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Human torque is not present in chimpanzee brain

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Abstract: We searched for positional brain surface asymmetries measured as displacements between corresponding vertex pairs in relation to a mid-sagittal plane in Magnetic Resonance (MR) images of the brains of 223 humans and 70 chimpanzees. In humans deviations from symmetry were observed: 1) a Torque pattern comprising right-frontal and left-occipital "petalia" together with downward and rightward "bending" of the occipital extremity, 2) leftward displacement of the anterior temporal lobe and superior temporal sulcus (STS), and 3) posteriorly in the position of left occipito-temporal surface accompanied by a clockwise rotation of the left Sylvian Fissure around the left-right axis. None of these asymmetries was detected in the chimpanzee, nor was associated with a sex difference. However, 4) an area of cortex with its long axis parallel to the olfactory tract in the orbital surface of the frontal lobe was found in humans to be located higher on the left in females and higher on the right in males. In addition whereas the two hemispheres of the chimpanzee brain are equal in extent in each of the three dimensions of space, in the human brain the left hemisphere is longer ($p=3.6e-12$), and less tall ($p=1.9e-3$), but equal in width compared to the right. Thus the asymmetries in the human brain are potential correlates of the evolution of the faculty of language.

1. Cover Letter

Editor-in-Chief
Journal of NeuroImage

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06 September 2017

Re: COMPARATIVE STUDY OF IN-VIVO BRAIN ASYMMETRY IN HOMO SAPIENS AND PAN TROGLODYTES CONFIRMS YAKOVLEVIAN TORQUE IS HUMAN SPECIFIC(NIMG-17-1643R1)

Dear Dr. Marc Tittgemeyer,

Thank-you for forwarding the reports of three Reviewers concerning the above manuscript that we submitted for consideration for publication in NeuroImage.

We would like to thank the three Reviewers for their very helpful reports on this manuscript. We have responded in full to all of the advice and suggestions given and we believe this has led to significant improvements of the manuscript.

We hope you will find the revised manuscript suitable for publication in NeuroImage and look forward to hearing from you in due course.

Yours sincerely,
Professor Neil Roberts

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336.

HUMAN TORQUE IS NOT PRESENT IN CHIMPANZEE BRAIN

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Abstract

We searched for positional brain surface asymmetries measured as displacements between corresponding vertex pairs in relation to a mid-sagittal plane in Magnetic Resonance (MR) images of the brains of 223 humans and 70 chimpanzees. In humans deviations from symmetry were observed: 1) a Torque pattern comprising right-frontal and left-occipital "petalia" together with downward and rightward "bending" of the occipital extremity, 2) leftward displacement of the anterior temporal lobe and superior temporal sulcus (STS), and 3) posteriorly in the position of left occipito-temporal surface accompanied by a clockwise rotation of the left Sylvian Fissure around the left-right axis. None of these asymmetries was detected in the chimpanzee, nor was associated with a sex difference. However, 4) an area of cortex with its long axis parallel to the olfactory tract in the orbital surface of the frontal lobe was found in humans to be located higher on the left in females and higher on the right in males. In addition whereas the two hemispheres of the chimpanzee brain are equal in extent in each of the three dimensions of space, in the human brain the left hemisphere is longer (p=3.6e-12), and less tall (p=1.9e-3), but equal in width compared to the right. Thus the asymmetries in the human brain are potential correlates of the evolution of the faculty of language.

Keywords: Torque, petalia, occipital bending, asymmetry, chimpanzee, superior temporal sulcus

1. Introduction

As recorded by his son Gustave (Dax 1865), Marc Dax had reported the association of right hemiplegia with speech disturbance to the Montpellier Medical Society in 1836. Sixteen years later and within two years of publication of Darwin's Origin of Species, Paul Broca announced to the Société d'Anthropologie de Paris that a component of language is located in the frontal lobe on the left side of the brain (Broca 1861) and in 1877 he formulated the hypothesis that "Man is, of all the animals, the one whose brain … is the most asymmetrical. He is also the one who possesses the most acquired faculties. Among these faculties … the faculty of articulate language holds pride of place. It is this that distinguishes us the most clearly from the animals". Asymmetries of the Sylvian Fissure in the human brain were first described (Cunningham 1892; Eberstaller 1884; 1890) in the late nineteenth century (for a historical account of contributions relating to hemispheric function see (Harrington 1987)). Anatomical asymmetry was more widely discussed following a report (Geschwind and Levitsky 1968) of leftward area asymmetry of the planum temporale on the superior surface of the temporal lobe. The Sylvian Fissure was found to have an inclination closer to horizontal and of greater extent in the left hemisphere (Rubens et al., 1976).

Additional asymmetries have been reported (Witelson and Kigar 1988) of which perhaps the most prominent is a pattern first observed by (Eberstaller 1884) and referred to as the Yakovlevian Torque by LeMay (1976) following observation of corticospinal tract asymmetry by Yakovlev and Rakic (1966) in post-mortem brain. The Torque refers to an anticlockwise twist of the brain about the ventral-dorsal axis, especially in posterior regions (Glicksohn and Myslobodsky 1993; Maller et al., 2014), and is depicted, with artistic exaggeration for clarity, in Figure 2 of Toga and Thompson (2003). Since it is particularly evident on axial images produced by techniques such as X-Ray Computed Tomography (Bear et al., 1986; LeMay 1976) and Magnetic Resonance Imaging (MRI) (Kennedy et al., 1999; Watkins et al., 2001) the Torque has been extensively studied (Barrick et al., 2005) and is now perhaps the best known asymmetry of the human brain.

Chance et al. (2005) have proposed that the Torque is made up of two dissociable components. One of the components is a posterior shift of the left relative to the right cerebral hemisphere and which produces corresponding right frontal and left occipital "petalia" first reported as indentations of the inner surface of the cranium (e.g. in archaeological (Holloway and De La Costelareymondie 1982) and CT studies (LeMay 1976)). In a recent study, the typical combination of right frontal and left occipital petalia was reported to be found in 44% modern human brains (Balzeau et al., 2012). The second component of the Torque relates to differing distributions of cerebral tissue along the anterior-posterior dimension in each cerebral hemisphere. This has been studied in terms of lobar lengths (Bear et al., 1986; Highley et al., 1998), widths (LeMay 1976), and volumes (Barrick et al., 2005; Weinberger et al., 1982). However, in many studies, this Torque component may not have been separated from petalia (Barrick et al., 2005; Chance et al., 2005; Watkins et al., 2001).

An additional component of the Torque is "occipital bending" whereby in the occipital region brain tissue in the left cerebral hemisphere crosses the midline to displace tissue in the right hemisphere (Deutsch et al., 2000). In addition to crossing the midline the occipital pole of the left cerebral hemisphere is also displaced downwards (i.e. below) the occipital pole of the right hemisphere. Corballis and Morgan (1978) note that the direction of the Torque is opposite to that of the growth vector from left frontal to right occipital earlier reported for the formation of sulci by (Gratiolet 1839). Best (1988) conceived the diagonal trajectory across the left-right and antero-posterior dimensions as "a lateralized gradient of neuro-embryological development" that proceeds within a 3-dimensional frame that includes also the dorso-ventral axis; see also (Morgan 1991; Morgan and Corballis 1978).

The Torque and Sylvian Fissure asymmetries are the best established global and local asymmetries of the human brain. A further asymmetry in the Superior Temporal Sulcus (STS), reported to have a significantly greater depth in the right than the left cerebral hemisphere is proposed as a potential human-specific cerebral landmark (Leroy et al., 2015). Beneath the cortex the pyramidal tracts (Yakovlev and Rakic 1966) and the thalamic pulvinar (Highley et al., 2003) also exhibit asymmetries. However, particularly with reports of asymmetries in the chimpanzee (Cantalupo and Hopkins 2001; Gannon et al., 1998), whether any one of the anatomical asymmetries is specific to humans has been controversial (Crow 2004; Rogers 2004). In the present study 3D Magnetic Resonance Imaging (MRI) datasets were analysed to assess positional asymmetries in the human and chimpanzee brains and to investigate whether there is a difference in asymmetry between the two species. If the difference between the species is anatomically significant then it may be a potential correlate of the functional lateralisation that is widely reported to underlie language in humans and may therefore set a lower limit on the nature of the species transition, in particular whether these are gradual as Darwin believed, or whether (explicit in Broca's 1877 formulation) there is an element of saltation or discontinuity, i.e., a new genetic characteristic is introduced at a species boundary.

2. Materials and Methods

2.1 Subjects

MR images were acquired at the Montreal Neurological Institute (MNI), Montreal, Canada, West China Hospital, Chengdu, Peoples Republic of China (PRC) and Magnetic Resonance and Image Analysis Research Centre (MARIARC) University of Liverpool, UK, for 223 adult humans (101 females, 122 males) and at Yerkes National Primate Research Centre (YNPRC) in Atlanta, Georgia, USA for 70 chimpanzees (44 females, 26 males) with approval from the local Research Ethics Committee obtained by each institution. Chimpanzees were immobilized by ketamine injection (10 mg/kg) and subsequently anesthetized with propofol (40–60 mg/kg/hr) before transportation to the MRI facility where they remained anesthetized (total time ~2 hours) for the MR imaging and return to the home compound. Chimpanzees were scanned supine with a human head-coil.

Full details of data acquisition for the 142 Montreal human subjects (1 mm isotropic voxel resolution scans) are provided in Watkins et al. (2001). The 54 Chengdu human subjects were scanned using a 3T MRI system (Signa; GE Medical Systems) with a standard 8-channel phase array head coil. The acquisition parameters were: TR = 8.52 ms, TE = 3.4 ms, TI = 400 ms, Flip angle = 12, FOV = 240 mm x 240 mm and the images have a voxel resolution of 0.5 mm x 0.5 mm x 1 mm. The 27 Liverpool human subjects were scanned with a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) 3T MRI system (Trio; Siemens Medical Systems, Erlangen, Germany). The acquisition parameters were: TR = 2300 ms, TE = 4.4, TI = 1100 ms, Flip angle = 8, FOV = 200 mm x 200 mm and the images have an isotropic voxel resolution of 1 mm (Keller et al., 2009b). All human subjects in all three cohorts were in good health with no known neurological condition, psychiatric disorder or brain malformation. The 70 chimpanzees were scanned with identical acquisition parameters to the Liverpool human subjects except that voxel resolution was increased to 0.6 mm in the y direction giving an acquisition time of 36 min, compared to 12 min (y = 1 mm) in the Liverpool human subjects (Keller et al., 2009b). The chimpanzees were all reported to be healthy.

2.2 Post Image Analyses

A new image analysis pipeline was developed to examine positional asymmetry of the brain surface through study of the relationship between corresponding points in the two hemispheres on MRI scans of the brains for the combined database of 223 humans and 70 chimpanzees. The length, height and width of the left and right cerebral hemispheres in the two species were also computed to testify the global brain asymmetry using linear brain dimensions.

To examine cerebral asymmetries, the 3D T1-weighted MR images were first pre-processed in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) including skull strip, bias field correction and linear brain normalization using 7 degree of freedom transformations (i.e. 3 translations, 3 rotations and 1 uniform scaling). As a result, the extracted brains were normalized to the standard MNI coordinate system. Second, the processed brain images were analysed in the standard FreeSurfer processing stream (https://surfer.nmr.mgh.harvard.edu/), in which the surface-based module enables high quality pial surface reconstruction from the brain volume data by following the signal intensity gradient between grey matter and CSF with subvoxel accuracy (Dale 1999) on the 3D T1 weighted images.

Concerning the computation of the correspondence between vertices in the left and right cerebral hemispheres, a high dimensional non-linear registration was employed to match the vertices of each cerebral hemisphere to a pre-trained symmetrical reference based on a set of curvature-based descriptors (e.g. the spatial relationship of each vertex to neighbouring vertices) that was quantitatively computed at each surface location (i.e. vertex). Because both left and right cerebral hemispheres for each subject were registered to the same reference template the correspondence between the vertices in the two hemispheres as well as the correspondence between vertices in individual subjects were in turn revealed, which allows a statistical vertex-wise inter-hemispheric comparison of cortical morphology in corresponding folds (i.e. sulci and gyri) to be performed. The whole procedure is well established in FreeSurfer software and described in detail by (Greve et al., 2013).

2.3 Positional Asymmetry Computation

The computation of positional brain asymmetry is based on a Mid-Sagittal Plane (MSP) the accuracy of which is therefore essential. As part of the image processing pipeline described in above Section 2.2 the 3D MRI brain image has already been normalized to the MNI coordinate system in FSL. Thus, the three axes (i.e., x,y,z) of the MNI coordinate system by default correspond to the left-right, anterior-posterior and dorsal-ventral directions of the brain and the plane x=0 represents the MSP with respect to which the inter-hemisphere difference between corresponding voxels/vertices in the left and right cerebral hemisphere was often computed (Good et al., 2001; Lyttelton et al., 2009; Watkins et al., 2001). However, cautions must be paid to the potential bias introduced by plane x=0 (Balzeau and Gilissen 2010) given that the low-dimensional linear registration is likely to fail in aligning the true brain MSP to x=0 due to the asymmetric nature of the brain. In order to accurately measure positional brain asymmetry, a new reference MSP was defined in the present study as the least squares plane that best fits the 3D vertices on the medial surface of the brain lying within 5 mm to x=0 in the MNI coordinate system rather than all vertices across the brain surface. This MSP is therefore the plane representing the Inter-hemispheric Fissure unaffected by deviation particularly in the occipital portion of the human brain referred to as occipital bending, convexities and concavities of the medial surface of the brain, and asymmetries of the lateral surface of the brain. Following the computation of the brain-MSP, the three axes of MNI coordinate system were rotated by the 3D angle α between the surface normals of the brain-MSP and plane x=0 (i.e., x-axis). The positional differences between the two cerebral hemispheres were determined on a vertex basis to assess displacements along the left-right, antero-posterior and ventro-dorsal axes for each brain. In particular, antero-posterior brain asymmetry ($Asym^{AP}$) and the dorsal-ventral brain asymmetry ($Asym^{DV}$) were measured as the projections of the displacement vector between the left and right corresponding points along the refined anterior-posterior and dorsal-ventral axes; while the left-right brain asymmetry ($Asym^{LR}$) was computed as the distance of a vertex on the left hemispheric surface to brain-MSP subtracted from that of its corresponding vertex on the right hemispheric surface. The individual surface-asymmetry maps were further smoothed using a 15-mm full-width/half-maximum (FWHM) filter to increase the signal-to-noise ratio.

During inter-hemispheric registration both hemispheres of all 223 human and 70 chimpanzee subjects were registered to the same hemisphere-unbiased reference and therefore the resulting vertex-wise $Asym^{LR}$, $Asym^{AP}$ and $Asym^{DV}$ maps are inherently mapped to the standard surface space. For each species, a statistical analysis (one-sample t-test) was performed at each surface location for each asymmetry map (i.e., $Asym^{LR}$ or $Asym^{AP}$ or $Asym^{DV}$) independently against the null hypothesis that the brain is symmetric. The threshold level that is applied in the measurement of positional brain asymmetry is zero. To control for false positive error (Barch and Yarkoni 2013) in multiple comparisons, a correction was performed to identify clusters comprising vertices whose neighbouring vertices also show significant effects (i.e. the vertex-wise un-controlled p-value or cluster-forming vertex-wise p-value is less than 0.001). Subsequently, these clusters are thresholded to identify those with a size greater than a limit based on Gaussian Random Field (GRF) theory, validated with Monte Carlo simulations, and under the null hypothesis this cluster-wise threshold was set to $p<0.005$. The statistical analysis is well established in FreeSurfer software (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis) and a detailed description of the process can be found in (Greve et al., 2013; Hagler et al., 2006). The corrected p-value was rendered on corresponding 3D representations of the brain to represent the three components of the inter-hemispheric displacement (see Figures 1, 2 and 3, columns 1 and 4). A hot colour is used to indicate leftward asymmetry in the sense that i) the left cerebral hemisphere deviates further from the brain-MSP than the right in Asym^{LR}, ii) the left hemisphere shifts posteriorly compared to the right in Asym^{AP} or iii) the left hemisphere shifts superiorly compared to its right counterpart in Asym^{DV}; while a cool colour indicates a rightward asymmetry in the contrary sense.

Furthermore, in a Supplementary Analysis brain positional asymmetry was measured separately for the independent cohorts recruited at the imaging centres in three different countries in order to test whether the findings are consistent across cohorts and the findings are presented in Supplementary Information. If consistency is obtained in the results across cohorts this will support the suggestion that the effects are real and not due to false positive error. In addition, a Supplementary Analysis was performed to determine the effect of normalisation to a common human reference template or to respective human and chimpanzee specific templates.

2.4 Species Comparison Analysis

To evaluate potential group differences in brain surface positional asymmetry between human and chimpanzee a statistical analysis was performed at each vertex using a two-sample t-test (see column 2 in Figures 1, 2 and 3), followed by a cluster-wise multiple comparisons correction as mentioned above (with cluster-forming vertex-wise threshold of $p<0.001$ and cluster-wise threshold of $p<0.005$). The colours in columns 2 and 3 of Figures 1, 2 and 3 highlight regions of the brain surface where there is a significant species difference in positional asymmetry. In particular a hot colour means greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours, and to interpret the species difference one also needs to refer to asymmetry maps of individual species in columns 1 and 4.

In addition the average asymmetries in female and male brain for the human and chimpanzee were computed (see columns 1 and 3, and 4 and 6, of Figure 4, respectively) and subsequently the significant differences between the sexes in humans (column 2) and chimpanzees (column 4) were determined respectively at the cluster level corrected for multiple comparisons (with cluster-forming vertex-wise threshold of $p<0.001$ and cluster-wise threshold of $p<0.005$).

2.5 Brain Dimensions and Inter-Hemisphere Asymmetry

Besides comparison of positional asymmetry between corresponding cortical folds, asymmetries of overall brain dimensions (i.e. length, height and width) were investigated in the following steps for each brain: i) the whole brain surface was rotated through the 3D angle $-\alpha$ (i.e. the angle between the surface normals of brain-MSP and x=0 in MNI coordinate system estimated in Section 2.3) to align the brain-MSP parallel to the x=0 plane in MNI coordinate space, ii) for each surface of interest (i.e. hemisphere surfaces and whole brain surface), the smallest orthogonal parallelpiped box that just covers the surface with the edges of the bounding box parallel to the three axes in MNI coordinate space was fitted to the brain. The dimensions of the bounding box thus specify the length, height and width of each surface. In other words, the length, height and width are measured as the maximal extension of the brain along left-right, anterior-posterior and dorsal-ventral axes, respectively. To obtain the size in the real world, brain dimensions were further divided by the scaling factor previously computed and recorded from FSL in the brain normalization step (in Section 2.2). A one-tailed paired t-test was applied to investigate the inter-hemispheric asymmetries of the computed brain dimensions with a threshold of $p < 0.01$.

3. Results

3.1 Species Differences in Brain Asymmetry

Overall, the cerebral surface is more asymmetric in the human brain compared to the chimpanzee. To be specific, the percentage of the cerebral surface classed as asymmetrical is 69.8% in $Asym^{LR}$, 74.8% in $Asym^{AP}$ and 38.1% in $Asym^{DV}$ in human, respectively; while 31.1% in $Asym^{LR}$, 10.5% in $Asym^{AP}$ and 5.3% in $Asym^{DV}$ in the chimpanzee brain. Those features which distinguish the species by both vertex-wise and cluster-wise criteria along left-right ($Asym^{LR}$), antero-posterior ($Asym^{AP}$) and dorso-ventral ($Asym^{DV}$) axes can be seen in Figures 1 to 3, columns 2 and 3, respectively.

Two features distinguish the species in the left-right direction (Figure 1):
1) an area of brain surface encompassing the temporal pole and demarcating the superior temporal sulcus (STS) is leftwardly asymmetric (hot colour) in Figure 1 (row 2, columns 2 and 3), and

2) an area of rightward asymmetry (cool colour) extends over the occipital pole, and surrounds area 1 above on the occipito-temporal aspect of the human brain. On the medial aspect (row 4, columns 2 and 3) there is leftward asymmetry of the precuneus and rightward asymmetry of sulcus corporis callosi just beneath the cingulate gyrus, and in the para-cingulate (superior frontal) gyrus above it.

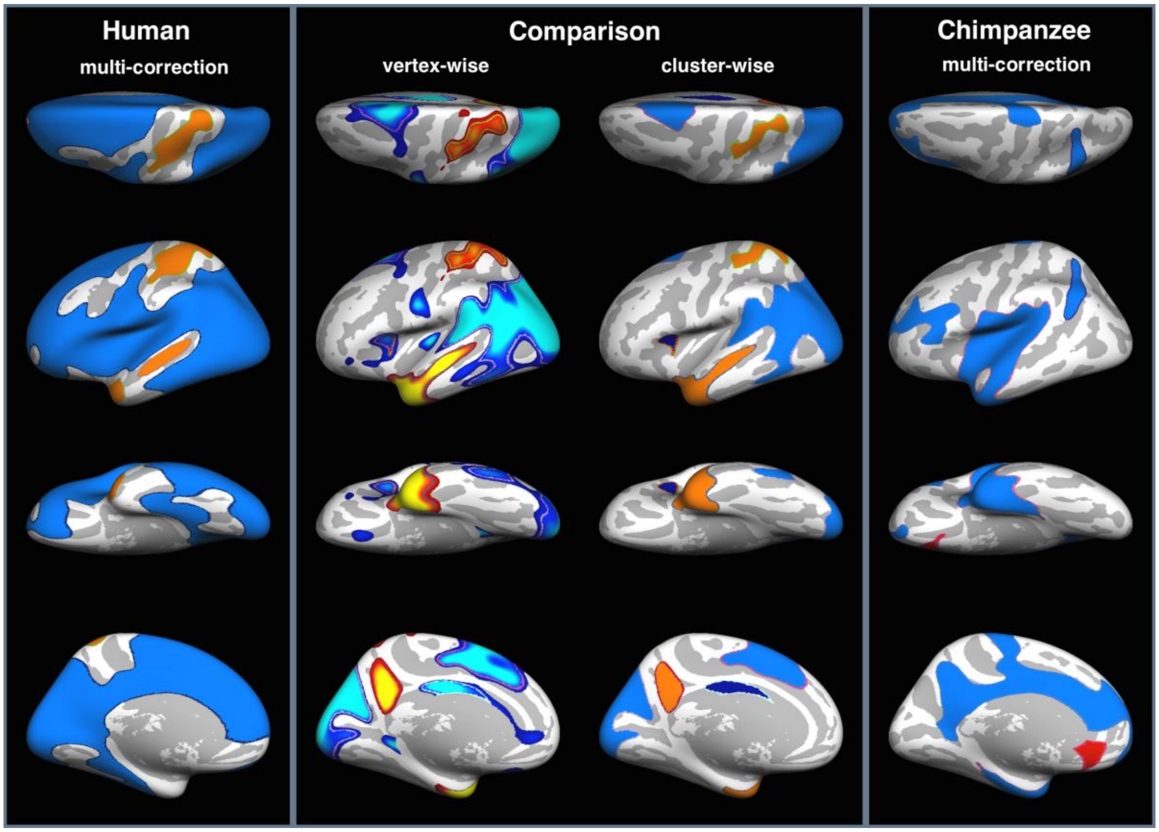

Figure 1: Species difference in left-right positional brain asymmetry (Asym^{LR}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value thresholded at p<0.01) are demonstrated for humans and chimpanzees respectively with hot colours indicating leftward deviations and cool colours for rightward deviations. Column 2 shows the p-value (thresholded at p<0.01) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3 shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 69.8% of the surface in the Asym^{LR} orientation in the human compared to 31.1% in the chimpanzee brain is classed as asymmetrical.

In the antero-posterior direction (Figure 2), the whole of the brain surface between the temporal and occipital poles is displaced posteriorly (columns 2 and 3, rows 1 to 3) in the left hemisphere relative to the right hemisphere in addition to a small patch at the frontal pole region in the human but not in the chimpanzee brain. This area of backward displacement extends onto the medial surface where it overlaps the cuneus and precuneus (row 4, columns 2 and 3). It is notable that both the frontal and occipital poles are involved in this posterior shift. Conversely, a structure that appears contiguous with the structure located in the sulcus corpus callosi in Figure 1 is displaced anteriorly (blue) across the cingulate gyrus in the left relative to the right cerebral hemisphere.

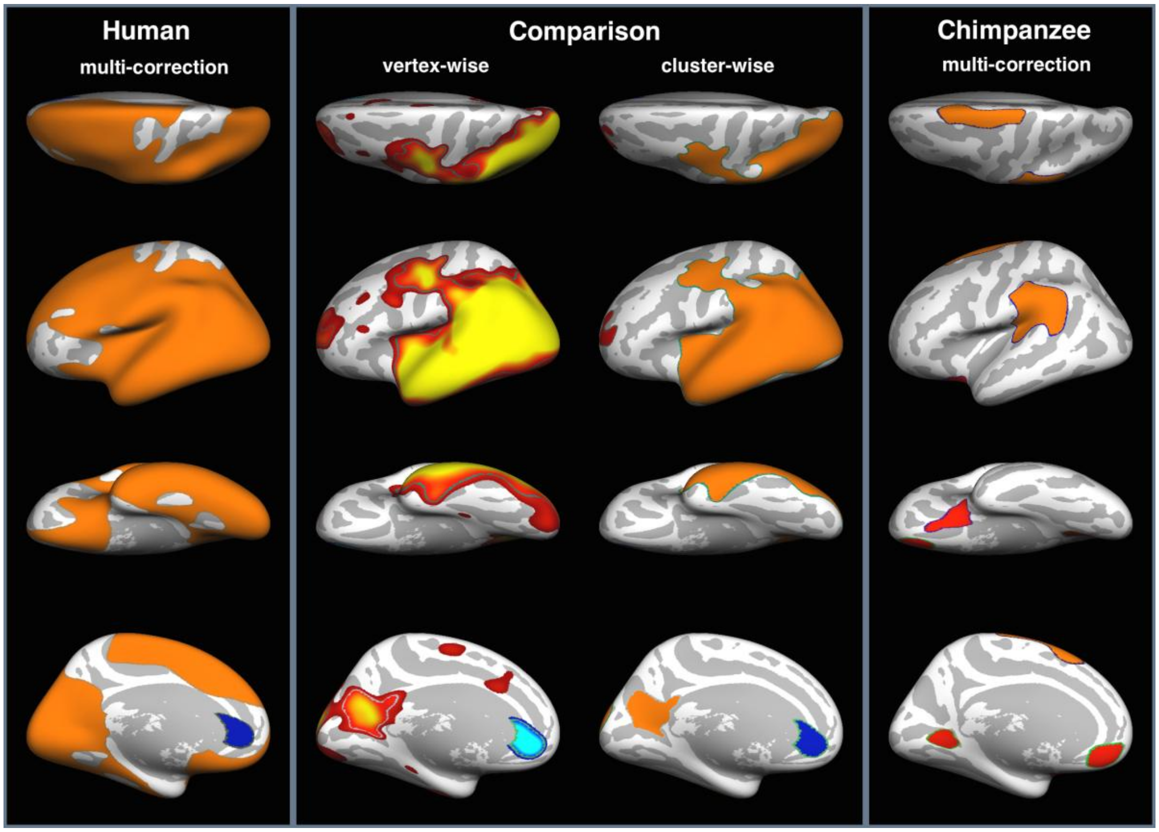

Figure 2: Species difference in antero-posterior positional brain asymmetry (Asym^{AP}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value thresholded at p<0.01) are demonstrated for humans and chimpanzees respectively. Hot colour indicates that a given structure in the left hemisphere is displaced posteriorly relative to the right and cool colours suggests that such a structure is displaced anteriorly relative to the right. Column 2 shows the p-value (thresholded at p<0.01) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3

shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 74.8% of the surface in the $Asym^{AP}$ orientation in the human compared to 10.5% in the chimpanzee brain is classed as asymmetrical.

With regard to the dorso-ventral direction (Figure 3) two asymmetries are observed on the lateral aspect of the cerebral hemisphere in humans:

1) the left temporal pole and frontal poles are elevated superiorly relative to the right and the occipital pole is displaced inferiorly in the left relative to the right cerebral hemisphere in humans, and

2) a region around the posterior Sylvian Fissure extending into the inferior parietal lobe is displaced downwards in the left compared to the right cerebral hemisphere in humans. Interestingly, there is suggestion of a possible Sylvian Fissure movement in the opposite direction in the chimpanzee brain, that is to say, the chimpanzee may have a higher posterior Sylvian point on the left compared to the right hemisphere.

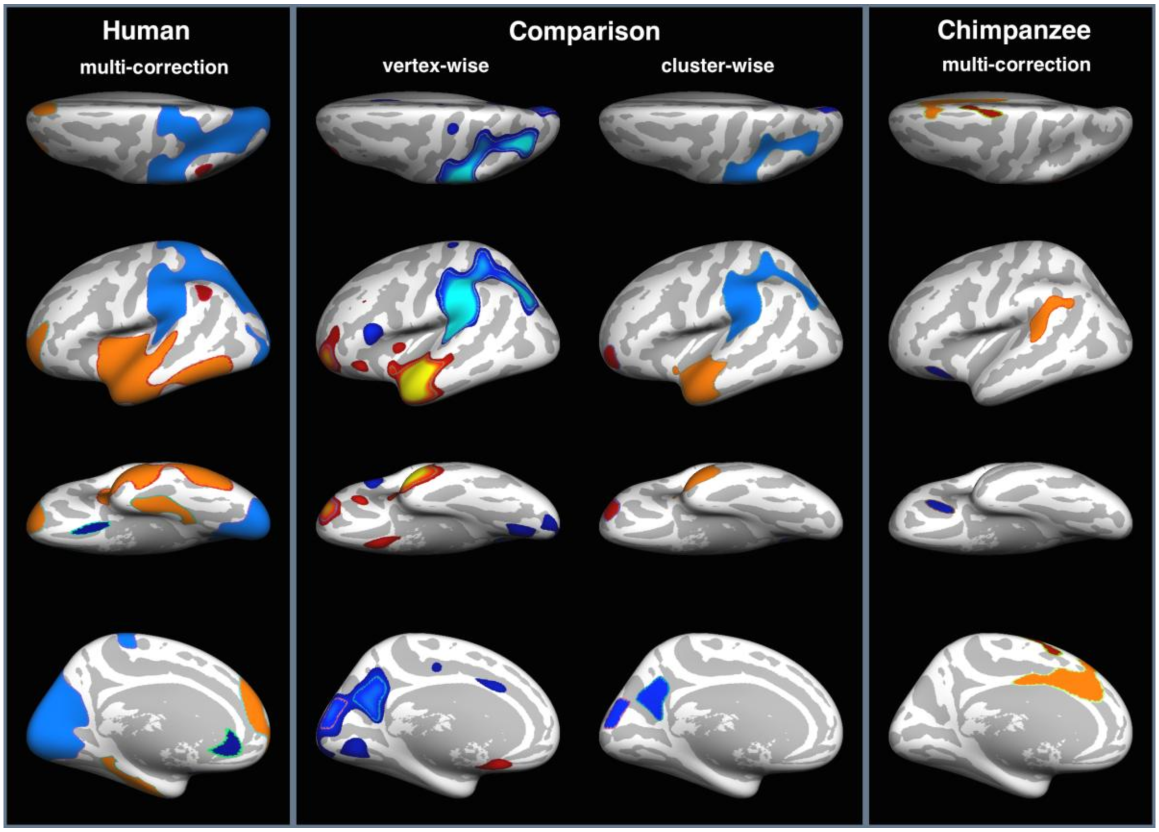

Figure 3: Species difference in dorso-ventral (i.e. up-down) positional brain asymmetry (Asym^{DV}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value) are demonstrated for humans and chimpanzees respectively with hot colour representing leftward dorsal deviations and cool colours for ventral deviations. Column 2 shows the p-value (thresholded at $p<0.01$) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3 shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 38.1% of the surface in the Asym^{DV} orientation in the human compared to 5.3% in the chimpanzee brain is classed as asymmetrical.

3.2 Sex Difference

Next, sex differences in surface positional asymmetry were assessed at each vertex in the two species corrected for multiple comparisons. In the left-right direction no sex difference survived correction for multiple comparisons in either species. This was also true in the antero-posterior direction although the rostral-most boundary of the structure identified as continuous with the sulcus corpus callosi (see Figures 1 and 2) was more prominent in human females than males in the uncorrected comparison. The single region of difference in asymmetry between the sexes that is significant after correction for multiple comparisons is in the dorso-ventral direction in the human brain. In particular, a region in the antero-lateral aspect of the orbital frontal surface (Figure 4, row 3, column 2) distinguishes females from males, such that males show relative downward displacement in the left relative to the right cerebral hemisphere that is significant, while in females the asymmetry is in the opposite direction although is not significant. However, in contrast to their relative displacement, when each sex was studied individually neither of these sex-specific asymmetries survives correction for multiple comparisons. No sex difference in asymmetry was observed in the chimpanzee brain.

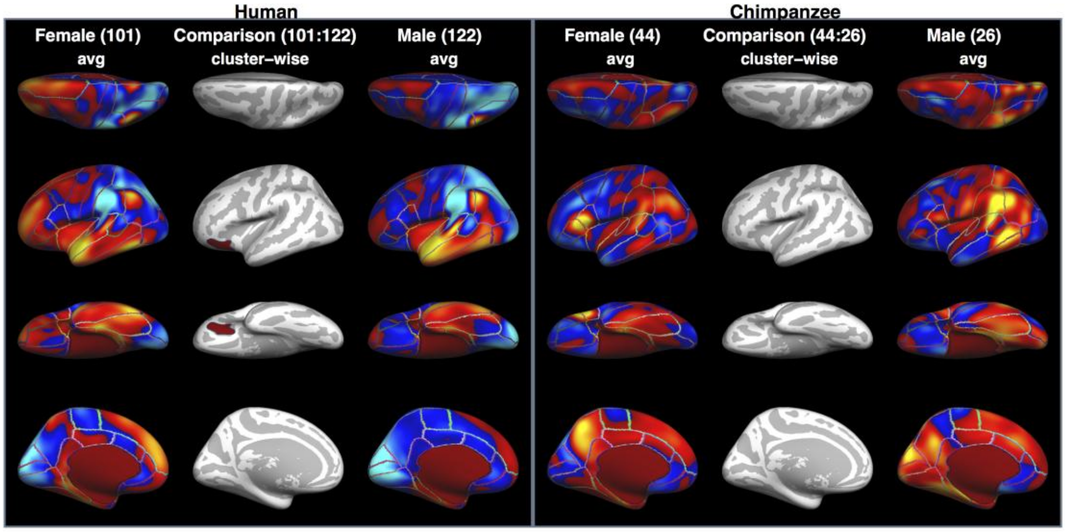

Figure 4: Sex difference in dorso-ventral positional brain asymmetry ($Asym^{DV}$). Columns 1 and 3 represent average asymmetries in human females and males respectively, and columns 4 and 6 represent average asymmetries in female and male chimpanzees respectively. Columns 2 and 5 represent the significant differences between the sexes assessed by cluster-wise analysis for humans (column 2) and chimpanzees (column 5) both corrected for multiple comparisons.

3.3 Brain Dimensions

Measurement of the length, height and width of the cerebral hemispheres for 223 human and 70 chimpanzee brains revealed that the left cerebral hemisphere of the human brain is significantly longer and of significantly less height, but unchanged in width, compared to the right cerebral hemisphere. By contrast the left cerebral hemisphere of the chimpanzee matches closely the right cerebral hemisphere in length, height and width (Table 1).

Human Brain Dimensions and Cross Hemisphere Asymmetry (in mm ± sd)									
	Left Hemisphere			**Right Hemisphere**			**Asymmetry (Left-Right)**		
	Length	**Height**	**Width**	**Length**	**Height**	**Width**	**Length**	**Height**	**Width**
AVG	170.8±8.6	115.2±5.4	70.5±3.9	169.9±8.6	115.8±5.7	70.6±3.9	0.9	-0.5	-0.0
pval	**LEFT>RIGHT, Left hemisphere is longer**						**3.6e-12**		
	LEFT<RIGHT, Left hemisphere is shorter							**1.9e-03**	
	No significant width difference between two hemispheres								0.9
Chimpanzee Brain Dimensions (in mm)									
AVG	110.5±4.4	74.5±3.4	45.1±20.8	110.4±4.3	74.4±3.5	45.0±2.1	0.1	0.1	0.1
pval	No significant length difference between two hemispheres						0.4		
	No significant height difference between two hemispheres							0.6	
	No significant width difference between two hemispheres								0.7

Table 1: Brain dimensions and inter-hemispherical asymmetries. By one-tailed paired t-tests the human brain has a left hemisphere that is significantly elongated and less tall in comparison to the right, but shows no width difference between the hemispheres. In contrast, the chimpanzee brain (below) shows no hemispheric asymmetry in any of the three dimensions.

4. Discussion

In this study, a surface-based approach that complements Voxel Based Morphometry (VBM) (Good et al., 2001; Watkins et al., 2001) was used to assess the positional asymmetry of the cortical surface. High-dimensional surface registration enhances fidelity of alignment to the brain folding pattern (Van Essen 2005; Van Essen et al., 2012). By contrast with studies that consider only the relative distances between the left and a mirrored right hemisphere at corresponding locations (Lyttelton et al., 2009; Van Essen et al., 2012; Zilles et al., 1996), and conventional VBM based studies that take only the left-right asymmetry into account, the new method considers both direction and magnitude by decomposing the asymmetries in three orthogonal directions. The approach therefore provides a detailed, comprehensive analysis of positional brain asymmetry.

We identify four major features of the brain surface that distinguish the brain of *Homo* sapiens from that of *Pan* troglodytes, on account of exhibiting significant hemispheric asymmetry in the former and being absent in the latter:

1) a Torque pattern (i.e., anticlockwise twist) comprising right frontal and left occipital petalia and rightward and downwards bending of the left occipital pole relative to the right occipital pole,

2) leftward asymmetry of the lateral surface of the anterior temporal lobe and STS. The leftward asymmetry of STS indicates that the sulcus depth of the STS in the right cerebral hemisphere is nearer to the MSP than it is in the left cerebral hemisphere whereas the adjacent brain surface (i.e., surrounding gyrus) shows the opposite effect. Taken together these facts are consistent with the conclusion that the human specific area identified with the STS is of greater depth in the right in the right than the left hemisphere (Leroy et al., 2015). Comparable asymmetries have been identified in antenatal (Kasprian et al., 2010) and neonatal (Glasel et al., 2011) human brains.

3) posterior expansion of the lateral surface of the left temporo-occipital region (including Heschl's gyrus and planum temporale) with clockwise rotation of the left Sylvian Fissure relative to the right around the left-right axis (observed from the dorsal-ventral asymmetry map),

4) an area of the orbito-frontal surface is found in females to be located higher (further dorsal) in the left compared to the right hemisphere and in males higher in the right compared to the left hemisphere.

If the above asymmetries are each characteristic of the human brain it is plausible that they are related. One possibility is that the leftward asymmetry that envelopes the temporal pole (see Figure 1, columns 2 and 3, rows 1 to 3) and tapers diagonally along the STS to end just short of the posterior termination point of the Sylvian Fissure is continuous with the rightward asymmetry that extends as a line between the corpus callosum below and the cingulate gyrus above to reach into the para-olfactory region in orbital cortex (see Figure 1, columns 2 and 3, row 4). Interestingly, a white matter pathway lying coincident with this trajectory is the indusium griseum (Di Ieva et al., 2015) which comprises four parallel tracts (the striae of Lancisi) that constitute a focus of generation of stem cells in the human brain.

The association of asymmetry with the human species is further illustrated by significant differences in length and height between the hemispheres in the human brain that are absent in that of the chimpanzee (Table 1). The overall length asymmetry is interpreted as an extension of the left cerebral hemisphere along the antero-posterior axis (3) that is in line with more prominent left occipital than right frontal petalia (Bear et al., 1986; Smith 1907). The posterior extension may also explain the greater length of Sylvian Fissure in the left than the right cerebral hemisphere, the leftward area asymmetry of the plana temporale and parietale (Lyttelton et al., 2009) and the phenomena of occipital bending (Deutsch et al., 2000). The height asymmetry is possibly related to the clockwise rotation at Sylvian Fissure (3), which produces a lesser angle of the posterior segment of the Fissure (Witelson and Kigar 1988), less high posterior Sylvian point (Rubens et al., 1976) and lower occipital pole in the left relative to the right cerebral hemisphere.

The fact that hardly any chimpanzee specific asymmetries can be documented is notable. Because the brains of both species are normalized to the size of the standard MNI template brain in the FSL pre-processing steps, the failure to detect asymmetries in chimpanzee should not be attributable to the relatively smaller brain size. We can also confirm that the findings i) are remarkably consistent between the subject cohorts and are therefore not due to type 1 error (see Figure 1S in the Supplementary Information) and ii) do not depend upon whether human and chimpanzee 3D MRI scans are normalized to a common human reference template or to respective human and chimpanzee specific templates (see Figure 2S in the Supplementary Information and also (Hopkins et al., 2016)).

The primary asymmetric feature observed is the Torque pattern in the human brain. In particular, the left occipital lobe shifts relatively more posteriorly ($asym^{AP}$), bends to the right ($asym^{LR}$) and moves downwards ($asym^{DV}$) relative to the right side; and the right frontal lobe protrudes further anteriorly compared to its left counterpart. These results are most closely comparable to a previous MRI study of 29 in-vivo brain of human males and 9 post-mortem brain of chimpanzees (Zilles et al., 1996, reviewed in Gilissen 2001). In that study, the authors investigated the inter-hemispheric discrepancy based on a subtraction of the 3D surface of the left cerebral hemisphere and the mirror image of the 3D surface of the right cerebral hemisphere. Comparable to our findings, significant asymmetry of the occipital lobe was observed only in the human brains. The absence of the Torque pattern in chimpanzees at the population-level also concurs with observations by Holloway and De La Costelareymondie (1982). In a study of 190 hominoid endocasts, the authors concluded that only modern *Homo* and hominids (*Australopithecus, Homo erectus*, Neanderthals) show a distinct left-occipital, right-frontal petalial pattern… and that the pattern is relatively invariant and has been for perhaps as much as 3 x 10^6 years. Balzeau and Gilissen (2010) approached the study of asymmetry in hominin evolution through examination of physical and virtual endocasts (computerized tomograms) from museum collections. With the use of seven cranial landmarks in CT scans of 36 *Pan* paniscus, 36 *Pan* troglodytes and 38 Gorilla these authors reported finding the same petalia in apes as was identified by LeMay (1976) although conceded that "analyzed as non-metric traits most ... were characterized by equal distributions between the right and left sides (ranging between 40% and –60% for each side)". A similar result was reproduced by the same group in another endocast study including 89 hominins samples in addition to 110 great apes, from which the authors concluded that the asymmetry is a pattern that is shared by great apes as well as humans (Balzeau et al., 2012). Differing findings in different studies may be due to differing definitions of the reference plane with respect to which the asymmetry is computed. In the present study, a best fitting Inter-hemispheric Fissure (i.e., MSP) was extracted from the data relating to the medial surface of each cerebral hemisphere to represent the Left-Right centre of the brain whereas in (Balzeau and Gilissen 2010; Balzeau et al., 2012), an "external and independent reference" of the brain, was built upon three anatomical landmarks manually selected on the mid-surface of the skull, namely glabella, inion, and basion. Other possible interpretations of the discrepancy are i) different measuring approaches, ii) different specimens and iii) different sample sizes. Based on a direct comparison between the live brains of modern humans and chimpanzees analyzed in an identical pipeline, our findings challenge claims for directional specificity of the Torque in the chimpanzee (Balzeau and Gilissen 2010; Balzeau et al., 2012; LeMay 1976) and provide the most robust evidence obtained to date to indicate that the Torque, at least, petalia and occipital bending, is human-specific. Although the role of the Torque in determining the laterality of brain functions is not known, it is interesting that an atypical Torque pattern has been associated with developing stuttering (Foundas et al., 2003).

The only sex difference in positional brain asymmetry is located in orbito-frontal cortex. No sex differences in cerebral asymmetry are seen elsewhere whereas here no asymmetry is apparent unless the sexes are separated, whereupon a sex difference in surface asymmetry is observed such that the left surface is displaced upward relative to right in females and downward relative to right in males (Figure 4 rows 2 and 3, column 2). No such interaction between sex and asymmetry is seen anywhere on the cerebral surface of the chimpanzee brain. Congruent evidence of a lateralized difference between the sexes in orbito-frontal cortex comes from a meta-analysis of studies of sex differences in the human brain (Ruigrok et al., 2014) in which it is reported that a cluster of increased grey matter density in left relative to right orbito-frontal cortex (see Figure 4c in reference 23) is present only in males. The position and extent of this cluster resemble those of the region denoting a sex difference in our Figure 4. This sex difference in asymmetry is not associated with the Torque, but may be related to unilateral responses in right orbito-frontal cortex following olfactory stimuli (Zatorre et al., 1992). In independent fMRI experiments such activations are greater in women (Yousem et al., 1999).

The literature on cortical asymmetry in chimpanzees, other great apes and primates is perplexing. Besides the equivocal reports of the Torque in apes mentioned above, in one study the cortical surface area of the planum temporale was greater in the left hemisphere than the right in 17 out of 18 chimpanzee brains (Gannon et al., 1998) and in another study area 44 described as Broca's area in the inferior frontal gyrus, bounded by fronto-orbital, and pre-central inferior sulci was of greater magnitude in the left than the right hemisphere in a group of 20 chimpanzees, 5 bonobos and two gorillas (Cantalupo and Hopkins 2001). These reports are not in agreement with aspects of our findings. In particular we do not find circumscribed asymmetries of cortical regions corresponding to Broca's and Wernicke's areas in humans. No specific relationship between the asymmetries of these regions and language has been found in language dominance studies (Greve et al., 2013; Keller et al., 2009a; Keller et al., 2011).

Furthermore, textbook descriptions of Broca's area imply a greater anatomical focus of speech disturbance than is justified by empirical investigation (Conrad 1954; Lenneberg 1967; Russell 1961) and however defined these areas have not been shown to have consistent cyto-architectonic correlates (Sholl 1956). In addition, based on modern imaging techniques (e.g., fMRI, PET), language-relevant areas should be expanded beyond the classic language regions (Price 2012; Tremblay and Dick 2016). In another investigation 4 of 11 sulci tested in chimpanzees and 1 out of 7 in macaques showed evidence of directional asymmetry (Bogart et al., 2012) but the one instance in macaques is in the STS which is judged to be a human-specific asymmetry by the same group in a later study (Leroy et al., 2015). In another endocast study, Balzeau et al. (2014) reported a lower position of the third frontal convolution (corresponding to Broca's area) on the left relative to the right which is unique in *Pan* troglodytes and not present in *Pan* paniscus and hominins. In the present study, no chimpanzee specific asymmetry can be observed in this region. Although, at a neighbouring orbital frontal region, an asymmetry in the same direction was found in chimpanzees, which is however also shared with humans (a blue patch in Figure 3, row3, columns 1 and 4). We suggest that there is merit in approaching the origins of language through inter-species comparisons in which the techniques applied are matched as closely as possible between species, without preconception concerning the functions of particular areas of cortex. By these criteria asymmetry between the hemispheres in the form of the Torque is not ruled out as the key to the capacity for language as Broca conjectured.

There are at least three limitations in the present study. First, with regard to the sex difference, the human group comprised 101 females and 122 males (0.8:1) and the chimpanzee group comprised 44 females and 26 males (1.7:1). Thus there is a potential bias in the sex ratio toward males in the human group which approximates doubling of the number of females compared to males in the chimpanzee group. Second, it is worth noting that although the surface-based non-linear registration in FreeSurfer works well on aligning folding patterns in general, the fidelity of registration can be weak at regions with high individual shape variability (Van Essen 2005; Van Essen et al., 2012), such as parietal cortex, to some extent. Cautions must be observed when interpreting the asymmetry in the associated regions and improvement in the registration algorithm is to be considered in the future. Nonetheless, this problem should not cause much concerns in the current study since the key findings are mostly located in the peri-Sylvian Fissure, temporal, occipital and frontal regions that are of comparatively low individual shape variability. Third, with regard to the cerebral Torque, further work needs to be performed aimed at deriving a quantitative measure of this prominent asymmetry.

5. Conclusion

Our findings suggest a particular lateralization (described as the Torque from right frontal to left occipital and notably more prominent in the posterior or sensory half of the cerebrum) distinguishes the human brain from that of our closest extant relative the chimpanzee. This finding should motivate research to elucidate whether the Torque has a specific role with respect to the capacity for language in humans.

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Author Contributions: X.L. devised the methods for analysing positional brain asymmetry on 3D MR images, applied the methods to all data-sets, conducted statistical analyses and prepared Figures. T.J.C. and N.R. devised and planned the project, co-ordinated analysis and wrote the paper with X.L.. W.D.H. instituted and managed MRI scanning of chimpanzees, and contributed to study design. Q.G. contributed MRI scans and data. All authors reviewed and approved the paper.

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Ms. No.: NIMG-17-1643

Title: (as originally submitted) COMPARATIVE STUDY OF IN-VIVO BRAIN ASYMMETRY IN HOMO SAPIENS AND PAN TROGLODYTES CONFIRMS YAKOVLEVIAN TORQUE IS HUMAN SPECIFIC

Revised title (on resubmission): HUMAN TORQUE IS NOT PRESENT IN CHIMPANZEE BRAIN

Corresponding Author: Professor Neil Roberts
Authors: X Li; T.J. Crow; W.D. Hopkins; Q. Gong;

We would like to thank the three Reviewers for their very helpful reports on this manuscript. We have responded in full to all of the advice and suggestions given and we believe this has led to significant improvements of the manuscript that we wish to re-submit for further consideration for publication in NeuroImage.

Below we provide a description of the responses made to each of the points raised by the Reviewers and an annotated version of the manuscript is attached in which the revisions can be identified via yellow highlighting of the appropriate text.

REVIEWER #1:

[1] With regard to the new method for measuring Positional Brain Asymmetry Reviewer #1 states: ***My main comment concerns the use of a MSP to quantify bilateral variations of the brain. The brain being asymmetric (and if not as the purpose it to test whether it is, the issue remain the same), the MSP is influenced by the asymmetry. As a result, what you describe influences the way you qualify the features. That's a real problem. Is not it possible with your method to use the interhemispheric fissure to quantify the bilateral differences between both hemispheres? Or at least to quantify the difference between the MSP and the interhemispheric fissure?***

And more specifically: ***What is a "best-fitting MSP"? I do not understand the constraint of "… lie within 5 mm of x=0". Does it mean that the msp is not defined in 3D? Only along the x axis?***

Also: ***The sentence "…produces a more accurate estimation of the location of the mid plane that separates the two hemispheres" is problematic for the reason explained above. Aren't they other solution (inter-hemispheric or plane defined relatively to the skull…).***

Also: ***"The relationship between corresponding points" how the points are defined as corresponding points? Is it an orthogonal and equidistant projection relatively to the MSP?***

Also: ***At the end of the page "… corresponding vertex", again you do not explain how this correspondence is defined.***

Also: ***You state "… to represent the three components of the inter-hemispheric displacement", it is not true as you use a MSP.***

From consideration of the above, we understand that the Reviewer is essentially asking four questions:

(i) How is the MSP defined?
(ii) Is the definition of the MSP influenced by brain asymmetry?
(iii) How are the corresponding points defined?
(iv) How are the three components of displacement measured?

With respect to points (i) and (ii), the MSP is the plane representing the Inter-hemispheric Fissure of the brain and especially constructed so as not to be affected by the deviation frequently reported in the occipital portion of the human brain referred to as occipital bending (Glicksohn and Myslobodsky 1993; Maller et al. 2014) as well as potential frontal bending and significant convexities and concavities in the falx cerebri. This is achieved by computing the least squares plane that best fits the 3D vertices on the medial surface of the brain lying within 5 mm of x = 0 in the MNI coordinate system. The computed MSP is thus a highly reliable proxy of the Inter-hemispheric Fissure not influenced by the fact that the Inter-hemispheric Fissure is not entirely planar or by asymmetries of the lateral surface of the brain via the 5 mm constraint. A diagram illustrating the computation of the MSP for a human subject is provided in

Figure **1**. The relevant description of how the MSP is computed and why the MSP is not influenced by asymmetries of the brain has been further clarified in Section 2.3 on Page 8 of the manuscript.

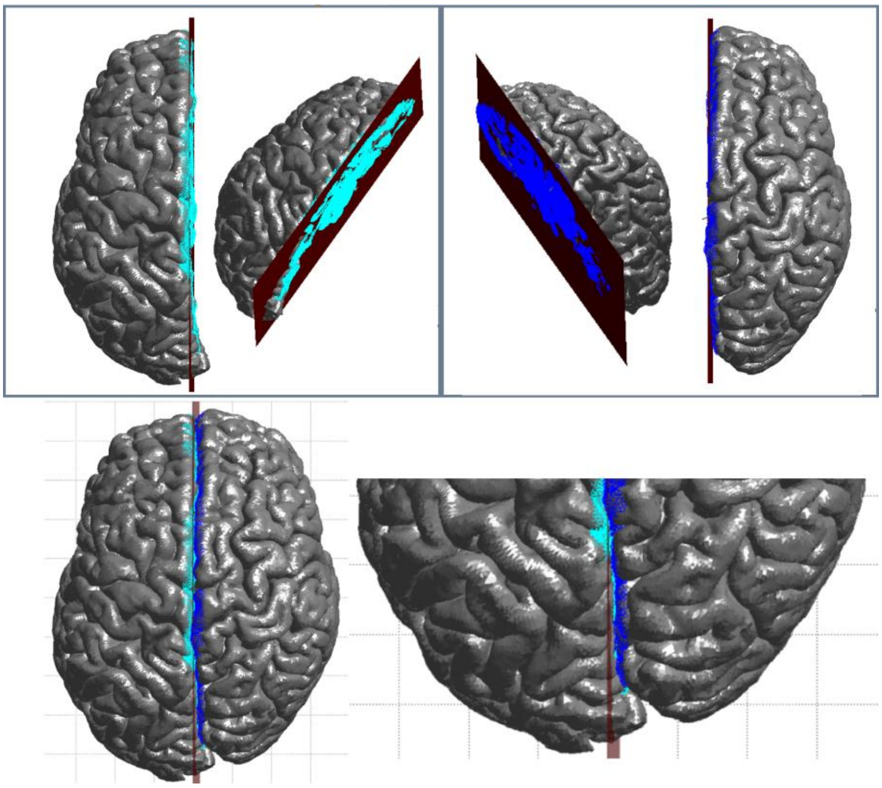

Figure 1: *Computation of the Middle Sagittal Plane (MSP). The MSP (shown in dark red) is computed as the least squares plane that best fits the 3D vertices on the medial surface of the brain that lie within 5 mm of x=0 in the MNI coordinate system. This eliminates the influence of potential occipital and frontal bending and asymmetry of the lateral surface. The vertices shown in turquoise and blue correspond to the medial surface of the left and right cerebral hemisphere that lie within 5 mm of x = 0 in the MNI coordinate system from which the MSP is computed.*

In their analysis of cerebral asymmetry Balzeau and Gilissen (2010) used an alternative approach convenient for studying the asymmetry of the skull. In particular, these authors hand-picked three anatomical reference points along the mid-line of the surface of the cranium of each subject, namely glabella, inion, and basion, used historically in many anthropometric studies based on calliper measurements. These three points define "an external and independent reference" based on two lines, one of which is through glabella and inion and the other is orthogonal to the first line and through basion. The positional asymmetries of the surface of the cranium are measured with respect this reference. However, these skull based landmarks are obviously not appropriate for analysis of the brain on 3D MR images and we have therefore computed the best fitting inter-hemispheric fissure from the data as described above. The approach of Balzeau and Gilissen (2010) and our analysis may be thought of as corresponding methods for studying the positional asymmetry of skulls and brains, respectively. In particular, Balzeau and Gilissen (2010) defined two perpendicular reference lines based on three anatomical landmarks on the skull surface that actually form a 'MSP', whereas we compute a reference MSP that best fits the 3D vertices belonging to the medial surface of the brain.

With respect to point (iii), the computation of the correspondence between vertices in the left and right cerebral hemispheres in 3D is completely independent of the MSP. The procedure is well established in FreeSurfer software and described in detail by Greve et al. (2013). In short, a non-linear registration is applied to separately match the vertices of each cerebral hemisphere to a symmetrical reference template based on local brain surface curvature and which in turn reveals the correspondence between the two hemispheres. The description is clarified in the last paragraph on Page 7 in the manuscript.

Concerning point (iv), the left-right component of positional brain asymmetry is measured between each pair of corresponding vertices at each surface location with respect to the MSP. The remaining components, namely anterior-posterior and dorsal-ventral, are measured along corresponding directions in MNI space rotated by the 3D angle α between the surface normal of the MSP and surface normal of the plane $x = 0$ in MNI space. This description is clarified in Section 2.3 starting at the end of Page 8 in the manuscript.

[2] With regard to Definition of Asymmetry Reviewer #1 states: ***How do you define that a surface is asymmetrical? Is there a level? Is it a statistical characterization?*** and that ***The threshold that is used to define what is asymmetric may miss small but significant AP occipital petalia in P. troglodytes that are reported in Balzeau and Gillisen (2010)***.

In the present study the threshold level that is applied in the measurement of positional brain asymmetry is zero and the statistical significance is measured by a one-sample t-test performed at each vertex of the brain surface in the standard space against the null hypothesis that the brain is symmetric, applied independently in the left-right, antero-posterior and dorso-ventral axes. As long as there is a difference in the position of the vertex along the corresponding axes between the two cerebral hemispheres that passes the statistical test (thresholded at $p<0.01$), the associated surface location is considered to be asymmetric. This description has been clarified in the second paragraph on Page 9 of the manuscript.

[3] With regard to Measurement of Asymmetry Reviewer #1 states: ***I would prefer to see "real" brain measurements. Could you use classic parameters to describe your data? (e.g. FA, DA, FA4a, skewness, kurtosis from Palmer) It would give a more complete view ono what happens with these measures.***

We thank the Reviewer for this suggestion. Our vertex-by-vertex analysis covering the whole surface of the brain has been designed to identify those regions where significant positional asymmetries are present in the three independent directions. We agree that in future developments of the method it will be interesting to analyse the distribution of the asymmetries both on a vertex-wise basis and potentially also as extracted for specific lobes or regions of interest.

[4] With regard to Handedness of Participants Reviewer #1 states: ***Do you have some information on the manual laterality/handedness of your human sample?***

Unfortunately, information regarding the manual laterality or handedness of the individual subjects was not obtained at the time of acquisition of the images and therefore we could not carry out an analysis of the potential relationship between positional brain asymmetry and handedness. The relationship between brain asymmetry and handedness is however suggested to be weak. For example Good et al (2001) found no significant interaction between brain asymmetry and handedness in a Voxel Based Morphometry (VBM) asymmetry study of 465 human subjects. However, we do not exclude that there may be a relationship between handedness and a component of brain asymmetry, such as Torque and are grateful for the suggestion made by the Reviewer. The primary objective of the present study was to identify brain asymmetries that may distinguish human and chimpanzee.

[5] With regard to Results in Individual Participants Reviewer #1 states: ***Why do not you give individual results with information on the orientation of the asymmetries? That would be interesting to have the information on handedness to see the influence of this parameter on your analyses (and depending on the proportion of R/L handed subjects on the results, indeed if you only have R handed guys).***

The major accomplishment of the present study as acknowledged by Reviewer #4 is that ***The approach presented here indeed provides a more detailed and comprehensive analysis of positional brain asymmetry than in previous studies***. In further work (as proposed on Page 25) we will address whether the positional asymmetry maps can be further analysed so as to allow computation of, for example, the magnitude of the cerebral Torque. At that point we will be able to study and compare the distribution of values in cohorts of interest. Meanwhile, we suggest that comparison of the positional asymmetry maps on a vertex-by-vertex basis between humans and chimpanzee represents a significant advance.

[6] With regard to First Frontal Convolution, Reviewer #1 states: ***Concerning your Figure 3, there is an area that is asymmetric on the brain of chimps in the area that might be the inferior part of the first frontal convolution. In my paper (Balzeau et al., 2014) I had observed that " that P. troglodytes is distinctive in having, among all of the specimens in our sample, a third frontal convolution that has a lower position on the left side relative to the right side". It seems that you find something similar. What was surprising for me is that this feature was unique to Pt and that Pp and Hs had a similar (and different) patterns.***

We thank Reviewer #1 for this interesting suggestion which we now refer to at the end of Page 24 and with some caution in that although the asymmetry is in the same direction in both analyses we have to acknowledge that the coordinates of the two features are not exactly the same. The patch in Figure 3 which belongs to the lateral orbitofrontal surface, therefore, may not be exactly the same structure referred to in Balzeau et al. (2014). The discrepancy is possibly due to (i) different methods of measurement, (ii) different sample materials (endocasts versus in-vivo brains) or (iii) sample size (36 *Pan* troglodytes versus 70 *Pan* troglodytes).

[7] With regard to Measurement of Hemisphere Dimensions Reviewer #1 states: ***How have you quantified the length, height and width of the hemispheres? Are they the maximal extension? Are they defined relatively to the MSP?***

Also: ***I understand here that length, height and width of the hemispheres were quantified relatively to a bounding box. You should explain why you have used this referential instead***

of true brain measurements. Is the width estimated relatively to the MSP or to the interhemispheric fissure? In the case of the length of the hemispheres, that would be interesting to compare with the length from the frontal pole to the occipital pole (a true 3D measurements) to quantify bilateral variations.

From consideration of the above, we understand that the Reviewer is asking:

(i) Are the measurements the maximal extension of the brain in each direction?
(ii) Why choose to use the maximal extension rather than a true 3D measurement?
(iii) Is the MSP used in obtaining the measurements in (i) above?

With respect to point (i), length, height and width are defined as the maximal extension of the brain in left-right, anterior-posterior and dorsal-ventral directions, respectively. This description has been clarified in Section 2.5 on Page 11.

With respect to point (ii), yes we could have readily computed a true 3D internal measurement of the length between the anterior and posterior pole of each cerebral hemisphere which we agree could form a basis for an interesting study, especially, for example, to address the fact that the occipital lobe of the left hemisphere is displaced dorsally relative to the right. Our main aim, however, was to develop an automatic method for measuring the dimensions of the cerebral hemisphere consistent with historical studies of the frontal and occipital petalia (see LeMay, 1976) and for this we developed our so-called “bounding box” analysis which is also consistent with our positional asymmetry analysis which has been performed with respect to the same left-right, anterior-posterior and dorsal-ventral directions.

With respect to point (iii), the brain-MSP is aligned to be parallel to the plane x=0 so that the “bounding box” can be cast on the reoriented brain surface to measure the maximal extension of the brain in left-right, anterior-posterior and dorsal-ventral directions. The detailed description has been clarified in Section 2.5 on Page 11.

[8] With regard to remarks on Species Transition in Introduction Reviewer #1 states: ***Nothing to say except for the last sentence. I do not think that you can address "the nature of species transition" by studying human and Pan troglodytes brains, neither if changes are gradual or discontinuous, simply because you will not know the state of the features by comparing two groups, nor when the changes occurred. Similarly, whatever you find, you cannot make any interpretation on the species boundary because the two groups you study are very far from each other from an evolutionary point of view.***

We especially agree that the present study cannot inform directly on the species boundary between humans and chimpanzees as the two species are indeed far apart from an evolutionary point of view and likely between 5 million (Ross et al. 2005) and 6 million (Williams et al. 2006) years. Nor of course can we define whether the changes have occurred gradually or as a “jump”. We suggest however that it is especially interesting to know whether there is a significant difference in brain asymmetry between humans and chimpanzees. A good deal has been written about the fact that language function may be especially related to lateralized function in the human brain. We were interested to define the potential brain structural asymmetry correlates of this functional lateralization in humans and which if any are also present in chimpanzees. The description is clarified on Page 5.

Furthermore, in respect of the species difference, we have revised the title to emphasise the primary finding of our study which is "***Human Torque is not present in chimpanzee brain***". In addition, other species differences in positional brain asymmetry have been summarised in a new paragraph on Page 20 and with those relating to the Superior Temporal Sulcus and anterior temporal lobe suggested to be potentially linked to the underlying indusium griseum.

[9] With regard to Discussion of Human Specificity of Findings Reviewer #1 states: ***Of course, I cannot agree with the statement that "our findings… provide the most robust evidence to indicate that petalia and occipital bending is human-specific". I think that there is a bias in your methods (using a msp) and that it affects the way small deviation are characterized on a smaller brain. I am not saying that your results are wrong. In my opinion, a global approach of the whole surface with some possible methodological issues (MSP, but also the threshold that is used to defined what is asymmetric or not) may miss the small but present and significant AP occipital petalia in P. troglodytes (Balzeau and Gilissen, 2010).***

As described in our response to point [1] above the new positional asymmetry analysis method that we have developed is not biased by the MSP and in the database which we have analysed we find no evidence of occipital petalia in chimpanzees.

REVIEWER #3:

[1] With regard to Description and Illustration of Torque Reviewer #3 states: ***Discussion of Torque could use a figure and needs clarification. The authors state (p. 4/35 according to the reviewer's computer) "The Torque refers to an anticlockwise twist of the brain about the ventral-dorsal axis of the body, especially in posterior regions, and can be seen clearly depicted in Figure 2 of Toga and Thompson (2003)." It would be good to include the Toga and Thompson figure that the authors refer to, but if it is reproduced here it needs to be noted that the figure has been exaggerated for illustrative purposes (as noted in TandT's figure legend). The term "anticlockwise twist" needs clarification, especially since Li et al. use "clockwise" when referring to Torque later in the manuscript (item 3, p. 19/35). Are they looking at the brain from a dorsal or basal perspective? The assertion that Torque is more pronounced in posterior than anterior regions (restated later in the manuscript) should not rely on the TandT exaggerated figure. What quantitative evidence supports this statement?***

We thank Reviewer #3 for their appealing suggestion to include Figure 2 of Toga and Thompson (2003) in our manuscript. However, it would appear that the motivation for this suggestion may in part stem from some confusion which we may have unfortunately caused by not making clear what is being referred to when we describe an anticlockwise twist and a clockwise rotation in the brain. In fact these descriptions refer to two entirely different features. The anticlockwise twist is a description of the cerebral Torque as viewed from above the transverse plane as revealed in the anterior-posterior (petalia) and left-right (occipital bending) positional asymmetry maps. Whereas the clockwise rotation refers to the appearance of the Sylvain Fissure in the left compared to the right cerebral hemisphere as viewed in the dorsal-ventral positional asymmetry map. We have now clarified this in the text inserted on Pages 19 and 20. We therefore do not consider the inclusion of Figure 2 of Toga and Thompson (2003) to be necessary but instead have referred directly to this important Figure as follows "The Torque refers to an anticlockwise twist … is depicted, with artistic exaggeration for clarity, in Figure 2 of Toga and Thompson (2003)" on Page 3.

With regard to our claim that the Torque is more pronounced posteriorly than anteriorly, this was to be predicted from previous studies, which we now cite, namely Glicksohn and Myslobodsky (1993) where the prominent posterior aspect of the Torque is referred to as deviation in the occipital region and Maller et al. (2014) where it is referred to as occipital bending. The relevant citations have been inserted on Page 3.

[2] With regard to Description of Petalia Reviewer #3 states: ***Page 20/35 states "…more prominent left occipital than right frontal petalia." As mentioned above, this needs a reference.***

The posterior component of the Torque referred to as occipital bending in the response to [1] above is the principal feature referred to as a twisting. An additional feature of the Torque corresponds to the greater posterior protrusion of the left hemisphere than the right hemisphere posteriorly and the greater anterior protrusion of the right than the left hemisphere anteriorly. These "petalia" have been described in a great many studies and we have now included citation to Elliot-Smith (1907) and Bear et al. (1986) which refer to the posterior petalia being more prominent than the anterior petalia. These additional citations have been inserted on Page 20.

[3] With regard to the Presentation of Results in Figures 1 to 3 Reviewer #3 states: ***Figures 1 to 3, columns 2 and 3. Please add a sentence or two clarifying how these comparisons were performed. Were chimp data subtracted from human data—do the colors refer to human asymmetries that remain after the subtraction?***

A two-sample t-test was performed to compare the vertex-wise positional asymmetry maps of humans and chimpanzees as presented in Figures 1 to 3. In column 2 of each Figure the p-value of the t-test is rendered on the brain surface thresholded at $p<0.01$ and in column 3 the p-value has been corrected for multiple comparisons. The colours highlight regions of the brain surface where there is a significant species difference in positional asymmetry. In particular a hot colour means greater positional asymmetry compared to chimpanzees and vice versa for cool colours. The relevant description is inserted in the last paragraph on Page 10 and also in the captions of Figures 1 to 3 on Pages 13, 14 and 16.

[4] With regard to Interpretation of Findings regarding Superior Temporal Sulcus (STS) Reviewer #3 states: ***Page 19/35 states "leftward asymmetry of the lateral surface of the anterior temporal lobe and STS. The positional asymmetry of STS is consistent with the human specific finding of greater depth in the right compared to the left cerebral hemisphere in the adult brain (Leroy et al. 2015)." Please explain this consistency—couldn't a fatter (i.e., leftward asymmetric) anterior temporal lobe and STS indicate greater depth of associated sulci on that side?***

The asymmetry detected with the new positional wise analysis of brain asymmetry is consistent with the findings of Leroy et al. (2015) concerning a deeper Superior Temporal Sulcus (STS) in the right than the left cerebral hemisphere. In particular, the extensive linear feature seen in red and corresponding to the STS in the left-right positional asymmetry map indicates that the depth of the STS in the right hemisphere is closer to the MSP than it is in the left hemisphere whereas the adjacent brain surface (i.e., surrounding gyrus) shows the opposite effect. Taken together this means that the STS is deeper on the right than the left. The interpretation is clarified in the last paragraph on Page 19.

[5] With regard to Interpretation of Rotation of the Sylvian fissure Reviewer #3 states: ***Page 19/35 states "…with clockwise rotation of the left Sylvian fissure around the left-right axis." This is confusing because Torques are usually described relative to the midline rather than the left-right axis (Toga and Thompson) and, according to TandT "structures surrounding the right Sylvian fissure are 'Torqued forward' relative to their counterparts on the left" (TandT 2003, legend for Fig. 2). Again, the authors should clarify the use of the term "clockwise" by specifying the view the brain is observed from (dorsal or ventral) when using the term.***

As described in response to [1] above, the remarks that we make regarding the Sylvian fissure and in particular that there is a potential clockwise rotation in the left relative to the right cerebral hemisphere are unrelated to the description of the cerebral Torque. The interpretation regarding a potential rotation of the Sylvain Fissure comes from inspection of the dorsal-ventral positional asymmetry map. In particular, looking toward the left hemisphere, regions of significant asymmetry near the posterior portion of the Sylvian Fissure show a dorsal displacement whereas regions of significant asymmetry near the anterior portion of the Sylvian Fissure show a ventral displacement. On Page 20 of the manuscript we have added the statement that "clockwise rotation of the left Sylvian Fissure relative to the right around the left-right axis (viewed from dorsal-ventral asymmetry map)".

[6] With regard to Whole Brain Volume and Cranial Capacity Reviewer #3 states: ***Brain Dimension and Inter-hemisphere Asymmetry: Why weren't whole brain volumes or cranial capacities included?***

The focus of the present manuscript is a presentation of the positional asymmetry of the brain and its difference between humans and chimpanzees. The reason that we have included an analysis of the length, height and width of the brain stems from the fact that the MSP computed to support the positional asymmetry analysis may also be used to adjust each brain which is already normalised in MNI space so that the MSP is co-planar and aligned with x=0 in MNI space. Thus a small amount of additional coding to place a so-called "bounding box" on each cerebral hemisphere allows extraction of the length, height and width of each brain. Besides, the brain volume information was provided elsewhere, namely in (Hopkins et al. 2016).

[7] With regard to Page Numbers Reviewer #3 states: ***Lack of page numbers on the manuscript makes it difficult to review.***

Page numbers have now been added.

[8] With regard to Citation of the paper by Keller et al. (2010) Reviewer #3 states: ***The manuscript cites Keller et al., 2010 (p. 8/35), but neither Keller reference in the references section is for this year.***

The citations to the two papers by Keller et al. (2009a, 2009b and 2011) are now correct, both in the manuscript and in the Reference list as follows:

Keller, S.S., Crow, T., Foundas, A., Amunts, K. and Roberts N. (2009a). Broca's area: Nomenclature, anatomy, typology and asymmetry. Brain and Language 109, 29-48.

Keller, S.S., Roberts, N., Garcia-Finana, M., Mohammadi, S., Ringelstein, E.B., Knecht, S. and Deppe, M. (2011). Can the language-dominant hemisphere be predicted by brain anatomy? Journal of Cognitive Neuroscience, 23, 2013-2029.

Keller, S.S., Roberts, N. and Hopkins, W. (2009b). A comparative magnetic resonance imaging study of the anatomy, variability, and asymmetry of Broca's area in the human and *Pan* troglodytes brain. Journal of Neuroscience, 29, 14607-14616.

[9] With regard to Nomenclature Reviewer #3 states: ***Homo and Pan should be italicized.***

This correction has now been made throughout the manuscript.

REVIEWER #4:

This paper is both a review and an in depth analysis of brain shape asymmetries (petalia and/or cerebral Torque) and their putative components. In many studies, the Torque component may not have been separated from the effect of petalia. The approach presented here indeed provides a more detailed and comprehensive analysis of positional brain asymmetry than in previous studies.

[1] With regard to Citation of work by Dax, Reviewer #4 states: ***In « Introduction », line 2 : Montpellier (with 2 "l"); line 4: Société d'Anthropologie de Paris.***

These spellings have been corrected on Page 3 of the manuscript.

[2] With regard to Citation of work by Eberstaller, Reviewer #4 states: ***In "Introduction", there are several references of historical connotation so in addition to Eberstaller O. 1884. Zur Oberflächenanatomie des Grosshirnhemispheren. Wiener Medizinische Blatter. 7:479-482. I suggest to citate his book: Eberstaller O. 1890. Das Stirnhirn. Ein Beitrag zur Anatomie der Oberfläche des Grosshirns. Urban and Schwarzenberg, Wien und Leipzig. 142 pages and 1 plate.***

This additional reference to the work of Eberstaller has been added on Page 3 of the manuscript.

[3] With regard to Citation of work by Balzeau and colleagues, Reviewer #4 states: ***A few references are wrong: "Balzeau et al. 2011" should be "Balzeau et al. 2012" This reference should be corrected in "References": Balzeau A, Gilissen E., Grimaud-Hervé D (2012) Shared pattern of endocranial shape asymmetries among great apes, anatomically modern humans, and fossil hominins.***

Also: ***"Balzeau and Gilissen (2012)" should be "Balzeau and Gilissen (2010)"***

Also: ***This reference to Balzeau A, Gilissen E. 2010. Endocranial shape asymmetries in Pan paniscus, Pan troglodytes and Gorilla gorilla assessed via skull based landmark analysis. J Hum Evol. 59: 54-69. is missing in "References" and should be added.***

The two papers by Balzeau and colleagues are now correctly cited on Pages 4, 8 and 22 of the manuscript and both appear correctly in the Reference list.

[4] With regard to Citation of work by Holloway and colleagues, Reviewer #4 states: ***"Holloway et al. (1982)" should be "Holloway and De La Costelareymondie (1982)".***

This paper is now correctly cited on Page 21 of the manuscript and in the Reference list.

[5] With regard to Citation of work by Gilissen and colleagues, Reviewer #4 states: ***In "Discussion", page 3, 1st paragraph: "These results are most closely comparable with a previous study of 29 in-vivo brain MRI scans of human males and 9 post-mortem brains of Pan troglodytes (Zilles et al. 1996, reviewed in Gilissen 2001)". The reference is: Gilissen E. 2001. Structural symmetries and asymmetries in human and Pan troglodytes brains. In: Falk D, Gibson KR, editors. Evolutionary Anatomy of the Primate Cerebral Cortex. Cambridge: Cambridge University Press. p. 187-215.***

We thank the Reviewer for bringing this interesting paper to our attention and which we now cite on Page 21 of the manuscript.

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Balzeau A and Gilissen E. 2010. Endocranial shape asymmetries in *pan* paniscus, *pan* troglodytes and gorilla gorilla assessed via skull based landmark analysis. Journal of Human Evolution. 59:54-69.

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*7. Manuscript
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HUMAN TORQUE IS NOT PRESENT IN CHIMPANZEE BRAIN

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Abstract

We searched for positional brain surface asymmetries measured as displacements between corresponding vertex pairs in relation to a mid-sagittal plane in Magnetic Resonance (MR) images of the brains of 223 humans and 70 chimpanzees. In humans deviations from symmetry were observed: 1) a Torque pattern comprising right-frontal and left-occipital “petalia” together with downward and rightward “bending” of the occipital extremity, 2) leftward displacement of the anterior temporal lobe and superior temporal sulcus (STS), and 3) posteriorly in the position of left occipito-temporal surface accompanied by a clockwise rotation of the left Sylvian Fissure around the left-right axis. None of these asymmetries was detected in the chimpanzee, nor was associated with a sex difference. However, 4) an area of cortex with its long axis parallel to the olfactory tract in the orbital surface of the frontal lobe was found in humans to be located higher on the left in females and higher on the right in males. In addition whereas the two hemispheres of the chimpanzee brain are equal in extent in each of the three dimensions of space, in the human brain the left hemisphere is longer ($p=3.6e-12$), and less tall ($p=1.9e-3$), but equal in width compared to the right. Thus the asymmetries in the human brain are potential correlates of the evolution of the faculty of language.

Keywords: Torque, petalia, occipital bending, asymmetry, chimpanzee, superior temporal sulcus

1. Introduction

As recorded by his son Gustave (Dax 1865), Marc Dax had reported the association of right hemiplegia with speech disturbance to the Montpellier Medical Society in 1836. Sixteen years later and within two years of publication of Darwin's Origin of Species, Paul Broca announced to the Société d'Anthropologie de Paris that a component of language is located in the frontal lobe on the left side of the brain (Broca 1861) and in 1877 he formulated the hypothesis that "Man is, of all the animals, the one whose brain … is the most asymmetrical. He is also the one who possesses the most acquired faculties. Among these faculties … the faculty of articulate language holds pride of place. It is this that distinguishes us the most clearly from the animals". Asymmetries of the Sylvian Fissure in the human brain were first described (Cunningham 1892; Eberstaller 1884; 1890) in the late nineteenth century (for a historical account of contributions relating to hemispheric function see (Harrington 1987)). Anatomical asymmetry was more widely discussed following a report (Geschwind and Levitsky 1968) of leftward area asymmetry of the planum temporale on the superior surface of the temporal lobe. The Sylvian Fissure was found to have an inclination closer to horizontal and of greater extent in the left hemisphere (Rubens et al., 1976).

Additional asymmetries have been reported (Witelson and Kigar 1988) of which perhaps the most prominent is a pattern first observed by (Eberstaller 1884) and referred to as the Yakovlevian Torque by LeMay (1976) following observation of corticospinal tract asymmetry by Yakovlev and Rakic (1966) in post-mortem brain. The Torque refers to an anticlockwise twist of the brain about the ventral-dorsal axis, especially in posterior regions (Glicksohn and Myslobodsky 1993; Maller et al., 2014), and is depicted, with artistic exaggeration for clarity, in Figure 2 of Toga and Thompson (2003). Since it is particularly evident on axial images produced by techniques such as X-Ray Computed Tomography (Bear et al., 1986; LeMay 1976) and Magnetic Resonance Imaging (MRI) (Kennedy et al., 1999; Watkins et al., 2001) the Torque has been extensively studied (Barrick et al., 2005) and is now perhaps the best known asymmetry of the human brain.

Chance et al. (2005) have proposed that the Torque is made up of two dissociable components. One of the components is a posterior shift of the left relative to the right cerebral hemisphere and which produces corresponding right frontal and left occipital "petalia" first reported as indentations of the inner surface of the cranium (e.g. in archaeological (Holloway and De La Costelareymondie 1982) and CT studies (LeMay 1976)). In a recent study, the typical combination of right frontal and left occipital petalia was reported to be found in 44% modern human brains (Balzeau et al., 2012). The second component of the Torque relates to differing distributions of cerebral tissue along the anterior-posterior dimension in each cerebral hemisphere. This has been studied in terms of lobar lengths (Bear et al., 1986; Highley et al., 1998), widths (LeMay 1976), and volumes (Barrick et al., 2005; Weinberger et al., 1982). However, in many studies, this Torque component may not have been separated from petalia (Barrick et al., 2005; Chance et al., 2005; Watkins et al., 2001).

An additional component of the Torque is "occipital bending" whereby in the occipital region brain tissue in the left cerebral hemisphere crosses the midline to displace tissue in the right hemisphere (Deutsch et al., 2000). In addition to crossing the midline the occipital pole of the left cerebral hemisphere is also displaced downwards (i.e. below) the occipital pole of the right hemisphere. Corballis and Morgan (1978) note that the direction of the Torque is opposite to that of the growth vector from left frontal to right occipital earlier reported for the formation of sulci by (Gratiolet 1839). Best (1988) conceived the diagonal trajectory across the left-right and antero-posterior dimensions as "a lateralized gradient of neuro-embryological development" that proceeds within a 3-dimensional frame that includes also the dorso-ventral axis; see also (Morgan 1991; Morgan and Corballis 1978).

The Torque and Sylvian Fissure asymmetries are the best established global and local asymmetries of the human brain. A further asymmetry in the Superior Temporal Sulcus (STS), reported to have a significantly greater depth in the right than the left cerebral hemisphere is proposed as a potential human-specific cerebral landmark (Leroy et al., 2015). Beneath the cortex the pyramidal tracts (Yakovlev and Rakic 1966) and the thalamic pulvinar (Highley et al., 2003) also exhibit asymmetries. However, particularly with reports of asymmetries in the chimpanzee (Cantalupo and Hopkins 2001; Gannon et al., 1998), whether any one of the anatomical asymmetries is specific to humans has been controversial (Crow 2004; Rogers 2004). In the present study 3D Magnetic Resonance Imaging (MRI) datasets were analysed to assess positional asymmetries in the human and chimpanzee brains and to investigate whether there is a difference in asymmetry between the two species. If the difference between the species is anatomically significant then it may be a potential correlate of the functional lateralisation that is widely reported to underlie language in humans and may therefore set a lower limit on the nature of the species transition, in particular whether these are gradual as Darwin believed, or whether (explicit in Broca's 1877 formulation) there is an element of saltation or discontinuity, i.e., a new genetic characteristic is introduced at a species boundary.

2. Materials and Methods

2.1 Subjects

MR images were acquired at the Montreal Neurological Institute (MNI), Montreal, Canada, West China Hospital, Chengdu, Peoples Republic of China (PRC) and Magnetic Resonance and Image Analysis Research Centre (MARIARC) University of Liverpool, UK, for 223 adult humans (101 females, 122 males) and at Yerkes National Primate Research Centre (YNPRC) in Atlanta, Georgia, USA for 70 chimpanzees (44 females, 26 males) with approval from the local Research Ethics Committee obtained by each institution. Chimpanzees were immobilized by ketamine injection (10 mg/kg) and subsequently anesthetized with propofol (40–60 mg/kg/hr) before transportation to the MRI facility where they remained anesthetized (total time ~2 hours) for the MR imaging and return to the home compound. Chimpanzees were scanned supine with a human head-coil.

Full details of data acquisition for the 142 Montreal human subjects (1 mm isotropic voxel resolution scans) are provided in Watkins et al. (2001). The 54 Chengdu human subjects were scanned using a 3T MRI system (Signa; GE Medical Systems) with a standard 8-channel phase array head coil. The acquisition parameters were: TR = 8.52 ms, TE = 3.4 ms, TI = 400 ms, Flip angle = 12, FOV = 240 mm x 240 mm and the images have a voxel resolution of 0.5 mm x 0.5 mm x 1 mm. The 27 Liverpool human subjects were scanned with a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) 3T MRI system (Trio; Siemens Medical Systems, Erlangen, Germany). The acquisition parameters were: TR = 2300 ms, TE = 4.4, TI = 1100 ms, Flip angle = 8, FOV = 200 mm x 200 mm and the images have an isotropic voxel resolution of 1 mm (Keller et al., 2009b). All human subjects in all three cohorts were in good health with no known neurological condition, psychiatric disorder or brain malformation. The 70 chimpanzees were scanned with identical acquisition parameters to the Liverpool human subjects except that voxel resolution was increased to 0.6 mm in the y direction giving an acquisition time of 36 min, compared to 12 min (y = 1 mm) in the Liverpool human subjects (Keller et al., 2009b). The chimpanzees were all reported to be healthy.

2.2 Post Image Analyses

A new image analysis pipeline was developed to examine positional asymmetry of the brain surface through study of the relationship between corresponding points in the two hemispheres on MRI scans of the brains for the combined database of 223 humans and 70 chimpanzees. The length, height and width of the left and right cerebral hemispheres in the two species were also computed to testify the global brain asymmetry using linear brain dimensions.

To examine cerebral asymmetries, the 3D T1-weighted MR images were first pre-processed in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) including skull strip, bias field correction and linear brain normalization using 7 degree of freedom transformations (i.e. 3 translations, 3 rotations and 1 uniform scaling). As a result, the extracted brains were normalized to the standard MNI coordinate system. Second, the processed brain images were analysed in the standard FreeSurfer processing stream (https://surfer.nmr.mgh.harvard.edu/), in which the surface-based module enables high quality pial surface reconstruction from the brain volume data by following the signal intensity gradient between grey matter and CSF with subvoxel accuracy (Dale 1999) on the 3D T1 weighted images.

Concerning the computation of the correspondence between vertices in the left and right cerebral hemispheres, a high dimensional non-linear registration was employed to match the vertices of each cerebral hemisphere to a pre-trained symmetrical reference based on a set of curvature-based descriptors (e.g. the spatial relationship of each vertex to neighbouring vertices) that was quantitatively computed at each surface location (i.e. vertex). Because both left and right cerebral hemispheres for each subject were registered to the same reference template the correspondence between the vertices in the two hemispheres as well as the correspondence between vertices in individual subjects were in turn revealed, which allows a statistical vertex-wise inter-hemispheric comparison of cortical morphology in corresponding folds (i.e. sulci and gyri) to be performed. The whole procedure is well established in FreeSurfer software and described in detail by (Greve et al., 2013).

2.3 Positional Asymmetry Computation

The computation of positional brain asymmetry is based on a Mid-Sagittal Plane (MSP) the accuracy of which is therefore essential. As part of the image processing pipeline described in above Section 2.2 the 3D MRI brain image has already been normalized to the MNI coordinate system in FSL. Thus, the three axes (i.e., x,y,z) of the MNI coordinate system by default correspond to the left-right, anterior-posterior and dorsal-ventral directions of the brain and the plane x=0 represents the MSP with respect to which the inter-hemisphere difference between corresponding voxels/vertices in the left and right cerebral hemisphere was often computed (Good et al., 2001; Lyttelton et al., 2009; Watkins et al., 2001). However, cautions must be paid to the potential bias introduced by plane x=0 (Balzeau and Gilissen 2010) given that the low-dimensional linear registration is likely to fail in aligning the true brain MSP to x=0 due to the asymmetric nature of the brain. In order to accurately measure positional brain asymmetry, a new reference MSP was defined in the present study as the least squares plane that best fits the 3D vertices on the medial surface of the brain lying within 5 mm to x=0 in the MNI coordinate system rather than all vertices across the brain surface. This MSP is therefore the plane representing the Inter-hemispheric Fissure unaffected by deviation particularly in the occipital portion of the human brain referred to as occipital bending, convexities and concavities of the medial surface of the brain, and asymmetries of the lateral surface of the brain. Following the computation of the brain-MSP, the three axes of MNI coordinate system were rotated by the 3D angle α between the surface normals of the brain-MSP and plane x=0 (i.e., x-axis). The positional differences between the two cerebral hemispheres were determined on a vertex basis to assess displacements along the left-right, antero-posterior and ventro-dorsal axes for each brain. In particular, antero-posterior brain asymmetry (Asym^{AP}) and the dorsal-ventral brain asymmetry (Asym^{DV}) were measured as the projections of the displacement vector between the left and right corresponding points along the refined anterior-posterior and dorsal-ventral axes; while the left-right brain asymmetry (Asym^{LR}) was computed as the distance of a vertex on the left hemispheric surface to brain-MSP subtracted from that of its corresponding vertex on the right hemispheric surface. The individual surface-asymmetry maps were further smoothed using a 15-mm full-width/half-maximum (FWHM) filter to increase the signal-to-noise ratio.

During inter-hemispheric registration both hemispheres of all 223 human and 70 chimpanzee subjects were registered to the same hemisphere-unbiased reference and therefore the resulting vertex-wise Asym^{LR}, Asym^{AP} and Asym^{DV} maps are inherently mapped to the standard surface space. For each species, a statistical analysis (one-sample t-test) was performed at each surface location for each asymmetry map (i.e., Asym^{LR} or Asym^{AP} or Asym^{DV}) independently against the null hypothesis that the brain is symmetric. The threshold level that is applied in the measurement of positional brain asymmetry is zero. To control for false positive error (Barch and Yarkoni 2013) in multiple comparisons, a correction was performed to identify clusters comprising vertices whose neighbouring vertices also show significant effects (i.e. the vertex-wise un-controlled p-value or cluster-forming vertex-wise p-value is less than 0.001). Subsequently, these clusters are thresholded to identify those with a size greater than a limit based on Gaussian Random Field (GRF) theory, validated with Monte Carlo simulations, and under the null hypothesis this cluster-wise threshold was set to $p<0.005$. The statistical analysis is well established in FreeSurfer software (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis) and a detailed description of the process can be found in (Greve et al., 2013; Hagler et al., 2006). The corrected p-value was rendered on corresponding 3D representations of the brain to represent the three components of the inter-hemispheric displacement (see Figures 1, 2 and 3, columns 1 and 4). A hot colour is used to indicate leftward asymmetry in the sense that i) the left cerebral hemisphere deviates further from the brain-MSP than the right in Asym^{LR}, ii) the left hemisphere shifts posteriorly compared to the right in Asym^{AP} or iii) the left hemisphere shifts superiorly compared to its right counterpart in Asym^{DV}; while a cool colour indicates a rightward asymmetry in the contrary sense.

Furthermore, in a Supplementary Analysis brain positional asymmetry was measured separately for the independent cohorts recruited at the imaging centres in three different countries in order to test whether the findings are consistent across cohorts and the findings are presented in Supplementary Information. If consistency is obtained in the results across cohorts this will support the suggestion that the effects are real and not due to false positive error. In addition, a Supplementary Analysis was performed to determine the effect of normalisation to a common human reference template or to respective human and chimpanzee specific templates.

2.4 Species Comparison Analysis

To evaluate potential group differences in brain surface positional asymmetry between human and chimpanzee a statistical analysis was performed at each vertex using a two-sample t-test (see column 2 in Figures 1, 2 and 3), followed by a cluster-wise multiple comparisons correction as mentioned above (with cluster-forming vertex-wise threshold of $p<0.001$ and cluster-wise threshold of $p<0.005$). The colours in columns 2 and 3 of Figures 1, 2 and 3 highlight regions of the brain surface where there is a significant species difference in positional asymmetry. In particular a hot colour means greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours, and to interpret the species difference one also needs to refer to asymmetry maps of individual species in columns 1 and 4.

In addition the average asymmetries in female and male brain for the human and chimpanzee were computed (see columns 1 and 3, and 4 and 6, of Figure 4, respectively) and subsequently the significant differences between the sexes in humans (column 2) and chimpanzees (column 4) were determined respectively at the cluster level corrected for multiple comparisons (with cluster-forming vertex-wise threshold of $p<0.001$ and cluster-wise threshold of $p<0.005$).

2.5 Brain Dimensions and Inter-Hemisphere Asymmetry

Besides comparison of positional asymmetry between corresponding cortical folds, asymmetries of overall brain dimensions (i.e. length, height and width) were investigated in the following steps for each brain: i) the whole brain surface was rotated through the 3D angle $-\alpha$ (i.e. the angle between the surface normals of brain-MSP and x=0 in MNI coordinate system estimated in Section 2.3) to align the brain-MSP parallel to the x=0 plane in MNI coordinate space, ii) for each surface of interest (i.e. hemisphere surfaces and whole brain surface), the smallest orthogonal parallelpiped box that just covers the surface with the edges of the bounding box parallel to the three axes in MNI coordinate space was fitted to the brain. The dimensions of the bounding box thus specify the length, height and width of each surface. In other words, the length, height and width are measured as the maximal extension of the brain along left-right, anterior-posterior and dorsal-ventral axes, respectively. To obtain the size in the real world, brain dimensions were further divided by the scaling factor previously computed and recorded from FSL in the brain normalization step (in Section 2.2). A one-tailed paired t-test was applied to investigate the inter-hemispheric asymmetries of the computed brain dimensions with a threshold of $p < 0.01$.

3. Results

3.1 Species Differences in Brain Asymmetry

Overall, the cerebral surface is more asymmetric in the human brain compared to the chimpanzee. To be specific, the percentage of the cerebral surface classed as asymmetrical is 69.8% in $Asym^{LR}$, 74.8% in $Asym^{AP}$ and 38.1% in $Asym^{DV}$ in human, respectively; while 31.1% in $Asym^{LR}$, 10.5% in $Asym^{AP}$ and 5.3% in $Asym^{DV}$ in the chimpanzee brain. Those features which distinguish the species by both vertex-wise and cluster-wise criteria along left-right ($Asym^{LR}$), antero-posterior ($Asym^{AP}$) and dorso-ventral ($Asym^{DV}$) axes can be seen in Figures 1 to 3, columns 2 and 3, respectively.

Two features distinguish the species in the left-right direction (Figure 1):
1) an area of brain surface encompassing the temporal pole and demarcating the superior temporal sulcus (STS) is leftwardly asymmetric (hot colour) in Figure 1 (row 2, columns 2 and 3), and

2) an area of rightward asymmetry (cool colour) extends over the occipital pole, and surrounds area 1 above on the occipito-temporal aspect of the human brain. On the medial aspect (row 4, columns 2 and 3) there is leftward asymmetry of the precuneus and rightward asymmetry of sulcus corporis callosi just beneath the cingulate gyrus, and in the para-cingulate (superior frontal) gyrus above it.

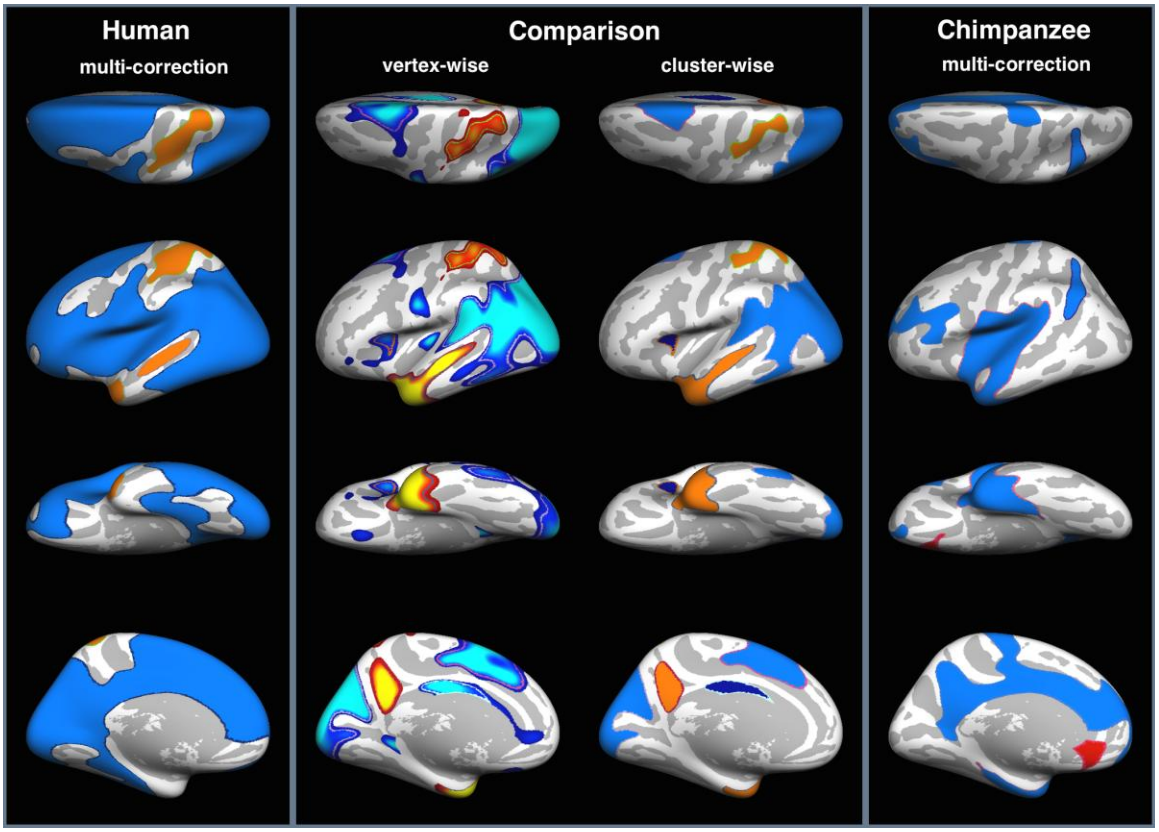

Figure 1: Species difference in left-right positional brain asymmetry (Asym^{LR}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value thresholded at $p<0.01$) are demonstrated for humans and chimpanzees respectively with hot colours indicating leftward deviations and cool colours for rightward deviations. Column 2 shows the p-value (thresholded at $p<0.01$) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3 shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 69.8% of the surface in the Asym^{LR} orientation in the human compared to 31.1% in the chimpanzee brain is classed as asymmetrical.

In the antero-posterior direction (Figure 2), the whole of the brain surface between the temporal and occipital poles is displaced posteriorly (columns 2 and 3, rows 1 to 3) in the left hemisphere relative to the right hemisphere in addition to a small patch at the frontal pole region in the human but not in the chimpanzee brain. This area of backward displacement extends onto the medial surface where it overlaps the cuneus and precuneus (row 4, columns 2 and 3). It is notable that both the frontal and occipital poles are involved in this posterior shift. Conversely, a structure that appears contiguous with the structure located in the sulcus corpus callosi in Figure 1 is displaced anteriorly (blue) across the cingulate gyrus in the left relative to the right cerebral hemisphere.

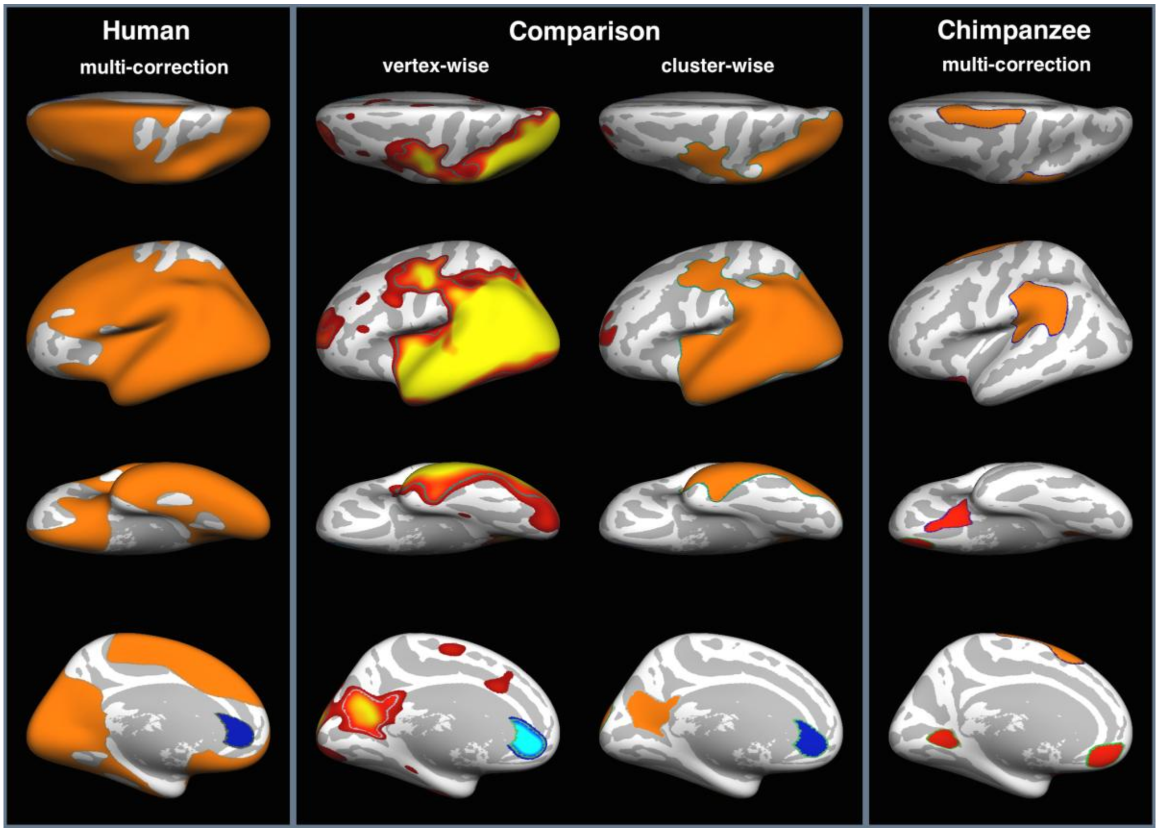

Figure 2: Species difference in antero-posterior positional brain asymmetry (Asym^{AP}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value thresholded at p<0.01) are demonstrated for humans and chimpanzees respectively. Hot colour indicates that a given structure in the left hemisphere is displaced posteriorly relative to the right and cool colours suggests that such a structure is displaced anteriorly relative to the right. Column 2 shows the p-value (thresholded at p<0.01) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3

shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 74.8% of the surface in the Asym^{AP} orientation in the human compared to 10.5% in the chimpanzee brain is classed as asymmetrical.

With regard to the dorso-ventral direction (Figure 3) two asymmetries are observed on the lateral aspect of the cerebral hemisphere in humans:

1) the left temporal pole and frontal poles are elevated superiorly relative to the right and the occipital pole is displaced inferiorly in the left relative to the right cerebral hemisphere in humans, and

2) a region around the posterior Sylvian Fissure extending into the inferior parietal lobe is displaced downwards in the left compared to the right cerebral hemisphere in humans. Interestingly, there is suggestion of a possible Sylvian Fissure movement in the opposite direction in the chimpanzee brain, that is to say, the chimpanzee may have a higher posterior Sylvian point on the left compared to the right hemisphere.

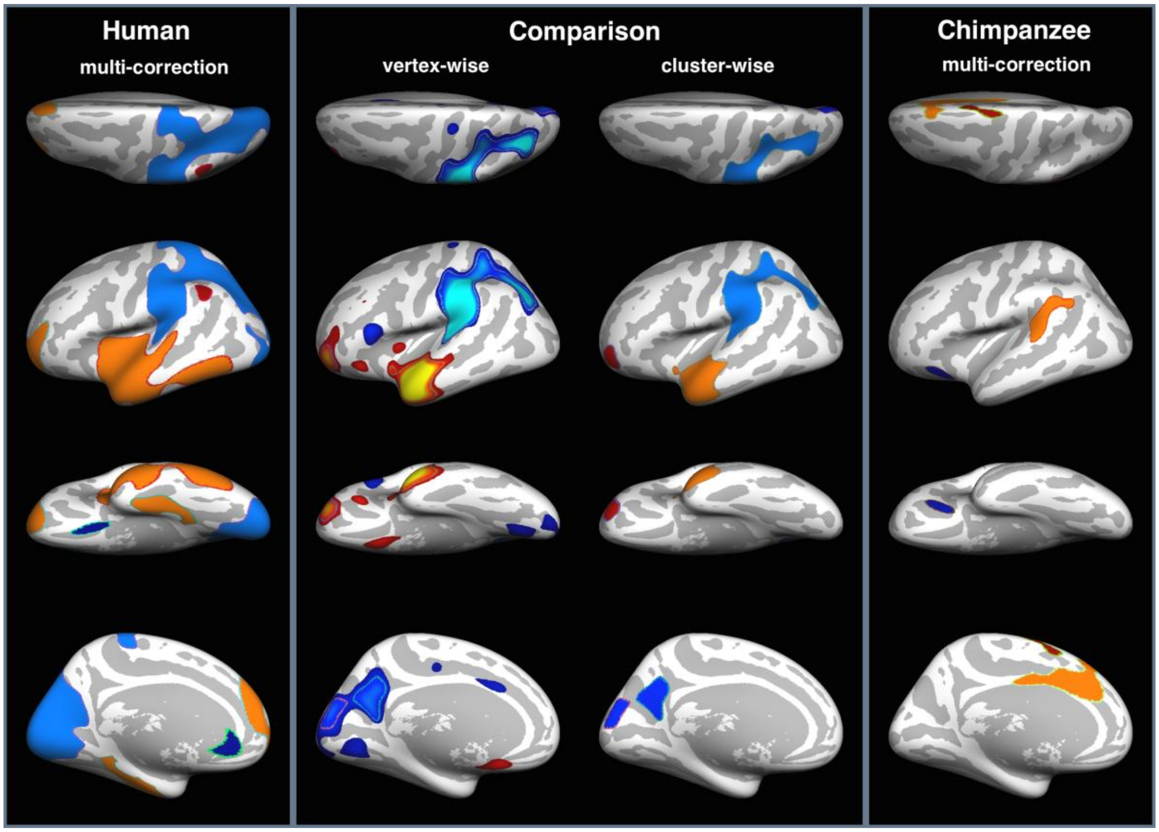

Figure 3: Species difference in dorso-ventral (i.e. up-down) positional brain asymmetry (Asym^{DV}). In columns 1 and 4, the regions with significant positional asymmetries (corrected p-value) are demonstrated for humans and chimpanzees respectively with hot colour representing leftward dorsal deviations and cool colours for ventral deviations. Column 2 shows the p-value (thresholded at $p<0.01$) of the inter-species differences assessed using a statistical two-sample t-test between asymmetry maps of humans and chimpanzees on a vertex-by-vertex basis and column 3 shows the p-value corrected for multiple comparisons with hot colours indicating greater positional asymmetry in humans compared to chimpanzees and vice versa for cool colours. By the criteria adopted 38.1% of the surface in the Asym^{DV} orientation in the human compared to 5.3% in the chimpanzee brain is classed as asymmetrical.

3.2 Sex Difference

Next, sex differences in surface positional asymmetry were assessed at each vertex in the two species corrected for multiple comparisons. In the left-right direction no sex difference survived correction for multiple comparisons in either species. This was also true in the antero-posterior direction although the rostral-most boundary of the structure identified as continuous with the sulcus corpus callosi (see Figures 1 and 2) was more prominent in human females than males in the uncorrected comparison. The single region of difference in asymmetry between the sexes that is significant after correction for multiple comparisons is in the dorso-ventral direction in the human brain. In particular, a region in the antero-lateral aspect of the orbital frontal surface (Figure 4, row 3, column 2) distinguishes females from males, such that males show relative downward displacement in the left relative to the right cerebral hemisphere that is significant, while in females the asymmetry is in the opposite direction although is not significant. However, in contrast to their relative displacement, when each sex was studied individually neither of these sex-specific asymmetries survives correction for multiple comparisons. No sex difference in asymmetry was observed in the chimpanzee brain.

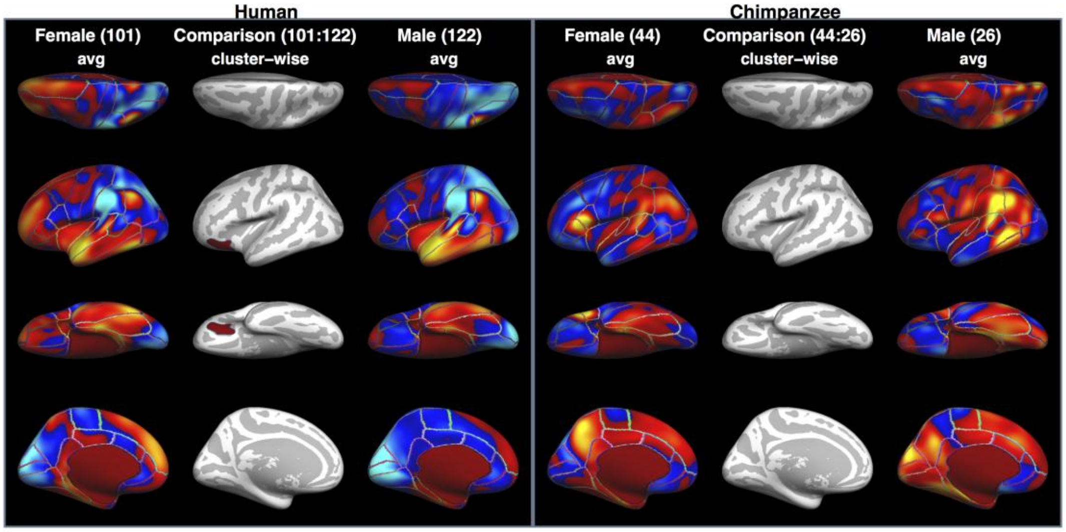

Figure 4: Sex difference in dorso-ventral positional brain asymmetry (Asym^{DV}). Columns 1 and 3 represent average asymmetries in human females and males respectively, and columns 4 and 6 represent average asymmetries in female and male chimpanzees respectively. Columns 2 and 5 represent the significant differences between the sexes assessed by cluster-wise analysis for humans (column 2) and chimpanzees (column 5) both corrected for multiple comparisons.

3.3 Brain Dimensions

Measurement of the length, height and width of the cerebral hemispheres for 223 human and 70 chimpanzee brains revealed that the left cerebral hemisphere of the human brain is significantly longer and of significantly less height, but unchanged in width, compared to the right cerebral hemisphere. By contrast the left cerebral hemisphere of the chimpanzee matches closely the right cerebral hemisphere in length, height and width (Table 1).

Human Brain Dimensions and Cross Hemisphere Asymmetry (in mm ± sd)									
	Left Hemisphere			**Right Hemisphere**			**Asymmetry (Left-Right)**		
	Length	**Height**	**Width**	**Length**	**Height**	**Width**	**Length**	**Height**	**Width**
AVG	170.8±8.6	115.2±5.4	70.5±3.9	169.9±8.6	115.8±5.7	70.6±3.9	0.9	-0.5	-0.0
pval	**LEFT>RIGHT, Left hemisphere is longer**						**3.6e-12**		
	LEFT<RIGHT, Left hemisphere is shorter							**1.9e-03**	
	No significant width difference between two hemispheres								0.9
Chimpanzee Brain Dimensions (in mm)									
AVG	110.5±4.4	74.5±3.4	45.1±20.8	110.4±4.3	74.4±3.5	45.0±2.1	0.1	0.1	0.1
pval	No significant length difference between two hemispheres						0.4		
	No significant height difference between two hemispheres							0.6	
	No significant width difference between two hemispheres								0.7

Table 1: Brain dimensions and inter-hemispherical asymmetries. By one-tailed paired t-tests the human brain has a left hemisphere that is significantly elongated and less tall in comparison to the right, but shows no width difference between the hemispheres. In contrast, the chimpanzee brain (below) shows no hemispheric asymmetry in any of the three dimensions.

4. Discussion

In this study, a surface-based approach that complements Voxel Based Morphometry (VBM) (Good et al., 2001; Watkins et al., 2001) was used to assess the positional asymmetry of the cortical surface. High-dimensional surface registration enhances fidelity of alignment to the brain folding pattern (Van Essen 2005; Van Essen et al., 2012). By contrast with studies that consider only the relative distances between the left and a mirrored right hemisphere at corresponding locations (Lyttelton et al., 2009; Van Essen et al., 2012; Zilles et al., 1996), and conventional VBM based studies that take only the left-right asymmetry into account, the new method considers both direction and magnitude by decomposing the asymmetries in three orthogonal directions. The approach therefore provides a detailed, comprehensive analysis of positional brain asymmetry.

We identify four major features of the brain surface that distinguish the brain of *Homo* sapiens from that of *Pan* troglodytes, on account of exhibiting significant hemispheric asymmetry in the former and being absent in the latter:

1) a Torque pattern (i.e., anticlockwise twist) comprising right frontal and left occipital petalia and rightward and downwards bending of the left occipital pole relative to the right occipital pole,

2) leftward asymmetry of the lateral surface of the anterior temporal lobe and STS. The leftward asymmetry of STS indicates that the sulcus depth of the STS in the right cerebral hemisphere is nearer to the MSP than it is in the left cerebral hemisphere whereas the adjacent brain surface (i.e., surrounding gyrus) shows the opposite effect. Taken together these facts are consistent with the conclusion that the human specific area identified with the STS is of greater depth in the right in the right than the left hemisphere (Leroy et al., 2015). Comparable asymmetries have been identified in antenatal (Kasprian et al., 2010) and neonatal (Glasel et al., 2011) human brains.

3) posterior expansion of the lateral surface of the left temporo-occipital region (including Heschl's gyrus and planum temporale) with clockwise rotation of the left Sylvian Fissure relative to the right around the left-right axis (observed from the dorsal-ventral asymmetry map),

4) an area of the orbito-frontal surface is found in females to be located higher (further dorsal) in the left compared to the right hemisphere and in males higher in the right compared to the left hemisphere.

If the above asymmetries are each characteristic of the human brain it is plausible that they are related. One possibility is that the leftward asymmetry that envelopes the temporal pole (see Figure 1, columns 2 and 3, rows 1 to 3) and tapers diagonally along the STS to end just short of the posterior termination point of the Sylvian Fissure is continuous with the rightward asymmetry that extends as a line between the corpus callosum below and the cingulate gyrus above to reach into the para-olfactory region in orbital cortex (see Figure 1, columns 2 and 3, row 4). Interestingly, a white matter pathway lying coincident with this trajectory is the indusium griseum (Di Ieva et al., 2015) which comprises four parallel tracts (the striae of Lancisi) that constitute a focus of generation of stem cells in the human brain.

The association of asymmetry with the human species is further illustrated by significant differences in length and height between the hemispheres in the human brain that are absent in that of the chimpanzee (Table 1). The overall length asymmetry is interpreted as an extension of the left cerebral hemisphere along the antero-posterior axis (3) that is in line with more prominent left occipital than right frontal petalia (Bear et al., 1986; Smith 1907). The posterior extension may also explain the greater length of Sylvian Fissure in the left than the right cerebral hemisphere, the leftward area asymmetry of the plana temporale and parietale (Lyttelton et al., 2009) and the phenomena of occipital bending (Deutsch et al., 2000). The height asymmetry is possibly related to the clockwise rotation at Sylvian Fissure (3), which produces a lesser angle of the posterior segment of the fissure (Witelson and Kigar 1988), less high posterior Sylvian point (Rubens et al., 1976) and lower occipital pole in the left relative to the right cerebral hemisphere.

The fact that hardly any chimpanzee specific asymmetries can be documented is notable. Because the brains of both species are normalized to the size of the standard MNI template brain in the FSL pre-processing steps, the failure to detect asymmetries in chimpanzee should not be attributable to the relatively smaller brain size. We can also confirm that the findings i) are remarkably consistent between the subject cohorts and are therefore not due to type 1 error (see Figure 1S in the Supplementary Information) and ii) do not depend upon whether human and chimpanzee 3D MRI scans are normalized to a common human reference template or to respective human and chimpanzee specific templates (see Figure 2S in the Supplementary Information and also (Hopkins et al., 2016)).

The primary asymmetric feature observed is the Torque pattern in the human brain. In particular, the left occipital lobe shifts relatively more posteriorly ($asym^{AP}$), bends to the right ($asym^{LR}$) and moves downwards ($asym^{DV}$) relative to the right side; and the right frontal lobe protrudes further anteriorly compared to its left counterpart. These results are most closely comparable to a previous MRI study of 29 in-vivo brain of human males and 9 post-mortem brain of chimpanzees (Zilles et al., 1996, reviewed in Gilissen 2001). In that study, the authors investigated the inter-hemispheric discrepancy based on a subtraction of the 3D surface of the left cerebral hemisphere and the mirror image of the 3D surface of the right cerebral hemisphere. Comparable to our findings, significant asymmetry of the occipital lobe was observed only in the human brains. The absence of the Torque pattern in chimpanzees at the population-level also concurs with observations by Holloway and De La Costelareymondie (1982). In a study of 190 hominoid endocasts, the authors concluded that only modern *Homo* and hominids (*Australopithecus, Homo erectus*, Neanderthals) show a distinct left-occipital, right-frontal petalial pattern… and that the pattern is relatively invariant and has been for perhaps as much as 3 x 10^6 years. Balzeau and Gilissen (2010) approached the study of asymmetry in hominin evolution through examination of physical and virtual endocasts (computerized tomograms) from museum collections. With the use of seven cranial landmarks in CT scans of 36 *Pan* paniscus, 36 *Pan* troglodytes and 38 Gorilla these authors reported finding the same petalia in apes as was identified by LeMay (1976) although conceded that "analyzed as non-metric traits most ... were characterized by equal distributions between the right and left sides (ranging between 40% and –60% for each side)". A similar result was reproduced by the same group in another endocast study including 89 hominins samples in addition to 110 great apes, from which the authors concluded that the asymmetry is a pattern that is shared by great apes as well as humans (Balzeau et al., 2012). Differing findings in different studies may be due to differing definitions of the reference plane with respect to which the asymmetry is computed. In the present study, a best fitting Inter-hemispheric Fissure (i.e., MSP) was extracted from the data relating to the medial surface of each cerebral hemisphere to represent the Left-Right centre of the brain whereas in (Balzeau and Gilissen 2010; Balzeau et al., 2012), an "external and independent reference" of the brain, was built upon three anatomical landmarks manually selected on the mid-surface of the skull, namely glabella, inion, and basion. Other possible interpretations of the discrepancy are i) different measuring approaches, ii) different specimens and iii) different sample sizes. Based on a direct comparison between the live brains of modern humans and chimpanzees analyzed in an identical pipeline, our findings challenge claims for directional specificity of the Torque in the chimpanzee (Balzeau and Gilissen 2010; Balzeau et al., 2012; LeMay 1976) and provide the most robust evidence obtained to date to indicate that the Torque, at least, petalia and occipital bending, is human-specific. Although the role of the Torque in determining the laterality of brain functions is not known, it is interesting that an atypical Torque pattern has been associated with developing stuttering (Foundas et al., 2003).

The only sex difference in positional brain asymmetry is located in orbito-frontal cortex. No sex differences in cerebral asymmetry are seen elsewhere whereas here no asymmetry is apparent unless the sexes are separated, whereupon a sex difference in surface asymmetry is observed such that the left surface is displaced upward relative to right in females and downward relative to right in males (Figure 4 rows 2 and 3, column 2). No such interaction between sex and asymmetry is seen anywhere on the cerebral surface of the chimpanzee brain. Congruent evidence of a lateralized difference between the sexes in orbito-frontal cortex comes from a meta-analysis of studies of sex differences in the human brain (Ruigrok et al., 2014) in which it is reported that a cluster of increased grey matter density in left relative to right orbito-frontal cortex (see Figure 4c in reference 23) is present only in males. The position and extent of this cluster resemble those of the region denoting a sex difference in our Figure 4. This sex difference in asymmetry is not associated with the Torque, but may be related to unilateral responses in right orbito-frontal cortex following olfactory stimuli (Zatorre et al., 1992). In independent fMRI experiments such activations are greater in women (Yousem et al., 1999).

The literature on cortical asymmetry in chimpanzees, other great apes and primates is perplexing. Besides the equivocal reports of the Torque in apes mentioned above, in one study the cortical surface area of the planum temporale was greater in the left hemisphere than the right in 17 out of 18 chimpanzee brains (Gannon et al., 1998) and in another study area 44 described as Broca's area in the inferior frontal gyrus, bounded by fronto-orbital, and pre-central inferior sulci was of greater magnitude in the left than the right hemisphere in a group of 20 chimpanzees, 5 bonobos and two gorillas (Cantalupo and Hopkins 2001). These reports are not in agreement with aspects of our findings. In particular we do not find circumscribed asymmetries of cortical regions corresponding to Broca's and Wernicke's areas in humans. No specific relationship between the asymmetries of these regions and language has been found in language dominance studies (Greve et al., 2013; Keller et al., 2009a; Keller et al., 2011).

Furthermore, textbook descriptions of Broca's area imply a greater anatomical focus of speech disturbance than is justified by empirical investigation (Conrad 1954; Lenneberg 1967; Russell 1961) and however defined these areas have not been shown to have consistent cyto-architectonic correlates (Sholl 1956). In addition, based on modern imaging techniques (e.g., fMRI, PET), language-relevant areas should be expanded beyond the classic language regions (Price 2012; Tremblay and Dick 2016). In another investigation 4 of 11 sulci tested in chimpanzees and 1 out of 7 in macaques showed evidence of directional asymmetry (Bogart et al., 2012) but the one instance in macaques is in the STS which is judged to be a human-specific asymmetry by the same group in a later study (Leroy et al., 2015). In another endocast study, Balzeau et al. (2014) reported a lower position of the third frontal convolution (corresponding to Broca's area) on the left relative to the right which is unique in *Pan* troglodytes and not present in *Pan* paniscus and hominins. In the present study, no chimpanzee specific asymmetry can be observed in this region. Although, at a neighbouring orbital frontal region, an asymmetry in the same direction was found in chimpanzees, which is however also shared with humans (a blue patch in Figure 3, row3, columns 1 and 4). We suggest that there is merit in approaching the origins of language through inter-species comparisons in which the techniques applied are matched as closely as possible between species, without preconception concerning the functions of particular areas of cortex. By these criteria asymmetry between the hemispheres in the form of the Torque is not ruled out as the key to the capacity for language as Broca conjectured.

There are at least three limitations in the present study. First, with regard to the sex difference, the human group comprised 101 females and 122 males (0.8:1) and the chimpanzee group comprised 44 females and 26 males (1.7:1). Thus there is a potential bias in the sex ratio toward males in the human group which approximates doubling of the number of females compared to males in the chimpanzee group. Second, it is worth noting that although the surface-based non-linear registration in FreeSurfer works well on aligning folding patterns in general, the fidelity of registration can be weak at regions with high individual shape variability (Van Essen 2005; Van Essen et al., 2012), such as parietal cortex, to some extent. Cautions must be observed when interpreting the asymmetry in the associated regions and improvement in the registration algorithm is to be considered in the future. Nonetheless, this problem should not cause much concerns in the current study since the key findings are mostly located in the peri-Sylvian Fissure, temporal, occipital and frontal regions that are of comparatively low individual shape variability. Third, with regard to the cerebral Torque, further work needs to be performed aimed at deriving a quantitative measure of this prominent asymmetry.

5. Conclusion

Our findings suggest a particular lateralization (described as the Torque from right frontal to left occipital and notably more prominent in the posterior or sensory half of the cerebrum) distinguishes the human brain from that of our closest extant relative the chimpanzee. This finding should motivate research to elucidate whether the Torque has a specific role with respect to the capacity for language in humans.

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Author Contributions: X.L. devised the methods for analysing positional brain asymmetry on 3D MR images, applied the methods to all data-sets, conducted statistical analyses and prepared Figures. T.J.C. and N.R. devised and planned the project, co-ordinated analysis and wrote the paper with X.L.. W.D.H. instituted and managed MRI scanning of chimpanzees, and contributed to study design. Q.G. contributed MRI scans and data. All authors reviewed and approved the paper.

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Figure 1

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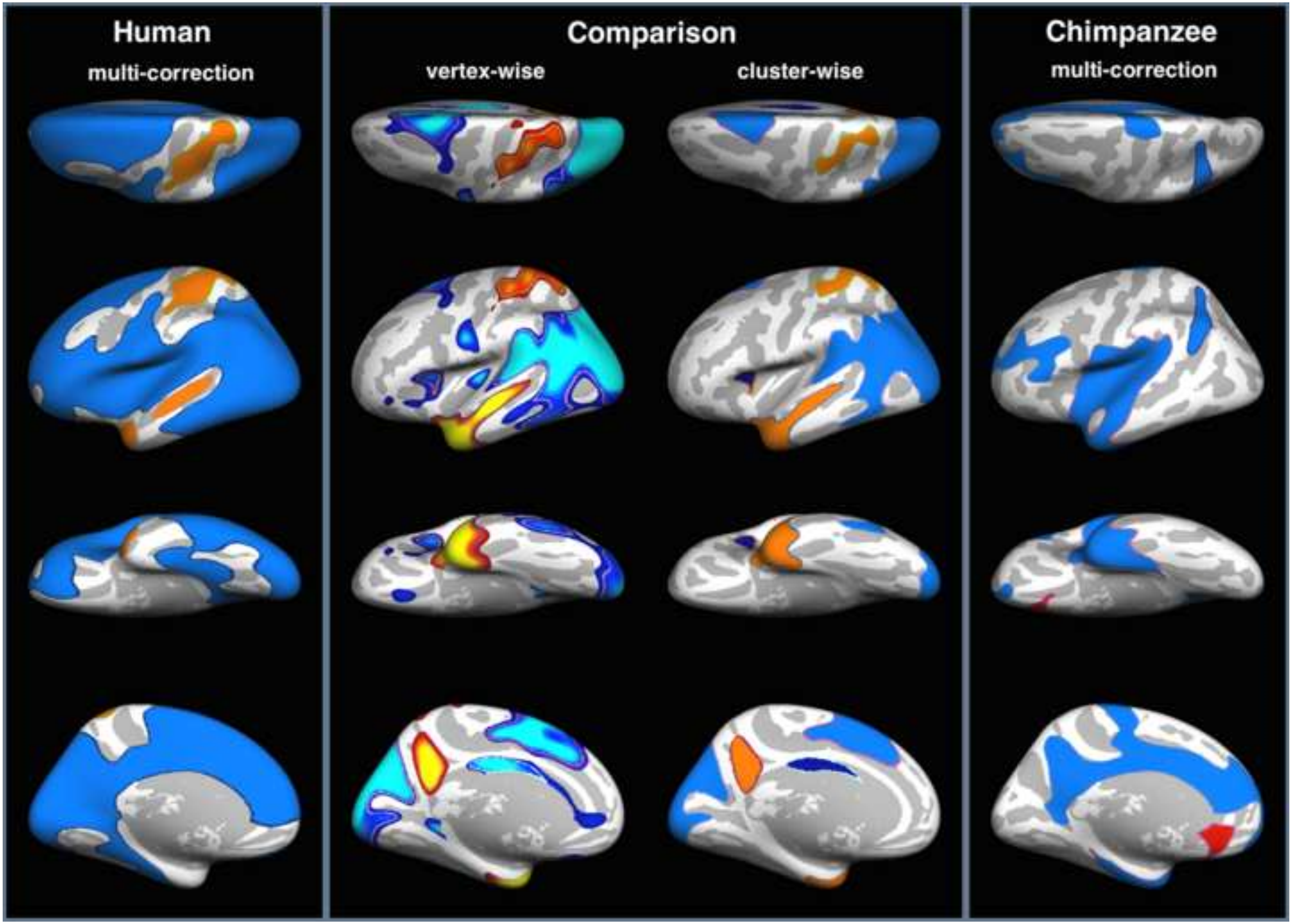

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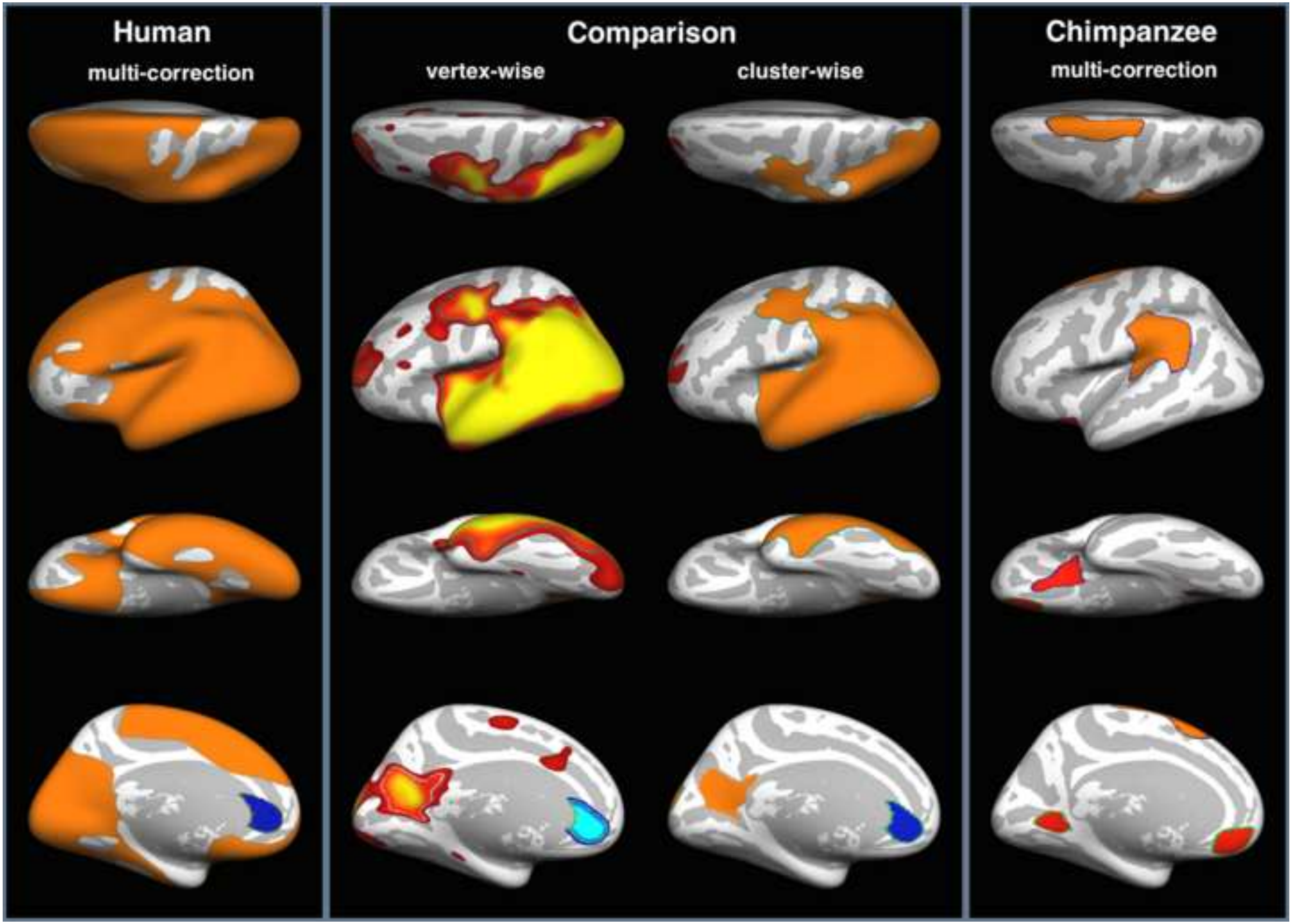

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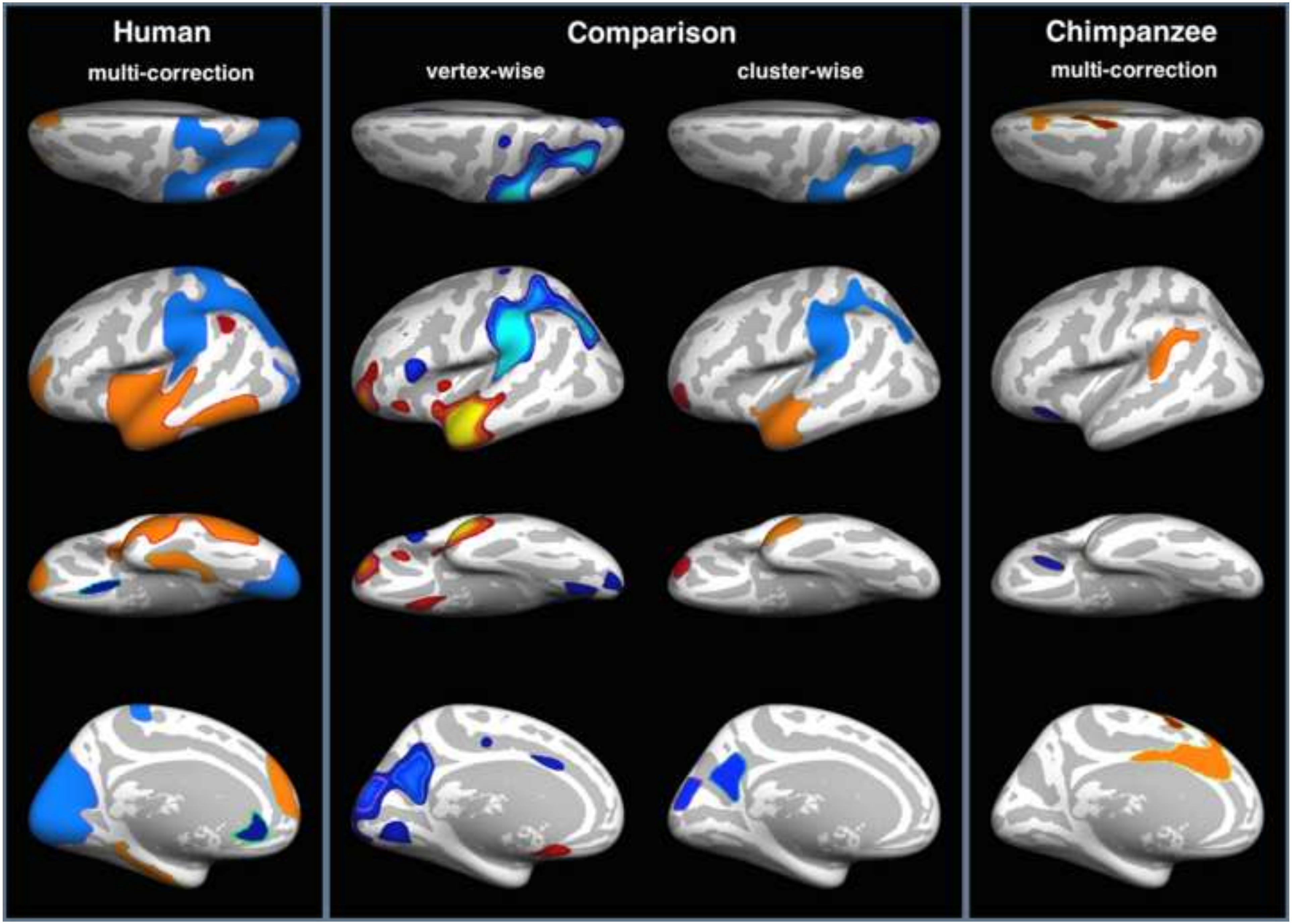

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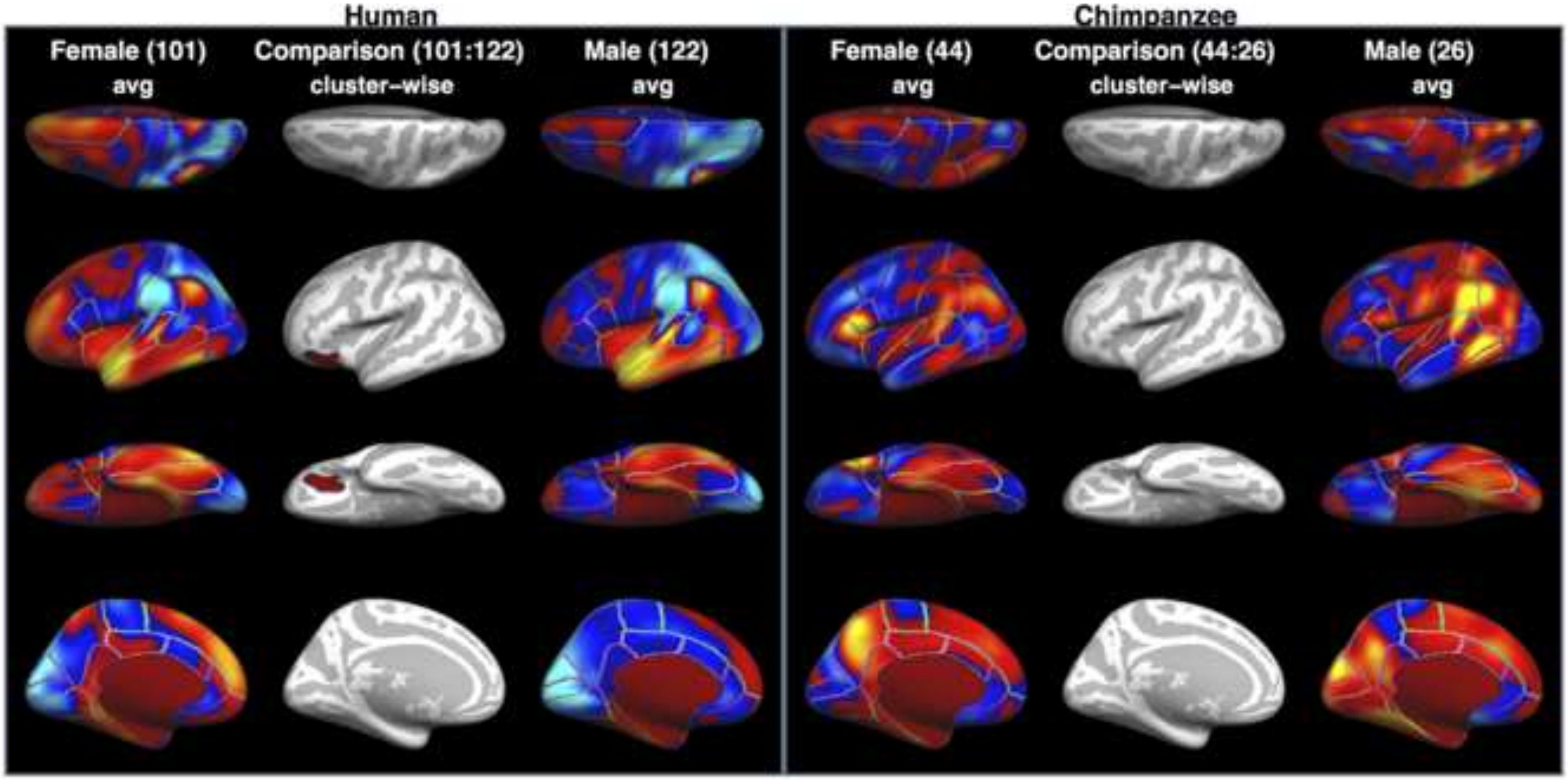

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