The heritability of chimpanzee and human brain asymmetry

Aida Gómez-Robles[1], William D. Hopkins[2,3], Steven J. Schapiro[4], Chet C. Sherwood[1]

[1]Department of Anthropology and Center for the Advanced Study of Human Paleobiology, The George Washington University, Washington, DC 20052

[2]Neuroscience Institute, Georgia State University, Atlanta, GA 30302

[3]Division of Developmental and Cognitive Neuroscience, Yerkes National Primate Research Center, Atlanta, GA 30322

[4]National Center for Chimpanzee Care, Department of Veterinary Sciences, The University of Texas MD Anderson Cancer Center, Bastrop, TX 78602

Author for correspondence:

Aida Gómez-Robles

e-mail: agomezrobles@gwu.edu, aidagomezr@yahoo.es

ABSTRACT

Human brains are markedly asymmetric in structure and lateralized in function, which suggests a relationship between these two properties. The brains of other closely related primates, such as chimpanzees, show similar patterns of asymmetry, but to a lesser degree, indicating an increase in anatomical and functional asymmetry during hominin evolution. We analyzed the heritability of cerebral asymmetry in chimpanzees and humans using classic morphometrics, geometric morphometrics and quantitative genetic techniques. In our analyses, we separated directional

asymmetry and fluctuating asymmetry, which is indicative of environmental influences during development. We show that directional patterns of asymmetry, those that are consistently present in most individuals in a population, do not have significant heritability when measured through simple linear metrics, but they have marginally significant heritability in humans when assessed through three-dimensional configurations of landmarks that reflect variation in the size, position and orientation of different cortical regions. Furthermore, genetic correlations between left and right hemispheres are substantially lower in humans than in chimpanzees, which points to a relatively stronger environmental influence on left-right differences in humans. We also show that the level of fluctuating asymmetry has significant heritability in both species in some regions of the cerebral cortex. This suggests that brain responsiveness to environmental influences, which may reflect plasticity, has genetic bases in both species. These results have implications for the evolvability of brain asymmetry and plasticity among humans and our close relatives.

Keywords: Brain evolution, primates, environment, geometric morphometrics, fluctuating asymmetry, quantitative genetics

INTRODUCTION

For more than a century, anatomical observations and functional studies have demonstrated that human brains are markedly asymmetric. This asymmetry is especially noticeable in areas of the brain that are involved in higher-order cognition and language, such as the inferior frontal, superior temporal, and inferior parietal regions [1–4]. For example, functional studies have shown a high density of unilateral activation peaks for language-related tasks in these frontal and parietal perisylvian areas, particularly in the left hemisphere [5]. These findings suggest that

47 anatomical asymmetry is linked to functional lateralization [6,7], which is thought to optimize
48 processing speed and synchronization through minimized wiring in large brains [8].
49
50 Subsequent studies have demonstrated that chimpanzees, one of the closest living relatives of
51 humans, also show similar anatomical asymmetries, although to a lesser degree [9–12]. Other
52 studies have further demonstrated that behavioral lateralization, especially handedness for
53 different tasks, is common in chimpanzees and other great apes, although population-level
54 handedness is not as pronounced as in humans [13–15]. Additionally, neuroimaging studies of
55 chimpanzees have shown functional lateralization in Broca's area homolog related to
56 communicative behavior [16] and in the hand knob, the motor-hand region of the precentral
57 gyrus, in relation to reach-and-grasping responses [17]. These observations, together with
58 endocranial changes evident in the hominin fossil record [18–20], indicate that cerebral
59 asymmetry was present in the last common ancestor of chimpanzees and humans by 6-8 million
60 years ago and in early hominins, but that it has increased during hominin evolution, probably in
61 parallel with the evolution of greater functional lateralization [21].
62
63 Most previous studies have focused on directional patterns of cerebral asymmetry. Directional
64 asymmetries are defined as those that are consistently identified in most individuals in a given
65 population and are considered to have a genetic origin. We have recently shown, however, that
66 the human brain is characterized not only by a strong degree of directional asymmetry as
67 compared with chimpanzees, but also by a high degree of fluctuating asymmetry [12].
68 Fluctuating asymmetry corresponds to random departures from the population-specific mean
69 directional asymmetry, and it is usually considered to result from the impact of environmental

influences on developmental processes [22]. The most classic account for fluctuating asymmetry is that it is the outcome of developmental instability, that is the inability of individuals to buffer the effects of various perturbations during development [23]. We have proposed, however, that the high degree of fluctuating asymmetry observed in healthy human brains is more likely indicative of a high level of developmental plasticity, a hypothesis that is further supported by the low heritability for cortical anatomy observed in human brains compared to chimpanzees [24].

The available evidence, therefore, indicates that certain aspects of brain asymmetry are genetically determined, whereas other features of anatomical lateralization might be the result of environmental influences during development. In order to tease apart the causal factors underlying the phenotypic expression of brain asymmetry and their evolution, in the current study we evaluate the heritability of different forms of brain asymmetry and the genetic correlations between variables measured in the left and the right side in humans and chimpanzees. Based on the observation that human brains are structurally and functionally more asymmetric than chimpanzee brains, as well as more plastic, we have three major hypotheses. First, we hypothesize that heritability for directional cerebral asymmetry will be higher in human than in chimpanzee brains. Second, we hypothesize that environmental influences on brain asymmetry will be stronger in humans. Third, we hypothesize that fluctuating asymmetry will be genetically heritable, reflecting the capacity for plasticity to evolve.

MATERIALS AND METHODS

Samples and MRI scans.

A sample of 206 chimpanzee (79 males, 127 females, age range: 8-53 years) and 218 human (87 males, 131 females, age range: 22-30 years) MRI scans was used. Chimpanzees used in this study were housed at the Yerkes National Primate Research Center (YNPRC) in Atlanta, GA, and at the National Center for Chimpanzee Care (NCCC) at The University of Texas MD Anderson Cancer Center (UTMDACC) in Bastrop, TX. Chimpanzees were scanned using a 3T scanner (Siemens Trio, Siemens Medical Solutions, Malvern, USA) or a 1.5T scanner (Phillips, Model 51, Philips Medical Systems, N.A., Bothell, Washington, USA). Technical details regarding scanning procedures and processing can be found in ref. [25]. Scanning procedures in chimpanzees 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. No paternity tests were conducted for the purposes of this study, but a well-documented pedigree is available for these chimpanzees, which includes information on mother, father and offspring identity for many individuals.

Human MRI scans were obtained from the Human Connectome Project (HCP) database [26]. Individuals were scanned with a Siemens Skyra 3T scanner. Technical details regarding scanning procedures and processing in human subjects can be found in refs. [26,27]. Consent from human participants was obtained in the context of the Human Connectome Project, and data-use terms for open and restricted data were accepted and observed as per HCP requirement [28]. The HCP database includes monozygotic twins, non-monozygotic twins and non-twin siblings. In order to maximize sample size and minimize inter-population variability due to genetic ancestry, which might correlate with general brain anatomy [29], only individuals with the same ancestry (as self-reported) were selected.

116

117 **3D reconstructions and landmarks**

118 Three-dimensional models of the cerebral cortical surface were reconstructed from MRI scans
119 using BrainVisa software [30] for chimpanzees and FreeSurfer software [31] for humans (3D
120 models were directly obtained from the HCP database for the human sample). Thirty-two
121 anatomically homologous landmarks (16 bilateral landmarks) were placed on the intersections
122 and extreme points of the most constant sulci on the chimpanzee and human cortical surface
123 [12,24] (Figure S1, Table S1). Because of the anatomical complexity of the human cortical
124 surface, which makes it difficult to identify some sulci, landmark placement was aided by a
125 comparison with automatically parcellated models. These parcellated models, obtained with
126 FreeSurfer software version 5.3.0 according to the Desikan surface atlas [32], are provided in the
127 HCP database. These or similar configurations of landmarks have been previously used in our
128 other studies of brain variation in chimpanzees and humans [12,24,33].

129

130 **Linear metrics and asymmetry quotients**

131 Linear distances were calculated between several pairs of landmarks as a measure of the general
132 proportions of the major lobes of the brain and of the length of the most prominent sulci (Table
133 S2). These distances are linear approximations and they do not include variation along the course
134 of a given sulcus. Linear distances were measured separately for the right and the left side in
135 order to measure heritabilities for each side and genetic correlations between correspondent
136 variables in each hemisphere (see below). Additionally, linear distances were used to measure
137 asymmetry quotients (AQs) for all the variables, the heritability of which was estimated as well.
138 AQs were calculated as the value of a variable in the right hemisphere minus the value of that

variable in the left hemisphere, divided by the mean of that variable in both hemispheres (R-L)*100/((R+L)*0.5). Linear metrics were measured in Procrustes-superimposed configurations of landmarks (see below) because original distances are highly influenced by brain size, even if brain size has a quantitatively very small effect on sulcal anatomy [12]. However, some of the studied variables, such as AQs, are independent of total size, so this transformation does not have any effect in this case.

Geometric morphometrics

Configurations of landmarks were also studied in a geometric morphometric context. Original configurations of landmarks were Procrustes-superimposed to remove information regarding the location, orientation and size of the original specimens [34]. Each configuration was later mirror-imaged and relabeled following ref. [35]. The mean of the original and mirror-imaged configurations yielded a symmetric consensus configuration for each individual, whereas the difference between both configurations corresponded to the asymmetric component of shape variation [35]. The asymmetric component of variation was analyzed through separate principal components analyses (PCAs) for each species. The first 5 PCs for each species were explored in further detail.

PCs were tested for their association with the pattern of directional asymmetry (DA) typical of each species, which was calculated by averaging the asymmetric components of shape variation of each individual for each species (in other words, directional asymmetry in shape was calculated simply as the mean shape asymmetry for each species). These comparisons tested if variation associated with each PC is similar to the pattern of directional asymmetry observed in

the population or whether variation is not aligned with this population-typical pattern. The association between each PC and directional asymmetry was measured by calculating the angle between each eigenvector and the species-specific DA vector, which was calculated as the arccosine of the inner product of both vectors. An angle of 0 degrees indicates a correlation of 1 between two vectors, whereas an angle of 90 degrees indicates a correlation of 0. Significance was tested against a null distribution of 1,000 angles formed between randomly selected vectors. For vectors of the length included in our study, 78.42 degrees is the significance threshold above which vectors are uncorrelated.

Additionally, fluctuating asymmetry (FA) scores were calculated for each individual as the difference between individual configurations of landmarks and the norm directional asymmetry configuration within the species-specific sample population [36,37]. FA scores are calculated across all landmarks and represent the extent to which each individual departs from the norm DA pattern. A FA score of 0 indicates that a given individual shows exactly the same pattern of asymmetry that is defined as characteristic of the population, whereas a high FA score indicates that individuals depart from this population-specific pattern, regardless of the identity of the particular anatomical variation that is driving this departure.

Quantitative genetics

Variance components and heritabilities were estimated using an animal model approach implemented in the R package *MCMCglmm* [38]. In evolutionary biology and quantitative genetics, an 'animal model' is a particular type of mixed-effects statistical model that can be used to decompose phenotypic variance into different genetic and environmental sources and to

185 estimate key parameters such as the heritability and the genetic correlation between traits [39].
186 For humans, the classic implementation of *MCMCglmm* was changed as proposed in ref. [40] to
187 use the kinship matrix instead of a pedigree, which was necessary to include the degree of
188 genetic similarity corresponding to monozygotic twins. All data were standardized prior to
189 analysis by subtracting the mean from each individual value and dividing the difference by the
190 standard deviation. Sex, age and the interaction between sex and age were used as fixed effects
191 in both species. Additionally, scanner type was included in chimpanzee analyses to account for
192 the possible effect of using two different scanners. Phenotypic and genetic correlations between
193 corresponding left and right variables were tested using bivariate animal models, which used the
194 same fixed effects. Following other studies [41], we used slightly informative priors of the form
195 ($V = Vp/r$, $\eta = 1$), where Vp is the phenotypic variance and r the number of random factors,
196 modified as ($V = diag(n)*Vp/r$, $\eta = n$), where n is the number of traits, for bivariate analyses.
197 Because all variables were standardized to a variance of 1 and all models included only one
198 random factor, priors had the form ($V=1$, $\eta = 1$) for univariate models and ($V = diag(2)$, $\eta = 2$)
199 for bivariate models. Parameter-expanded priors [42,43] yielded similar overall results, but they
200 more often tended to result in null estimates. Models were run for 1,000,000 iterations, during
201 which model parameters were updated. As it is the standard procedure, the first 500,000
202 iterations were discarded as a burn-in period. Posterior distributions were sampled every 100^{th}
203 iteration to a final amount of 5,000 samples.
204
205 Significance of fixed effects was evaluated by assessing if 95% highest posterior density
206 intervals include 0, which is indicative of non-significance. The significance of phenotypic and
207 genetic correlations can be tested in the same way. Variance components from which heritability

is estimated, however, are bound to be positive and posterior distributions will not overlap 0, even if their effect is not significant. We tested the significance of heritability estimates by comparing the deviance information criterion (DIC) in models including pedigree/kinship information and in models excluding it, which yielded a DIC differential value (ΔDIC). The significance of heritability was assessed using a simulation approach consisting of measuring the heritability of random variables using the same models [44]. By construction, these variables do not have significant heritability as values are randomly assigned to individuals. P-values were calculated as the proportion of 1,000 simulations yielding higher ΔDIC than each evaluated variable.

RESULTS

Description of asymmetry

Asymmetry quotients based on interlandmark distances are roughly consistent with previous studies of AQs based on detailed sulcal anatomy [25]. In general, chimpanzees and humans show the same direction of AQ patterns, although values are greater in humans (Fig. 1). Distances related to the perisylvian region, such as the inferior parietal length and the lengths of the Sylvian fissure and of the superior temporal sulcus show a clear leftward bias in both species, although it is stronger in humans than in chimpanzees. Variables related to other regions, such as the frontal and occipital lobes, do not show as consistent asymmetry patterns, either between species or across different variables within each region.

Geometric morphometric analyses show that directional asymmetric variation is concentrated in the inferior parietal area in both species, although those changes are much more marked in

humans, where they also involve a strong reorientation of the Sylvian fissure that is not observed in chimpanzees (Fig. 2). The general pattern of directional asymmetry in humans also includes some changes in the inferior frontal and in the occipital regions. The distribution of individuals in PCA plots shows additional evidence of the stronger degree of directional asymmetry in humans, as demonstrated by the off-centered position of more symmetric individuals with respect to the range of variation of the population in humans, but not in chimpanzees (Fig. 2).

Heritabilities and genetic correlations

Our results show that both chimpanzees and humans have significant heritability in most lobe proportions, with the exception of frontal dimensions in the left hemisphere in humans (Tables S3 and S4). Although some studies have evaluated the evolution of lateralization through differential heritability in the left and the right sides [45,46], as well as through different evolutionary trends of variables measured in the left and the right hemisphere [47], our study does not show consistently higher heritabilities for one hemisphere or the other, barring the two non-significant values in humans, which correspond to the left hemisphere. Genetic correlations between corresponding left and right lobe proportions are high in chimpanzees (Fig. 1, Table S5). Genetic correlations are also high in humans, although they are slightly lower than in chimpanzees (Fig. 1, Table S5).

Heritability for sulcal lengths is substantially higher in chimpanzees than in humans, as has been demonstrated previously [24]. As with lobe proportions, no consistent pattern of higher heritabilities in the left or right hemisphere is observed in either species (Table S6 and S7). Genetic correlations between matching left and right sulcal lengths are in general significant and

relatively high for chimpanzees, although there are some exceptions (Fig. 1, Table S8). In humans, most genetic correlations between sulcal lengths in the left and the right hemispheres are not significant, with the exception of the correlation between the left and right central sulci, and the left and right Sylvian fissures (Fig. 1, Table S8). These results indicate that covariation between the left and the right hemispheres is more strongly genetically determined in chimpanzees, whereas it is exposed to higher environmental influence in humans.

Heritability of asymmetry

The analysis of the heritability of asymmetry quotients for lobe proportions and sulcal lengths results in generally non-significant values and in marginally significant values only for a few AQs (Tables S9 and S10). This result is initially surprising, because some of these patterns of asymmetry are known to represent very consistent directional asymmetry patterns, which are expected to be genetically determined. However, it is possible that asymmetry quotients based on linear metrics do not have sufficient resolution to detect the genetic origin of brain asymmetries. We further explored this by measuring the heritability of particular aspects of asymmetric shape variation summarized by PC1-PC5 (Tables S11 and S12). These principal components of shape are based on 3D configurations of landmarks, and include all aspects of shape variation, such as the size, position and orientation of the cortical regions included in those configurations. In humans, PC1 and PC2 are the only principal components of asymmetric shape variation that have marginally significant heritability as inferred from our simulation-based significance threshold (PC1: h^2=0.25, ΔDIC=16.15, P=0.096; PC2: h^2=0.29, ΔDIC=17.86, P=0.081; Fig. 2, Table S12). Interestingly, PC1 is the principal component of shape variation that shows the closest correspondence with directional asymmetry in humans (α=36.4º; P<0.0001; Table S12).

277 In chimpanzees, no single PC is strongly associated with the directional asymmetry vector,
278 although PC2 shows a slight correlation with DA (α=64.7º; P<0.0001; Table S11). Principal
279 components of asymmetric shape variation in chimpanzees tend not to show significant or
280 marginally significant heritability.
281
282 Individual fluctuating asymmetry scores are substantially higher in humans than in chimpanzees
283 (Fig. 3), which is consistent with our previous report based on Procrustes ANOVAs [12]. When
284 calculating fluctuating asymmetry scores for total cortical anatomy and for the three major lobes
285 of the brain (frontal, temporo-parietal and occipital), we observed that one of these values has
286 significant heritability for each species: occipital FA for humans (h^2=0.43, ΔDIC=46.6, P=0.005)
287 and total FA for chimpanzees (h^2=0.41, ΔDIC=33.3, P=0.028), with chimpanzees showing also
288 marginally significant heritability for the frontal lobe (h^2=0.32, ΔDIC=23.7, P=0.074). This
289 result shows that the general level of fluctuating asymmetry, which is indicative of the
290 propensity to have a brain that departs from species' typical configurations regardless of the
291 particular changes motivating this departure, is in part genetically heritable in both species.
292
293 **DISCUSSION**
294 Comparisons of heritability values across different populations or species are unavoidably
295 influenced by the different environmental conditions in which different groups live. Indeed,
296 heritability estimates are specific to the groups and conditions in which they were obtained, and
297 they cannot be generalized to other circumstances. This point is particularly important because of
298 the very different environmental conditions corresponding to our chimpanzee and human
299 samples, with chimpanzees living in the more homogenous conditions typical of captive habitats.

These differences, however, are much more likely to be reflected in behavioral phenotypes than in anatomical phenotypes. However, differences in the relatedness structure of the chimpanzee and human samples are likely to have a stronger effect on our results. Analyses of brain size have shown that heritability estimates based on twins (as in our human sample) tend to be higher than those based on extended pedigrees (as in our chimpanzee sample) [48]. An implication of this observation is that human heritabilities yielded by our analyses are likely to be overestimated in comparison with chimpanzee heritabilities. With this in mind, we focus our discussion on the comparison of the heritability of different variables within each species.

Our results shed light on the heritability of directional and fluctuating brain asymmetry in humans and chimpanzees. These two types of asymmetry have different bases in genetics and development, each with distinct implications for the evolutionary origin of neural structure and function. Classic studies of human brain anatomy have focused on directional asymmetries [1,4,45], as they are more consistent and, therefore, easier to identify, and because they have well known functional correlates. Our study, however, highlights the importance of fluctuating asymmetry, which, according to various lines of evidence [12,24], may be interpreted to reflect variation due to plasticity in normal brain development.

Directional asymmetry and functional lateralization

Because directional asymmetry of the brain is usually assumed to be genetically determined, our finding that most asymmetry quotients do not show significant heritability in either species does not fit our hypotheses and is initially surprising. Studies of heritability in human neuroanatomy have reported differential heritability for some variables (lobar volume and gray matter

distribution) in both hemispheres [45,46]. However, direct evaluations of the heritability of brain asymmetry in humans are not common in the literature [49], which may reflect a publication bias resulting from negative results. In chimpanzees, however, it has been reported that the asymmetry quotient of gray matter volume shows low but significant heritability in the posterior region of the superior temporal gyrus, but not in the inferior frontal gyrus [49]. Because our previous studies have demonstrated that fluctuating asymmetry is preferentially located in the inferior frontal region in chimpanzees [12], we hypothesize that significant heritability for directional asymmetry may be harder to identify in brain regions with strong fluctuating asymmetry. However, our study does not identify significant heritability for the AQ of the superior temporal sulcus, even though this region does not show particularly high fluctuating asymmetry in chimpanzees. This difference may result from the lack of separation between the anterior and posterior segments of the superior temporal sulcus in the present study, or it may indicate that directional asymmetry in gray matter volume is more heritable than landmark-based sulcal lengths.

When exploring more complex patterns of asymmetric shape variation as described by the 3D configurations of landmarks, chimpanzees and humans show some similarities in their major patterns of directional asymmetry, namely the difference in size and orientation between the left and right superior temporal sulci. In humans, the major pattern of directional asymmetry is strongly associated with the first principal component of shape variation, which is one of the PCs that show marginally significant heritability as determined by our simulation-based significance threshold. These results indicate that complex patterns of asymmetry, which include all parameters of shape variation (size, position and orientation of the different cortical regions with

346 respect to each other), may show moderate but significant heritability in larger samples and,
347 therefore, some level of genetic control.
348
349 Our results are consistent with studies showing low to moderate heritability for neuroanatomical
350 asymmetries in primates [49–51], which contrasts with other studies yielding substantially higher
351 heritability for behavioral lateralization in chimpanzees and humans, usually measured as
352 handedness [52,53]. This apparent paradox highlights the difficulty in drawing direct
353 associations between structural and functional asymmetry. Studies of heritability based on
354 functional neuroimaging in humans, which might serve as an interface between neuroanatomical
355 and behavioral studies, are particularly uncommon [54], which makes it challenging to bridge
356 both types of observations.
357
358 **Fluctuating asymmetry and plasticity**
359 Fluctuating asymmetry was indirectly measured in our study through the analysis of genetic
360 correlations between the left and the right hemispheres. These results show that inter-
361 hemispheric genetic correlations are high for all variables in chimpanzees. In humans, however,
362 general lobe proportions and evolutionary and developmentally primary sulci (such as the central
363 sulcus and the Sylvian fissure) show high genetic correlations between the left and the right side,
364 whereas other sulci show low and not significant correlations. This difference points to a greater
365 environmental influence on left-right differences in humans. Some authors have suggested that
366 “in the absence of differential developmental effects, the correlation between the two sides of the
367 same organ should be 1” (ref. [55], p. 708). This expectation is true for perfectly symmetric
368 organs and for those showing genetically-determined directional asymmetry. Lower inter-

hemispheric genetic correlations observed in human brains reflect greater non-genetic developmental effects than in chimpanzees. We interpret this result to reflect a high level of developmental plasticity in human brains, which is consistent with other lines of evidence (see also refs. [12,24]). Our results have been obtained from a healthy human population for which a high level of developmental instability due to stress or illness, which may be another cause of fluctuating asymmetry, would not be expected. In addition, microstructural and gene expression studies show that human evolution has been characterized by increases in the level of cerebral plasticity, as evident by an extended period of environment-dependent myelination [56] and upregulation of genes associated with synaptogenesis [57]. The results of the current study provide further support from an analysis of brain anatomy that elevated plasticity characterizes the human cerebral cortex compared to other primate species. In addition, developmental changes are known to have occurred during hominin evolution that have extended the period of time during which brain maturation is exposed to a complex extra-uterine environment [58]. Studies based on endocranial anatomy, furthermore, also show that the level of fluctuating asymmetry observed in modern human endocasts is higher than that observed in great apes, including chimpanzees, bonobos and gorillas [59].

Even if particular plastic changes are not genetically heritable, the general propensity to have a more plastic brain that will be more responsive to environmental influences can be coded by genes. This is what our results show, at least partially, by revealing significant heritability for fluctuating asymmetry scores in some brain areas in chimpanzees and humans. Indeed, our analyses yield unexpected results because the heritability of some aspects of fluctuating asymmetry is substantially higher than the heritability of asymmetry quotients and principal

components of asymmetric shape variation, which are more reflective of directional asymmetry. Although this result should be confirmed in other samples and using additional methods to characterize cortical organization, it seems to indicate that brain anatomy's responsiveness to environmental influences is more strongly genetically controlled than structural asymmetry itself. The finding of non-significant heritability for fluctuating asymmetry in some areas of the brain may reflect more complex patterns of inheritance, or the inability of our relatively small samples to detect heritability levels that are expected to be moderate [60]. In fact, several studies have demonstrated that human-specific variants of certain genes are associated with increases in the level of plasticity in the formation of cortico-basal neural circuits [61] and in the maturation of synaptic spines [62]. The evolution of neural plasticity can be also mediated in part by epigenetic mechanisms that allow for context-dependent changes of synapses and circuits [63]. Taken together with the findings from the current analysis, these observations indicate that the level of brain plasticity in the chimpanzee-human clade has a genetic basis and, therefore, is heritable and evolvable.

Data accessibility.

The datasets supporting this article are available in Dryad database at http://dx.doi.org/10.5061/dryad.n04r6.

Authors' contributions

A.G.-R. and C.C.S. conceived of the study; W.D.H. and S.J.S. collected chimpanzee scan data; A.G.-R. collected morphometric data, designed and performed analyses; A.G.-R. and C.C.S. wrote the manuscript, with contributions from W.D.H. and S.J.S.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by a National Institutes of Health grant NS042867; and James S. McDonnell Foundation grant 220020293. Chimpanzees at UTMDACC were supported by NIH Cooperative Agreement U42 OD-011197. Human data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

REFERENCES

1. Geschwind N, Levitsky W. 1968 Human brain: Left-right asymmetries in temporal speech region. *Science* **161**, 186–187. (doi:10.1126/science.161.3837.186)

2. Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K. 1999 Broca's region revisited: Cytoarchitecture and intersubject variability. *J Comp Neurol* **412**, 319–341. (doi:10.1002/(SICI)1096-9861(19990920)412:2<319::AID-CNE10>3.0.CO;2-7)

435 3. Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL, Toga AW. 2002
436 Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo:
437 Maturation in perisylvian cortices. *Cereb. Cortex* **12**, 17–26. (doi:10.1093/cercor/12.1.17)

438 4. Toga AW, Thompson PM. 2003 Mapping brain asymmetry. *Nat. Rev. Neurosci.* **4**, 37–48.
439 (doi:10.1038/nrn1009)

440 5. Vigneau M *et al*. 2011 What is right-hemisphere contribution to phonological, lexico-
441 semantic, and sentence processing? Insights from a meta-analysis. *NeuroImage* **54**, 577–593.
442 (doi:10.1016/j.neuroimage.2010.07.036)

443 6. Tzourio N, Nkanga-Ngila B, Mazoyer B. 1998 Left planum temporale surface correlates
444 with functional dominance during story listening. *NeuroReport* **9**, 829–833.

445 7. Powell HWR *et al*. 2006 Hemispheric asymmetries in language-related pathways: A
446 combined functional MRI and tractography study. *NeuroImage* **32**, 388–399.
447 (doi:10.1016/j.neuroimage.2006.03.011)

448 8. Ringo JL, Doty RW, Demeter S, Simard PY. 1994 Time is of the essence: A conjecture that
449 hemispheric specialization arises from interhemispheric conduction delay. *Cereb. Cortex* **4**,
450 331–343. (doi:10.1093/cercor/4.4.331)

451 9. Gannon PJ, Holloway RL, Broadfield DC, Braun AR. 1998 Asymmetry of chimpanzee
452 planum temporale: Humanlike pattern of Wernicke's brain language area homolog. *Science*
453 **279**, 220–222. (doi:10.1126/science.279.5348.220)

454 10. Cantalupo C, Hopkins WD. 2001 Asymmetric Broca's area in great apes. *Nature* **414**, 505.
455 (doi:10.1038/35107134)

456 11. Gilissen EP. 2001 Structural symmetries and asymmetries in human and chimpanzee brains.
457 In *Evolutionary Anatomy of the Primate Cerebral Cortex* (eds D Falk, KR Gibson), pp. 187–
458 215. Cambridge: Cambridge University Press.

459 12. Gómez-Robles A, Hopkins WD, Sherwood CC. 2013 Increased morphological asymmetry,
460 evolvability and plasticity in human brain evolution. *Proc. R. Soc. B Biol. Sci.* **280**,
461 20130575. (doi:10.1098/rspb.2013.0575)

462 13. Hopkins WD. 2006 Comparative and familial analysis of handedness in great apes. *Psychol.*
463 *Bull.* **132**, 538–559. (doi:10.1037/0033-2909.132.4.538)

464 14. Hopkins WD, Russell JL, Lambeth S, Schapiro SJ. 2007 Handedness and neuroanatomical
465 asymmetries in captive chimpanzees: A summary of 15 years of research. In *The Evolution*
466 *of Hemispheric Specialization in Primates* (ed WD Hopkins), pp. 146–181. Elsevier.

467 15. Hopkins WD. 2013 Comparing human and nonhuman primate handedness: Challenges and a
468 modest proposal for consensus. *Dev. Psychobiol.* **55**, 621–636. (doi:10.1002/dev.21139)

469 16. Taglialatela JP, Russell JL, Schaeffer JA, Hopkins WD. 2008 Communicative signaling
470 activates 'Broca's' homolog in chimpanzees. *Curr. Biol.* **18**, 343–348.
471 (doi:10.1016/j.cub.2008.01.049)

17. Hopkins WD, Taglialatela JP, Russell JL, Nir TM, Schaeffer J. 2010 Cortical representation of lateralized grasping in chimpanzees (*Pan troglodytes*): A combined MRI and PET study. *PLoS ONE* **5**, e13383. (doi:10.1371/journal.pone.0013383)

18. LeMay M. 1976 Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann. N. Y. Acad. Sci.* **280**, 349–366. (doi:10.1111/j.1749-6632.1976.tb25499.x)

19. Holloway RL, Broadfield DC, Yuan MS, Schwartz JH, Tattersall I. 2004 *The human fossil record. Brain endocasts—The paleoneurological evidence (Vol. 3)*. Wiley-Liss, New York.

20. Balzeau A, Holloway RL, Grimaud-Herve D. 2012 Variations and asymmetries in regional brain surface in the genus *Homo*. *J. Hum. Evol.* **62**, 696–706. (doi:10.1016/j.jhevol.2012.03.007)

21. Falk D. 1987 Brain lateralization in primates and its evolution in hominids. *Am. J. Phys. Anthropol.* **30**, 107–125. (doi:10.1002/ajpa.1330300508)

22. Palmer AR, Strobeck C. 2003 Fluctuating asymmetry analyses revisited. In *Developmental Instability: Causes and Consequences* (ed M Polak), pp. 279–319. Oxford University Press.

23. Dongen SV. 2006 Fluctuating asymmetry and developmental instability in evolutionary biology: Past, present and future. *J. Evol. Biol.* **19**, 1727–1743. (doi:10.1111/j.1420-9101.2006.01175.x)

490 24. Gómez-Robles A, Hopkins WD, Schapiro SJ, Sherwood CC. 2015 Relaxed genetic control
491 of cortical organization in human brains compared with chimpanzees. *Proc. Natl. Acad. Sci.*
492 *USA* **112**, 14799–14804. (doi:10.1073/pnas.1512646112)

493 25. Bogart SL, Mangin JF, Schapiro SJ, Reamer L, Bennett AJ, Pierre PJ, Hopkins WD. 2012
494 Cortical sulci asymmetries in chimpanzees and macaques: A new look at an old idea.
495 *Neuroimage* **61**, 533–541. (doi:10.1016/j.neuroimage.2012.03.082)

496 26. Van Essen DC *et al*. 2012 The Human Connectome Project: a data acquisition perspective.
497 *NeuroImage* **62**, 2222–2231. (doi:10.1016/j.neuroimage.2012.02.018)

498 27. Glasser MF *et al*. 2013 The minimal preprocessing pipelines for the Human Connectome
499 Project. *NeuroImage* **80**, 105–124. (doi:10.1016/j.neuroimage.2013.04.127)

500 28. Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K. 2013 The WU-
501 Minn Human Connectome Project: An overview. *Mapp. Connect.* **80**, 62–79.
502 (doi:10.1016/j.neuroimage.2013.05.041)

503 29. Fan CC *et al*. 2015 Modeling the 3D geometry of the cortical surface with genetic ancestry.
504 *Curr. Biol.* **25**, 1988–1992. (doi:10.1016/j.cub.2015.06.006)

505 30. Cointepas Y, Mangin J-F, Garnero L, Poline J-B, Benali H. 2001 BrainVISA: Software
506 platform for visualization and analysis of multi-modality brain data. *NeuroImage* **13**, 98.
507 (doi:10.1016/S1053-8119(01)91441-7)

508 31. Fischl B. 2012 FreeSurfer. *NeuroImage* **62**, 774–781.
509 (doi:10.1016/j.neuroimage.2012.01.021)

510 32. Desikan RS *et al*. 2006 An automated labeling system for subdividing the human cerebral
511 cortex on MRI scans into gyral based regions of interest. *NeuroImage* **31**, 968–980.
512 (doi:10.1016/j.neuroimage.2006.01.021)

513 33. Gómez-Robles A, Hopkins WD, Sherwood CC. 2014 Modular structure facilitates mosaic
514 evolution of the brain in chimpanzees and humans. *Nat. Commun.* **5**, 4469.
515 (doi:10.1038/ncomms5469)

516 34. Rohlf FJ, Slice D. 1990 Extensions of the Procrustes method for the optimal superimposition
517 of landmarks. *Syst. Zool.* **39**, 40–59. (doi:10.2307/2992207)

518 35. Klingenberg CP, Barluenga M, Meyer A. 2002 Shape analysis of symmetric structures:
519 Quantifying variation among individuals and asymmetry. *Evolution* **56**, 1909–1920.
520 (doi:10.1554/0014-3820(2002)056[1909:SAOSSQ]2.0.CO;2)

521 36. Klingenberg CP, Monteiro LR. 2005 Distances and directions in multidimensional shape
522 spaces: Implications for morphometric applications. *Syst. Biol.* **54**, 678–688.
523 (doi:10.1080/10635150590947258)

524 37. Gonzalez PN, Lotto FP, Hallgrímsson B. 2014 Canalization and developmental instability of
525 the fetal skull in a mouse model of maternal nutritional stress. *Am. J. Phys. Anthropol.* **154**,
526 544–553. (doi:10.1002/ajpa.22545)

527 38. Hadfield JD. 2010 MCMC methods for multi-response generalized linear mixed models: The
528 MCMCglmm R package. *J. Stat. Softw.* **33**, 1–22.

529 39. Wilson AJ, Réale D, Clements MN, Morrissey MM, Postma E, Walling CA, Kruuk LEB,
530 Nussey DH. 2010 An ecologist's guide to the animal model. *J. Anim. Ecol.* **79**, 13–26.
531 (doi:10.1111/j.1365-2656.2009.01639.x)

532 40. Zhao JH. 2015 *gap: Genetic Analysis Package*. R package. Available at http://cran.r-
533 project.org/package=gap.

534 41. Teplitsky C, Mouawad NG, Balbontin J, De Lope F, Moller AP. 2011 Quantitative genetics
535 of migration syndromes: A study of two barn swallow populations. *J. Evol. Biol.* **24**, 2025–
536 2039. (doi:10.1111/j.1420-9101.2011.02342.x)

537 42. Gelman A. 2006 Prior distributions for variance parameters in hierarchical models. *Bayesian*
538 *Anal* , 515–534. (doi:10.1214/06-BA117A)

539 43. Hadfield J. 2015 *MCMCglmm Course Notes.* Available at http://cran.us.r-
540 project.org/web/packages/MCMCglmm/vignettes/CourseNotes.pdf.

541 44. Leder EH, McCairns RJS, Leinonen T, Cano JM, Viitaniemi HM, Nikinmaa M, Primmer
542 CR, Merilä J. 2015 The evolution and adaptive potential of transcriptional variation in
543 sticklebacks—Signatures of selection and widespread heritability. *Mol. Biol. Evol.* **32**, 674–
544 689. (doi:10.1093/molbev/msu328)

545 45. Thompson PM *et al*. 2001 Genetic influences on brain structure. *Nat. Neurosci.* **4**, 1253–
546 1258. (doi:10.1038/nn758)

547 46. Geschwind DH, Miller BL, DeCarli C, Carmelli D. 2002 Heritability of lobar brain volumes
548 in twins supports genetic models of cerebral laterality and handedness. *Proc Natl Acad Sci U*
549 *A* **99**, 3176–3181. (doi:10.1073/pnas.052494999)

550 47. Smaers JB, Steele J, Case CR, Cowper A, Amunts K, Zilles K. 2011 Primate prefrontal
551 cortex evolution: Human brains are the extreme of a lateralized ape trend. *Brain Behav Evol*
552 **77**, 67–78. (doi:10.1159/000323671)

553 48. Peper JS, Brouwer RM, Boomsma DI, Kahn RS, Hulshoff Pol HE. 2007 Genetic influences
554 on human brain structure: A review of brain imaging studies in twins. *Hum. Brain Mapp.* **28**,
555 464–473. (doi:10.1002/hbm.20398)

556 49. Hopkins WD, Misiura M, Pope SM, Latash EM. 2015 Behavioral and brain asymmetries in
557 primates: a preliminary evaluation of two evolutionary hypotheses. *Ann. N. Y. Acad. Sci.*
558 **1359**, 65–83. (doi:10.1111/nyas.12936)

559 50. Fears SC *et al*. 2011 Anatomic brain asymmetry in vervet monkeys. *PLoS One* **6**, e28243.
560 (doi:10.1371/journal.pone.0028243)

561 51. Cheverud JM, Falk D, Hildebolt C, Moore A, Helmkamp RC, Vannier M. 1990 Heritability
562 and association of cortical petalias in rhesus macaques (*Macaca mulatta*). *Brain. Behav.*
563 *Evol.* **35**, 368–372. (doi:10.1159/000115881)

564 52. Hopkins WD, Adams MJ, Weiss A. 2013 Genetic and environmental contributions to the
565 expression of handedness in chimpanzees (*Pan troglodytes*). *Genes Brain Behav.* **12**, 446–
566 452. (doi:10.1111/gbb.12044)

567 53. Lien Y-J, Chen WJ, Hsiao P-C, Tsuang H-C. 2015 Estimation of heritability for varied
568 indexes of handedness. *Laterality* **20**, 469–482. (doi:10.1080/1357650X.2014.1000920)

569 54. Jansen AG, Mous SE, White T, Posthuma D, Polderman TJC. 2015 What twin studies tell us
570 about the heritability of brain development, morphology, and function: A review.
571 *Neuropsychol. Rev.* **25**, 27–46. (doi:10.1007/s11065-015-9278-9)

572 55. Atkinson EG, Rogers J, Cheverud JM. 2016 Evolutionary and developmental implications of
573 asymmetric brain folding in a large primate pedigree. *Evolution* **70**, 707–715.
574 (doi:10.1111/evo.12867)

575 56. Miller DJ *et al*. 2012 Prolonged myelination in human neocortical evolution. *Proc. Natl.*
576 *Acad. Sci. USA* **109**, 16480–16485. (doi:10.1073/pnas.1117943109)

577 57. Cáceres M, Suwyn C, Maddox M, Thomas JW, Preuss TM. 2007 Increased cortical
578 expression of two synaptogenic thrombospondins in human brain evolution. *Cereb. Cortex*
579 **17**, 2312–2321. (doi:10.1093/cercor/bhl140)

580 58. Hublin J-J, Neubauer S, Gunz P. 2015 Brain ontogeny and life history in Pleistocene
581 hominins. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **370**, 20140062.
582 (doi:10.1098/rstb.2014.0062)

583 59. Balzeau A, Gilissen E, Grimaud-Hervé D. 2012 Shared pattern of endocranial shape
584 asymmetries among great apes, anatomically modern humans, and fossil hominins. *PLoS*
585 *ONE* **7**, e29581. (doi:10.1371/journal.pone.0029581)

586 60. Leamy LJ, Klingenberg CP. 2005 The genetics and evolution of fluctuating asymmetry.
587 *Annu. Rev. Ecol. Evol. Syst.* **36**, 1–21.

588 61. Enard W *et al*. 2009 A humanized version of Foxp2 affects cortico-basal ganglia circuits in
589 mice. *Cell* **137**, 961–971. (doi:10.1016/j.cell.2009.03.041)

590 62. Charrier C *et al*. 2012 Inhibition of SRGAP2 function by its human-specific paralogs induces
591 neoteny during spine maturation. *Cell* **149**, 923–935. (doi:10.1016/j.cell.2012.03.034)

592 63. Krubitzer L, Stolzenberg DS. 2014 The evolutionary masquerade: Genetic and epigenetic
593 contributions to the neocortex. *Neural Maps* **24**, 157–165. (doi:10.1016/j.conb.2013.11.010)

594

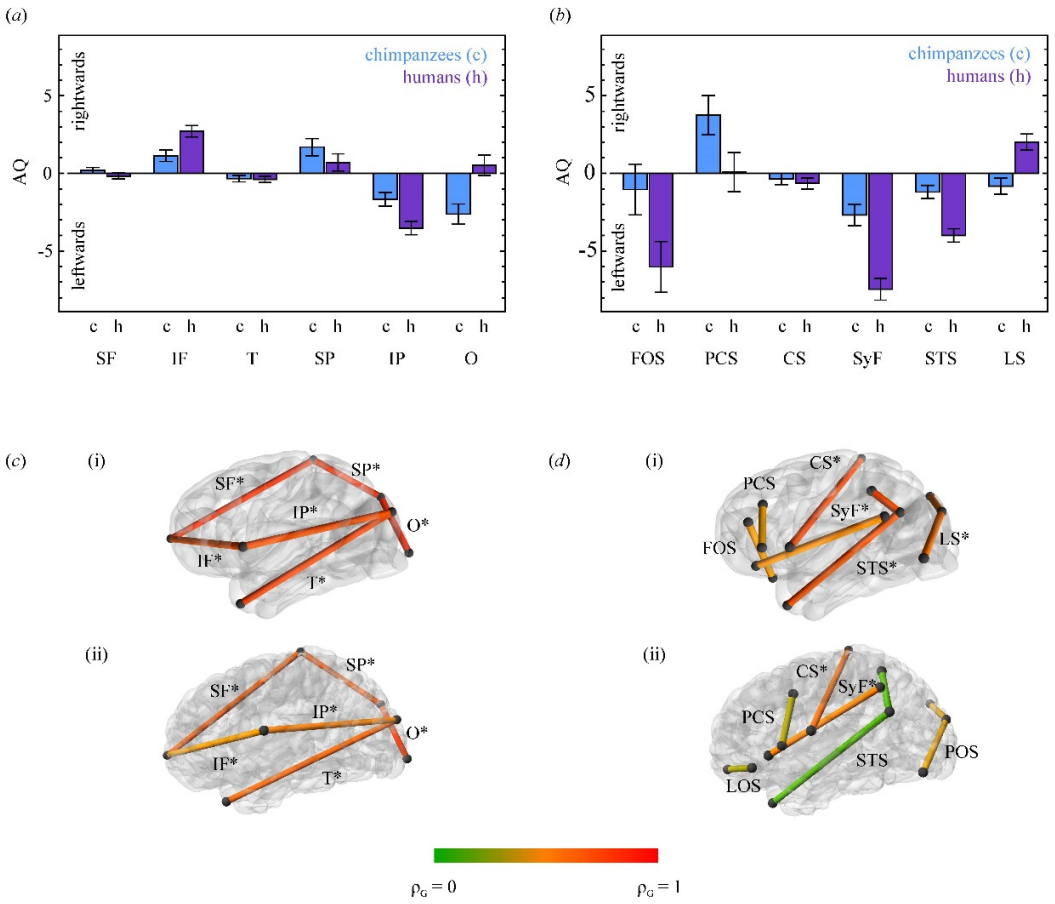
595

596

Table 1. Heritability of fluctuating asymmetry scores.

	Chimpanzees				Humans			
	h^2	**HPDI**	**ΔDIC (P)**	**Fixed**	**h^2**	**HPDI**	**ΔDIC (P)**	**Fixed**
Frontal	0.32	0.12-0.58	23.68 (0.074)	—	0.17	0.07-0.39	5.13 (0.415)	—
Temporo-parietal	0.21	0.08-0.47	9.30 (0.358)	—	0.17	0.08-0.36	2.58 (0.546)	—
Occipital	0.23	0.10-0.45	9.00 (0.373)	—	0.43	0.17-0.68	42.65 (0.005)	—
Total	0.41	0.14-0.63	33.28 (0.028)	—	0.19	0.08-0.40	5.56 (0.338)	—

h^2: heritability; HPDI: 95% highest posterior density interval (credible intervals indicating that the heritability of each trait has 95% of probability to lie between the lower and the upper bounds); ΔDIC (P): difference in the deviance information criterion between the model with and without pedigree information (P-value); Fixed: significant fixed effects.



603

604 **Figure 1. Analysis of asymmetry based on interlandmark linear distances.** (a) Asymmetry
605 quotients for lobe proportions (mean AQs and standard errors). (b) Asymmetry quotients for
606 sulcal lengths. (c) Genetic correlations between left and right lobe proportions in chimpanzees (i)
607 and humans (ii). (d) Genetic correlations between left and right sulcal lengths in chimpanzees (i)
608 and humans (ii). Asterisks mark significant genetic correlations in (c) and (d), but no AQ shows
609 significant heritability in (a). Numerical values for heritabilities and color-coded genetic
610 correlations are provided in Tables S5, S8, S9 and S10. SF: superior frontal length; IF: inferior
611 frontal length; T: temporal length; SP: superior parietal length; IP: inferior parietal length; O:
612 occipital length; FOS: fronto-orbital sulcus (latero-orbital sulcus —LOS— in humans); PCS:

precentral sulcus; CS: central sulcus; SyF: Sylvian fissure; STS: superior temporal sulcus; LS: lunate sulcus (parieto-occipital sulcus —POS— in humans).

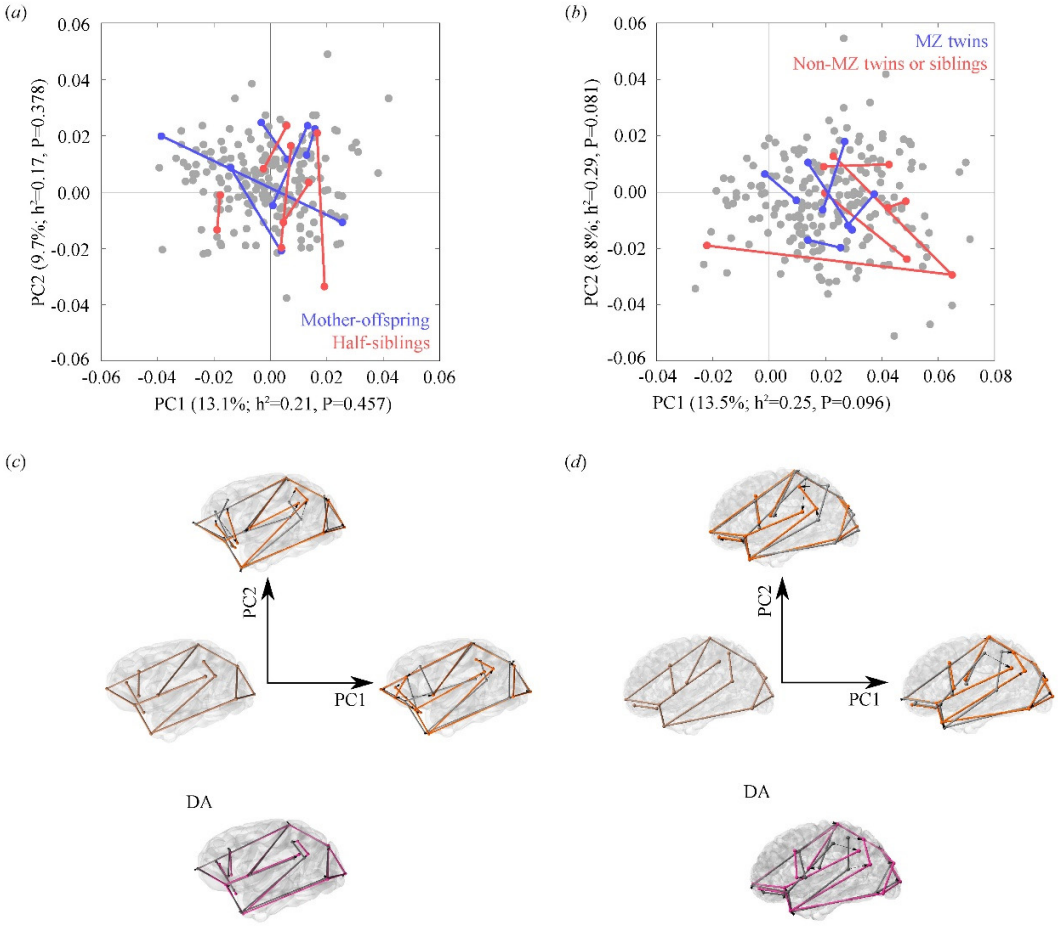
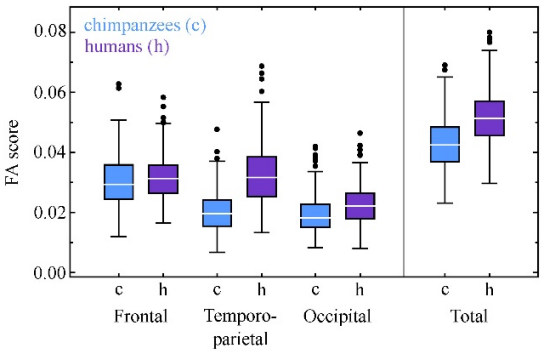


Figure 2. Geometric morphometric analysis of asymmetry. (a) Principal component analysis of asymmetric shape variation in chimpanzees showing five randomly selected mother-offspring and half-siblings pairs (50% versus 25% genetic similarity). (b) Principal component analysis of asymmetric shape variation showing five randomly selected pairs of monozygotic twins and of non-monozygotic twins or non-twin siblings (100% versus 50% genetic similarity). PCA plots in (a) and (b) are centered on a hypothetical perfectly symmetric individual. The percentage of variance explained by each PC and their heritabilities and P-values are provided (see tables S11 and S12 for extended information). (c) Major patterns of shape variation in chimpanzees. (d)

625 Major patterns of shape variation in humans. (c) and (d) show the symmetric consensus for each
626 species and major patterns of variation corresponding to the positive extremes of PC1 and PC2
627 (gray for the right hemisphere and orange for the left). The directional asymmetry (DA) pattern
628 for each species is shown on the bottom panels. For DA, gray corresponds to the right
629 hemisphere and magenta to the left hemisphere. PC1, PC2 and DA shape variation has been
630 exaggerated beyond the range observed in actual data to facilitate visualization.
631
632



633

634 **Figure 3. Fluctuating asymmetry scores for chimpanzees and humans.** FA scores have been
635 calculated as the residual variation in each individual after removing the DA pattern typical of
636 each species. Heritabilities of FA scores are provided in Table 1.

637