedure and magnet strength. With specific regard to rearing history, the findings reported here do not support any hypotheses suggesting that consistent, lateralized human handling in some way induces population-level asymmetries in chimpanzees. To be clear, we are not suggesting that early experiential factors have no influence on the development of brain asymmetries in chimpanzees; our results only suggest that early rearing either by conspecific mothers or in human nursery settings do not differentially influence the direction of PT asymmetries.

(c) Comparisons to other primates

Based on previous findings [37,39] and those reported here, chimpanzees show a population-level leftward asymmetry for the surface area, mean depth and grey matter volume of the PT [36,74]. Further, chimpanzees also show a leftward asymmetry in the cytoarchitectonic volume of BA22 or area Tpt [35]. Thus, leftward asymmetries in the PT are evident at multiple levels of analysis in chimpanzees. However, the evidence of population-level leftward asymmetries for the PT in other non-human primate species is less well established. For instance, there are few published data on PT asymmetries in other great apes, at either the morphological or cellular levels of analysis [75]. In more distantly related cercopithecid monkeys, baboons show a leftward asymmetry in the surface area of the PT [34] and, interestingly, there is some evidence that these asymmetries are present within the first few months of life similar to what is observed in humans [72]. By contrast, neither vervet nor rhesus monkeys show population-level asymmetries for the PT surface area and grey matter volume, when using traditional region-of-interest approaches [76–78]. In rhesus monkeys ranging between 1 and 19 month of age,

Xia *et al*. [78] used a voxel-based approach to measure asymmetries in surface area and cortical thickness, and reported leftward asymmetries for the PT. Finally, there is one report of significant leftward asymmetries in the volume of BA22 in rhesus monkeys based on histologically defined boundaries [76].

There have been a number of comparative studies in apes and monkeys that have quantified the length of the Sylvian fissure as a proxy to estimating PT asymmetries by direct measures on the cortical surface [79] or from three-dimensional reconstructions of sulci from MRI scans or endocasts [56,58,80–82]. In general, the evidence suggests that both chimpanzees and various monkey species show a leftward bias in Sylvian fissure length, but to what extent that reflects asymmetries in PT surface area or volume remains unclear. Indeed, Cantalupo and colleagues [83] compared the measurement of PT asymmetries in relation to variation in different components of lateralization in Sylvian fissure length (i.e. anterior versus posterior sections) and found only small or non-significant associations. In our view, the methods and landmarks used in this study to define the PT could be readily adapted to other nonhuman primate brains and would facilitate a more comprehensive and fair assessment of lateralization in the posterior superior temporal gyrus across primate species.

In conclusion, the present study provides important confirmatory data that the leftward asymmetries in the PT of chimpanzees is robust and is evident across two distinct genetically isolated populations. Further, leftward asymmetries in the PT were consistently found across two cohorts studied and were found to be independent of the (1) MRI magnet strength and scanning protocol, (2) the sex of the individual, and (3) early social rearing experiences. Surface area and mean depth of the PT were significantly heritable, and these patterns of results were largely consistent between the two chimpanzee populations. The collective findings suggest that asymmetries in the PT have a strong biological basis, and that this evolutionary foundation was probably evident in the last common ancestor of chimpanzees and humans, serving as a pre-adaptation for modern human language and speech [84]. The presence of PT asymmetries in the last common ancestor may have set the stage for the emergence of lateralization to the left hemisphere in language functions in modern humans.

Data accessibility. MR imaging data as used in this study may be accessed through the National Chimpanzee Brain Resource (NCBR) (https://www.chimpanzeebrain.org).

Authors' contributions. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design; collection and analysis of data; statistical analysis and interpretation; drafting of the manuscript: M.A.S., C.C.S., S.J.S. and W.D.H. Obtained funding: C.C.S. and W.D.H. Preparation of figures/tables: M.A.S. and W.D.H. Critical revision of the manuscript for important intellectual content: all authors.

Competing interests. We declare we have no competing interests.

Funding. This work was supported by the National Science Foundation (grant nos. BCS-0515484, BCS-0549117, BCS- BCS-0824531, DGE-0801634), the National Institutes of Health (grant nos. NS42867) and the James S. McDonnell Foundation (grant no. 22002078). MRI data were provided by the National Chimpanzee Brain Resource (www.chimapanzeebrain.org) which was supported by NIH grant no. NS092988.

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