

Extracting functional, phylogenetic and structural data from the subcortical brain: an exploratory geometric morphometric survey

Emiliano Bruner¹ & Nathan Jeffery²

1) Centro Nacional de Investigación sobre la Evolución Humana (CENIEH), Avda. de La Paz 28, 09004 Burgos (España)
e-mail: emiliano.bruner@cenieh.es

2) Division of Human Anatomy and Cell Biology, School of Biomedical Sciences, University of Liverpool, Ashton Street, Liverpool L69 3GE (UK)
e-mail: njeffery@liv.ac.uk

Summary - *The neocortical brain is notoriously difficult to research among extant and extinct primates because its complexity can negate assumptions of spatial and functional homology. Despite this, the neocortical brain remains the centre of attention whilst the subcortical brain is often dismissed as conserved and lacking in any significant phylogenetic or functional signal. However, it is possible that while the information held in the subcortical brain is limited it may also be more amenable to investigation and shed new light on the evolution of the primate brain. Here we use shape analysis to survey the changes of the subcortical brain across extant apes. Twenty-eight specimens covering nine primate species were examined through midsagittal magnetic resonance images (MRI). Co-ordinates for 10 2D-landmarks representing the subcortical morphology were collected from midsagittal scans and analysed with geometric morphometrics. The main axis of variation was size-related, and associated in most species with flexion of the encephalic trunk, anterior rotation of the corpus callosum, and geometric compression of the thalamic region. Gibbons and orangutans showed only minor shape changes, despite the differences in size. This similarity suggests a possible phylogenetic component that should be further investigated. Both hypotheses (allometric vs. phylogenetic variation) must be considered when taking into account the interaction between the brain cortical changes and the cranial base dynamics.*

Keywords - *Hominoid, Subcortical brain, Evolution, Primates.*

Introduction

The architectural and functional complexity of the neocortex bestows it with perhaps the greatest potential of all brain structures for enlightening our understanding of cognitive evolution, particularly among the hominoid primates (Kudo & Dunbar, 2001; Huxley, 1861; Huxley, 1862; Tilney & Riley, 1928; Kappers, 1929; Reader & Laland, 2002; Bonin, 1941; Passingham & Ettliger, 1974; Radinsky,

1975; Hofer, 1969; Stephan & Frahm, 1981; Lieberman, 2002). However, it is hard to realize this potential. On the one hand fossil endocasts only carry information pertaining to the external most surface of the neocortex (Holloway 1978; Bruner 2003) whilst on the other hand the very complexity that makes the neocortex so interesting negates most assumptions of structural and functional homology. This adds considerable noise to any study, leading to confusion and controversy. An alternative to

studying the strong yet often confusing signals from the neocortex would be to focus on extracting weaker signals from more conserved regions of the brain such as the subcortex.

The subcortex is not wholly conserved. It only seems so in comparison to the massive changes typical of the primate neocortex. In practice, the subcortex also undergoes considerable changes related to its numerous reciprocal connections with the neocortex and structural relationships with the underlying cranial base. Previous studies have shown that changes in the relative proportions of the different subcortical components can yield particularly useful insights. For instance, researchers have speculated that allometric changes of the corpus callosum are linked with the advancement of cognitive functions (de Lacoste & Woodward, 1988; Sanchez *et al.*, 1998; Rilling & Insel, 1999a), changes of the thalamus are associated with the increased integration of visual data with complex functions (Rapoport, 1990; Kaas, 2002) and changes of the encephalic trunk (midbrain, pons and medulla) are linked to phylogenetic modifications of the underlying cranial base (Hofer, 1969; Strait, 1999). Here, we set out to document shape changes of the subcortex using magnetic resonance images and geometric morphometric techniques. Generally the brain is investigated with volumetric analyses, to test differences in the dimensions of the neural components. Here we focus on the spatial organisation of the neural components that is essential to understand the evolutionary changes in the physical and functional relationships among these elements as well as the morphogenetic variation in the brain versus braincase dynamics. The results of this exploratory survey are discussed with regard to allometry, skull architecture as well as to brain function and primate evolution.

Materials and Methods

The MR image data used in the present study were kindly provided by Dr. J. Rilling (Emory

University, Atlanta). Images of anesthetized subjects were acquired using T1 weighted gradient echo protocol with an effective slice thickness of 0.6 -1.0mm and pixel resolution of 0.55 - 0.94mm (for further details see Rilling and Insel 1998, 1999a,b). Images were interpolated with the ImageJ (Rasband, W.S., U. S. National Institutes of Health, Bethesda) Transform plugin (Meijering, E., University Medical Centre Rotterdam, Netherlands) to form isometric voxels and then resliced along the midsagittal plane. The sample used in the present analysis (N=28) includes MRI data from *Homo sapiens* (6), *Pan troglodytes* (3), *Pan paniscus* (4), *Pongo pygmaeus* (2), *Hylobates lar* (4), *Papio cynocephalus* (2), *Cercocebus atys* (3) and *Macaca mulatta* (4). Although sexual differences used to have some influence in the neural and cranial morphology, in the present analysis sexes are pooled to have a minimum sample size per species. Anyway, sexual variation is supposed to have just a minor role when compared with the high-rank taxonomic biodiversity. All specimens are adult individuals.

A configuration of 10 two-dimensional landmarks was used to represent the shape of the subcortical areas on the midsagittal plane (Fig. 1): most anterior and most posterior points of the corpus callosum (at the centre of the splenium and genu), thalamus (centre), midbrain tectum (centre), and midbrain tegmentum (centre), most caudal, most rostral, and most projecting points of the pons, infundibulus, and optic chiasm. The first two points describe the length of the corpus callosum, the following three will be referred to as the "thalamic triangle", and the remaining are in tight contact with the endocranial base, associated with the anterior cranial fossa (chiasm and infundibulus) and with the clivus (pons).

Because of the less derived morphology, the subcortical structures are easier to recognise between the different taxa when compared with the neocortical areas. The intra-specific variation is rather limited, and the inter-specific comparisons are not affected by the considerable homology problems described for the pattern of cortical folding (e.g., Radinsky, 1972; Falk, 1978). Of course, minor differences do exist and

these should be investigated further. For example, it is worth noting that in the present sample gibbons seem to display a peculiar morphology of the corpus callosum. This structure is generally curved with a curving and enlarged caudal end, most of all in Hominoids. In contrast, *Hylobates* seem to show a straight corpus callosum, with the splenium not bending and aligned with the rest of the callosal body. Accordingly, the most anterior and most posterior points could not account for different morphology related to the overall shape of this structure. An ongoing study is considering also the curvature of the corpus callosum, by using outlines and semilandmarks.

Another minor problem can be represented by the midsagittal contour of the pons in Cercopithecoidea. In the parasagittal section the pons shows a clear enlargement and the boundaries of the bulging area are easily recognisable, but in the midsagittal section it is often flattened against the clivus by the basilar artery. This morphology makes the localisation of the respective landmarks more difficult and somewhat equivocal, especially toward the caudal end of the pons. Of course, such uncertainty is not relevant when compared with the overall variation of the whole subcortical morphology.

Data were visualised using MIMICS 7.0 (Materialise), and coordinates were sampled using tpsDIG 1.20 (Rohlf, 1998). Pairwise comparisons were performed using average configurations from each genus (*Homo*, *Pongo*, *Pan*, *Hylobates*) and from the Cercopithecoidea (*Cercocebus*, *Macaca*, and *Papio*, pooled) after superimposition. Coordinates were compared using both partial Procrustes and baseline superimpositions (see Zelditch *et al.*, 2004). The second method is a two-point registration that translates, rotates, and scales all the configurations to a common baseline (Bookstein, 1991). This approach is rather useful to compare geometrical differences relatively to a specific diameter with functional or structural meaning. In this case, the length of the corpus callosum was used as baseline. This baseline has been chosen for three different reasons, both anatomical and geometrical. First, the structure is clearly homologous, and the points easily recognised. Second, its length is comparable with the overall size of the configuration. In general in the baseline approaches, the more the baseline is large, the more the relative error is supposed to be small. Third, the position of the corpus callosum (central to the brain

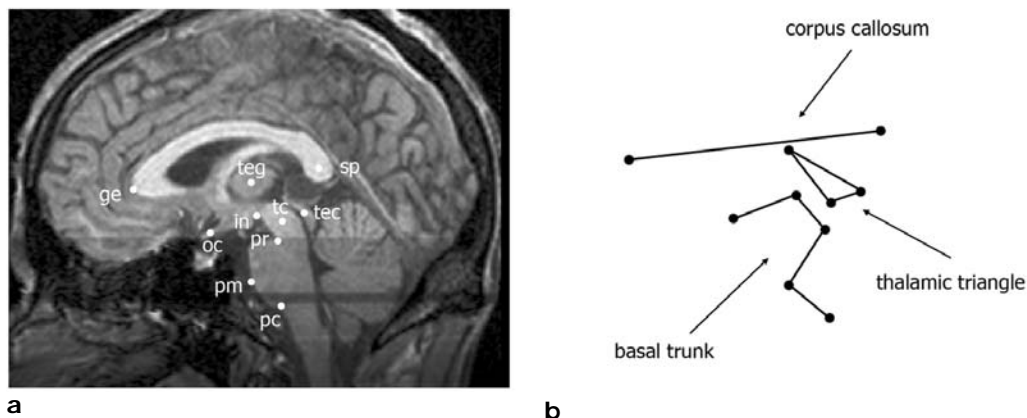


Fig. 1 - The configuration used in this analysis is based on 10 2D-landmarks from MR midsagittal section: *ge*: genu; *in*: infundibulum; *oc*: optic chiasm; *pc*: pons, caudal; *pm*: pons, middle; *pr*: pons, rostral; *sp*: splenium *tc*: thalamus, centre; *tec*: thalamus, tectum; *teg*: thalamus, tegmentum. The configuration is shown on a human MR image (a) and with the wireframe used in the following figures (b).

volume, midline between the two hemispheres) is fundamental to have information between the subcortical and cortical structures. Of course, the corpus callosum has also a relevant biological role, related to the communication between the left and right cortical areas.

The partial Procrustes superimposition translates all the configurations to a common centroid, scales the coordinate systems to unitary centroid size, and rotates them as to minimise the sum of squares of the differences between corresponding landmarks (Bookstein, 1991). This approach minimises and standardises the differences between geometric configurations. Of course, the application of a conventional and arbitrary scaling criterion requires some caution when results are finally interpreted (Richtsmeier *et al.*, 2002). After this superimposition, the new coordinates can be used for multivariate statistical analyses (Marcus *et al.*, 1993, 1996).

The pairwise comparisons were computed using MORPHEUS ET AL. (Slice, 2000). A

Principal Component Analysis on the shape components was performed using TPSRELW 1.42 (Rohlf, 2005a) and APS 2.41 (Penin, 2001). The relationship between shape variation and centroid size was tested using TPSREGR 1.31 (Rohlf, 2005b) and APS.

Results

Pairwise comparisons

Figure 2 shows the differences between the average configurations and the grand mean compared through baseline superimposition of the corpus callosum length. Accordingly, differences must be intended relatively to the position of this structure. Humans are characterised by a marked flexion of the encephalic trunk onto the anterior fossa, rotating forward and moving toward the optic chiasm. The area between the callosum and the base is compressed, and the thalamic triangle is relatively reduced and rotated

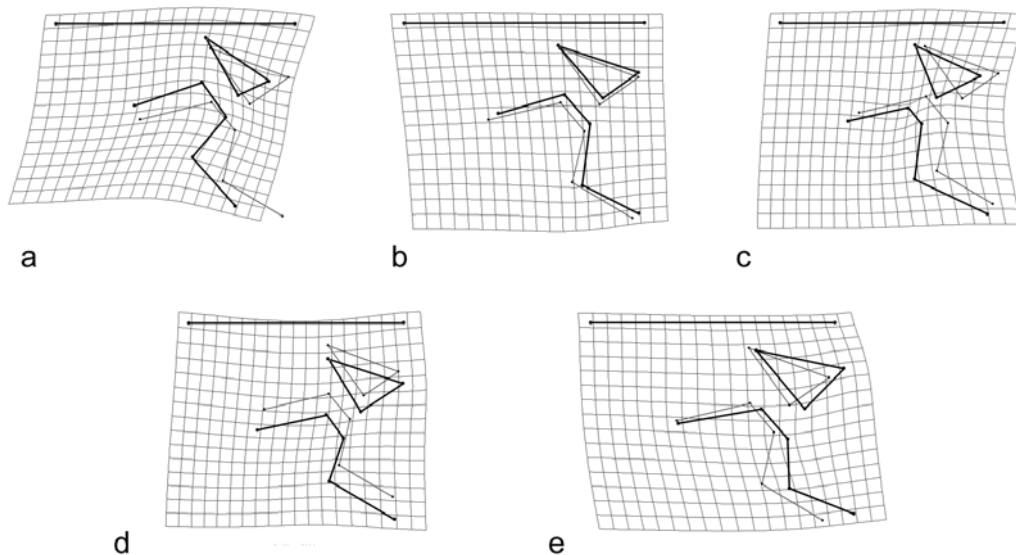


Fig. 2 - The mean configurations (bold links) from Homo (a), Pan (b), Pongo (c), Hylobates (d), and Cercopithecids (e) are compared with the overall consensus average shape (thin links) superimposing the baseline of the corpus callosum, genu to splenium, visualising the space deformation through the thin-plate spline deformation grids.

accordingly. Chimp mean is very close to the grand mean, showing just a minor compression and retroflexion of the pons. Orangs show, by contrast, a very distinctive shape, with the thalamic and basal structures both shifted anteriorly to the callosum and relatively enlarged (mostly considering the pons). This arrangement is achieved without apparent rotation of the angle between base and callosum, or between pons and chiasm. Gibbons are particularly characterised by a generalised vertical stretching, that is an increased distance between callosum and the rest of the subcortical volumes. Cercopithecoidea display a clear retroflexion of the pons and posterior stretching of the thalamic centres.

Figure 3 shows the differences between the average configurations and the grand mean compared through partial procrustes superimposition. In this case, residuals between landmarks are distributed all through the configurations by a minimum least-square criterion after normalisation of the centroid

size and translation to a common centroid. Accordingly, differences must be intended as relative to the whole shape. In humans, the flexion of the basal structures is associated with a counter rotation of the callosum. The thalamic triangle follows the basal flexion. This process involves a vertical stretching of the anterior and posterior surfaces, and compression in the mid-areas (anteriorly to the thalamic centres). Chimps once more display a shape very similar to the grand mean. Orangs show a relative enlargement of the basal areas, shifting the midbrain tegmentum anteriorly, and a minor anterior rotation of the callosum. Gibbons are again characterised by vertical stretching and minor enlargement of the pons. Cercopiths show that the retroflexion of the basal structures is associated with a certain degree of backward rotation of the callosum.

Multivariate analysis

The first four components of shape describe 43%, 19%, 11%, and 10% of the total variance

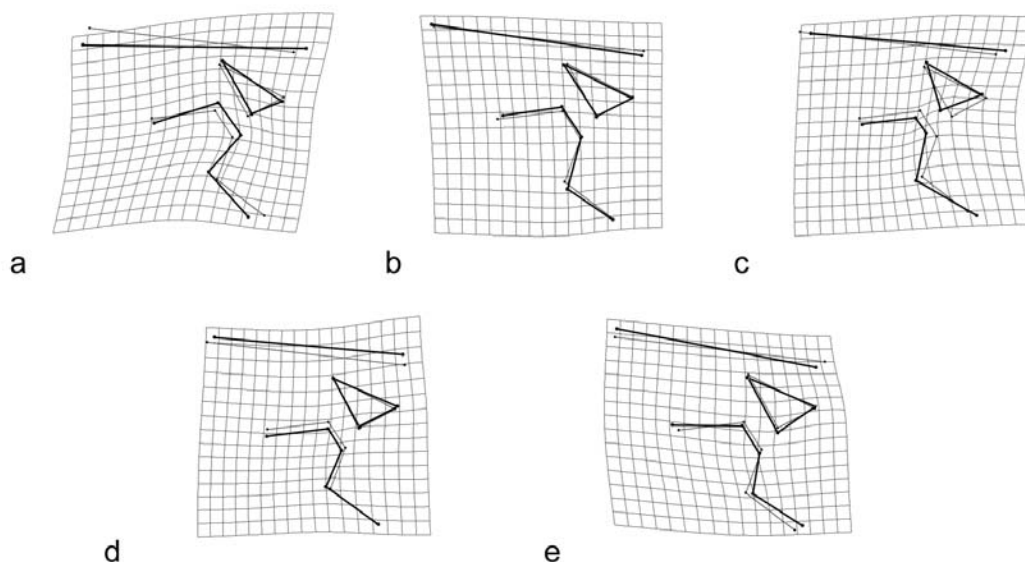


Fig. 3 - The mean configurations (bold links) from Homo (a), Pan (b), Pongo (c), Hylobates (d), and Cercopithecoidea (e) are compared with the overall consensus average shape (thin links) through Procrustes superimposition, visualising the space deformation through the thin-plate spline deformation grids.

respectively. Subsequent components explain less than 5% each and are not considered in the present analysis. Figure 4 shows the morphospace described by the first two components, with the distortion grids representing the opposite extremes. PC1 mostly separates cercopithecids, apes, and humans, with the humans more distinguished from the other groups. This shape vector involves (from mangabeys to humans) flexion and enlargement of the pons onto the anterior fossa with consequent closure of the interposed surface, anterior rotation of the callosum, and diagonal compression of the thalamic areas (Fig. 5a). In general, the subcortical configuration shortens and bends downward or, conversely, stretches antero-posteriorly and bends upward (accordingly, a compression/enlargement is visible around the thalamic centres). The second component mainly separates the Asian apes from chimps, and mangabeys from macaques. This vector is associated with (towards gibbons and orangs) a general vertical stretching (more marked

posteriorly), relative shortening of the corpus callosum, and compression at the basal structure through flexion and enlargement of the encephalic trunk (Fig. 5b). Interestingly, the taxonomic groups display very different degrees of variation within this morphological space. The current sample size does not allow a robust approach to the species-specific variance, but it is clear that this topic should be further investigated.

The correlation between shape components and centroid size is significant (Wilks' Lambda = 0.0940, $F_{16,11} = 6.68$, $p < 0.0015$; Generalized Goodall $F_{16,416} = 13.04$, $p < 0.0001$). A multivariate regression between centroid size and the first four principal components is also significant ($R^2 = 0.80$, $F_{4,23} = 19.52$, $p < 0.001$), but the normalised multivariate correlation coefficient shows that the allometric component is almost entirely loaded onto the PC1 ($R_{PC1} = -0.99$). The determination coefficient between centroid size and PC1 is 0.76 ($p < 0.001$). All groups show limited residuals from the least-square line fitting, except for the four gibbons

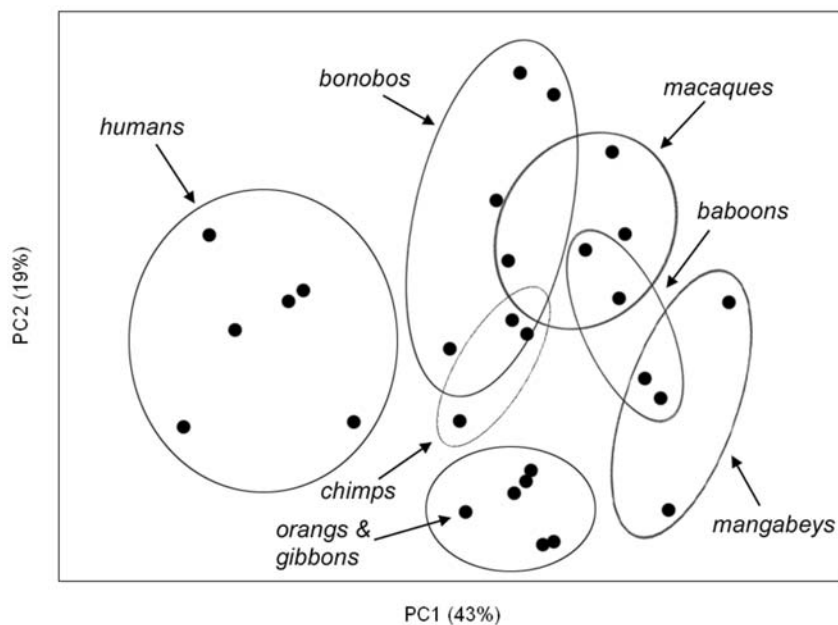


Fig. 4 - Principal Component Analysis of the shape variables: distribution of specimens and groups within the morphospace according to the first and second components.

which are a similar size to the cercopiths but have the overall shape of the great apes, at least considering this main size-related component (Fig. 6). Excluding *Hylobates* from the regression the correlation coefficient changes from -0.87 to -0.92 . As cautionary comment it is worth noting that, because the small species-specific sample size does not allow a group-wise comparison of the allometric trajectories, this vector should be presently intended as a general statistical trend, and not as a true biological pattern of structural covariation.

Although orangs and gibbons display a similar subcortical shape according to these two principal components of variation, they show some minor differences that are nonetheless relevant (Fig. 7). The Procrustes comparison shows in *Pongo* a lower corpus callosum and

upward rotation of the thalamic triangle. The baseline comparison is maybe even more clear to show the differences between the two genera: the subcortical shape in *Pongo* and *Hylobates* is very similar, but in the former the structures (trunk and thalamic areas) are shifted anteriorly and most of all closer to the corpus callosum.

Discussion

The neocortical area of the brain underwent major rearrangements within the mammalian radiation, particularly during primate evolution (Stephan, 1972). Within the evolution of the primate cortex there are many non-allometric variations. Regarding the genus *Homo*, neontological data suggest increased complexity in

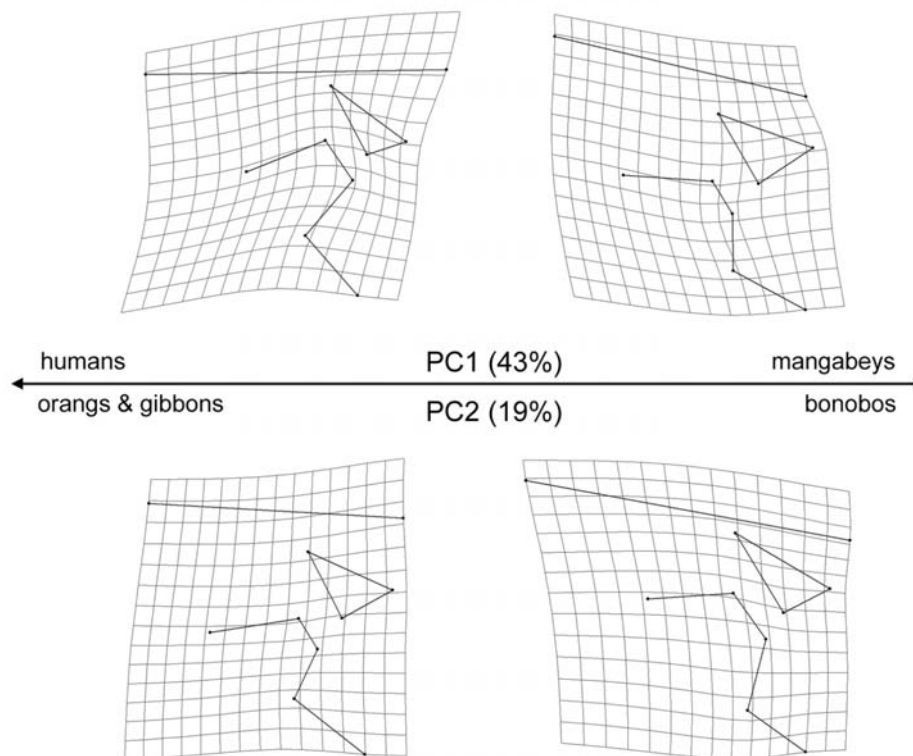


Fig. 5 - Shape changes along the PC1 (top) and PC2 (bottom) vectors, from the negative (left) to the positive (right) pole of the morphospace.

the prefrontal, temporal, and cerebellar structures (Rilling, 2006). Paleoneurological data indicate that the parietal areas may be involved in the evolution of cognitive functions associated with the emergence of anatomically modern humans (Bruner *et al.*, 2003; Bruner, 2004). By contrast, the subcortical anatomy shows a lesser degree of morphological variation between different primate taxa. Nevertheless, such variation has scarcely been investigated, and little information is available on related adaptations or structural constraints. The present paper describes some major patterns of the subcortical morphology in apes that include the possible influence of size onto shape differences as well as the relationships between the encephalic trunk, the thalamic area, and the corpus callosum.

The first component of variation within the present sample is size-related, separating cercopithecids, apes, and humans. Along this morphological vector, the first two groups are more contiguous, while the latter (humans) is more distinct. The morphological trends

are probably phylogenetically biased and independent contrasts based on larger sample would be required to clarify the exact nature of the allometric effects (Nunn & Barton, 2001). Modern humans were mainly characterised by a marked flexion of the basal areas (medulla, pons, infundibulus, optic chiasm). This neural arrangement was associated with the cranial base flexion described in relation to relative brain enlargement (Lieberman *et al.*, 2000; McCarthy, 2001; Ross *et al.*, 2004). It must be expected that the subcortical flexion described in modern humans should be interpreted in terms of causal covariation with the cranial base and its determinants rather than in terms of neurofunctional changes.

Among most of the species studied, the basal flexion was also associated with a geometric compression of the thalamic region. A shift in the relative position of the thalamic triangle (centre, tectum, tegmentum) seems to be associated with the changes of the encephalic trunk rather than with changes of the corpus callosum. This can

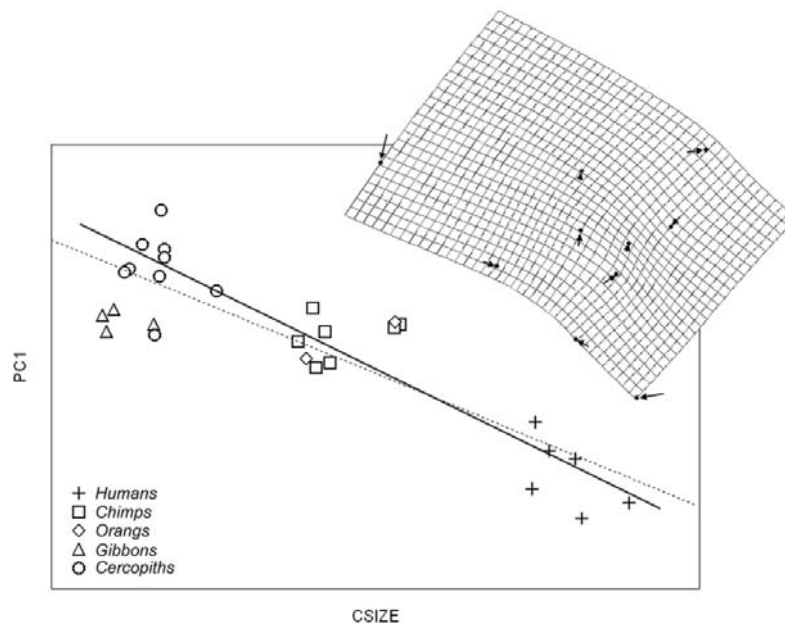


Fig. 6 - Correlation and least-square regression between centroid size and PC1, with (dotted line; $R = -0.87$) or without (solid line; $R = -0.92$) gibbons. The distortion grids shows the shape changes along the allometric vector, with the arrows pointing the relative shifting of the landmarks.

be illustrated using the baseline superimposition. Regions anterior and posterior to the thalamic area undergo a relative enlargement. Compared to the hominoids, the cercopithecoids (*Macaca*, *Papio*, *Cercocebus*) display a strong retroflexion of the encephalic trunk, with relative enlargement of the most posterior areas. Because the main focus of this preliminary analysis is the subcortical variation in Hominoids and we have a limited sample, the cercopithecoid genera have been grouped and their intra-specific differences will not be discussed. Nonetheless, this study suggests a remarkable difference within this group, which warrants further investigation.

Orangutans and gibbons display a slightly different pattern that probably also reflects differences of skull architecture. The subcortical shape in gibbons is characterised by a relative vertical stretching of the whole subcortex and a straight corpus callosum. In contrast, the orangs were characterised by enlargement and anterior displacement of the basal areas and thalamus relative to the corpus callosum but little or no flexion/retroflexion of the encephalic trunk. The cranial structure in *Pongo* is characterised by a strong *airorhynchy*, or rotation of the splanchnocranial axis onto the neurocranial one

(Shea, 1985; Penin & Baylac, 1999). According to this arrangement, the midface is flattened, and the maxilla enlarged. Probably because of its role as an interface between neurocranial and splanchnocranial regions (Lieberman, 2000), the browridge is much reduced (Shea, 1985). Interestingly, comparing the cranial shape of *Pongo* and *Pan* by Procrustes superimposition suggests that major differences are related to the facial and browridge configuration, the degree of vertical stretching of the braincase and nuchal widening, but not of the cranial base arrangement (Bruner *et al.*, 2004). In agreement with these results, the particular subcortical configuration described in orangs is not associated with a corresponding flexion/retroflexion of the encephalic trunk. In this framework, the relationship between the thalamic and basal structures relative to the corpus callosum could be interpreted as the result of *airorhynchy*, pulling anteriorly the lower half of the cranium (maxilla, endocranial base) and pushing posteriorly the upper half (orbits, braincase, neocortex, callosum). We also suspect that the same morphological network associated with *airorhynchy* and browridge modification explains the unusual morphology and reduced volume of some prefrontal cortical structures

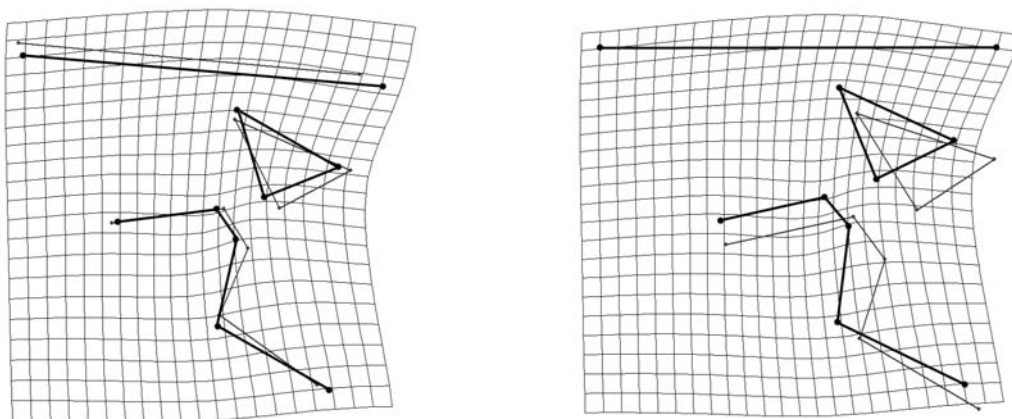


Fig. 7 - The mean configurations from *Hylobates* (thin links) is compared with the mean configurations from *Pongo* (bold links) by using Procrustes registration (left), baseline superimposition (right), and thin-plate spline deformation grids.

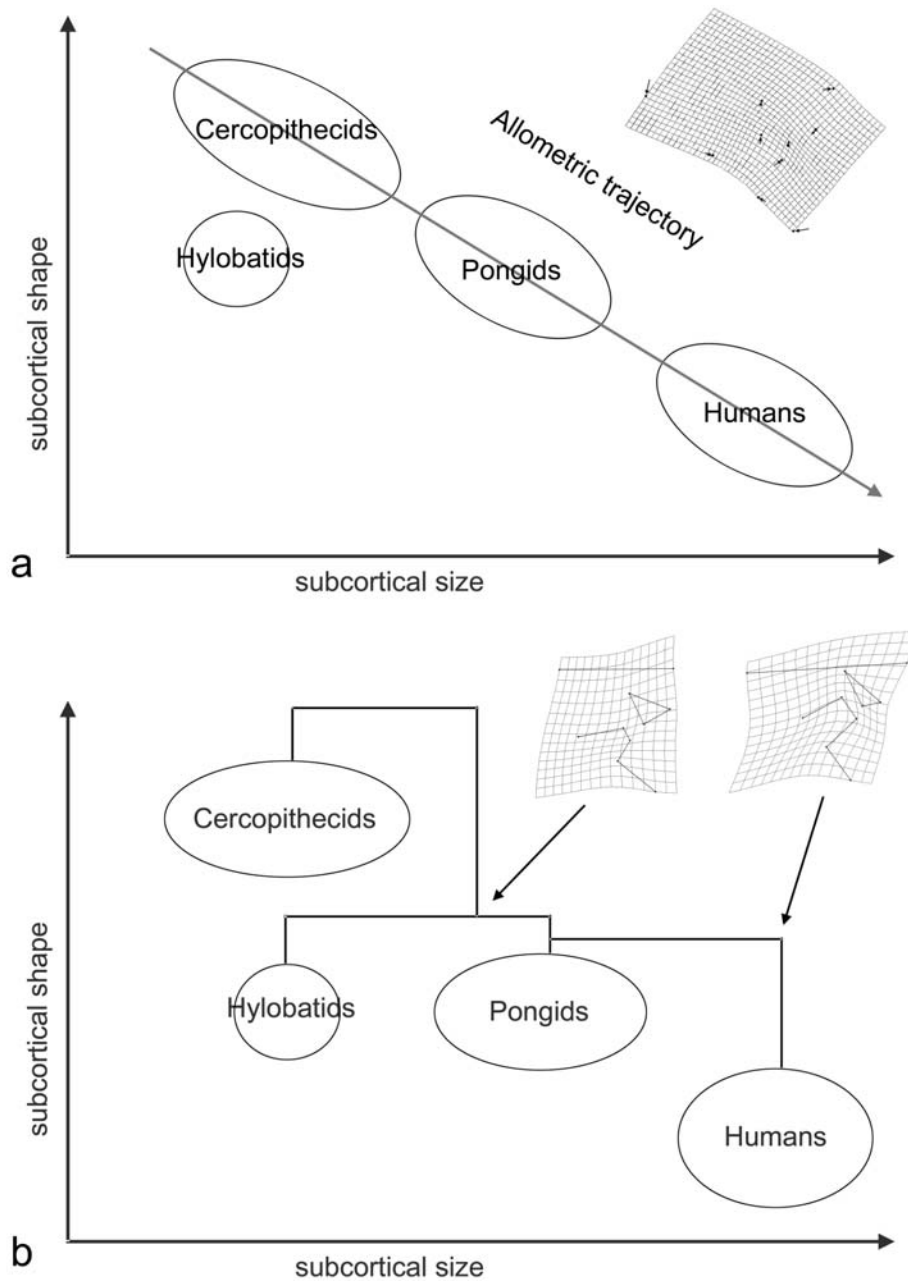


Fig. 8 - Two alternative hypotheses: a) the main pattern of shape variation of the subcortical areas is size-related, following a shared allometric trajectory, with gibbons departing from such trends and displaying a shape similar to the larger apes; b) the main pattern of shape variation of the subcortical areas is phylogeny-related, with a change associated with apes, and a change in the same direction associated with humans.

described for *Pongo* by Semendeferi and Damasio (1997). The lack of any strong specialisation in the cranial base can provide the basis for an overall similar subcortical shape in *Pongo* and *Hylobates*, while airohynchy in the former can lead to their differences, namely the supero-anterior position of the trunk and thalamus relatively to the corpus callosum in orangs.

The supposed allometric trajectory and the affinities between the Asian apes raise two possible explanations for the observed morphology of the subcortical shape (Fig. 8). First, the similarity may be due to an allometric trend across Catarrhines, and possibly all Anthropoids. In this case, a large part of the changes we observe in Cercopithecids, Pongids, and Hominids, would be related to variation in size, and the resulting changes in subcortical shape according to a common developmental/structural pattern. Gibbons would thus stand out of the allometric trajectory because of a specific evolutionary change, producing a certain phenetic resemblance with the orangs by parallelism. The second hypothesis is that there is no continuous allometric trend, but rather discrete and phylogenetically-based differences. Accordingly, a first evolutionary change can be recognised between cercopithecids and apes, and a second between apes and humans. There is no shared size-related pattern, but just variation in subcortical size superimposed on a different neurocranial template. In this case, the phenetic affinity between orangs and gibbons is more interesting because it maybe associated with some plesiomorphic Miocene retention. Such a hypothesis is contrary to the accepted allometry paradigm (e.g. Gould, 1966, 1977), which would suggest that a marked difference in size (*Hylobates* vs. *Pongo*) should be associated with a certain shape adjustment, making isometry improbable. It is worth noting that gibbons have been described as having a more enlarged cerebellum than anthropoids of comparable brain size (McLeod and Zilles, 2003) but not the volumetric development of the frontal cortex displayed by the other Hominoids (Semendeferi, 2002). This information suggests once more that the evolution of apes involved the admixture

of allometric and neomorphic variations, even considering the less encephalised taxa. Clearly, the separation of the allometric and phylogenetic effects is but a useful theoretical approach, and it seems likely that these two components may have act simultaneously, and with reciprocal effects.

The hypotheses described in this analysis should be first tested using larger samples and consequently a more robust statistical power, especially considering that subtle morphological differences can involve large physiological and evolutionary changes. Also, the curvature of the corpus callosum needs to be integrated within this geometrical framework, to better account for the spatial relationship between the subcortical and cortical volumes. Of course, the final aim is the possibility to produce neurofunctional interpretations of such differences. For example, the relative enlargement of the pons described along the allometric vector seems an interesting feature, considering that it carries fibers from the cerebral cortex to the cerebellum. Finally, differences in the spatial organisation and geometric relationships must be carefully taken into account when functions and morphogenesis are investigated in terms of neural wiring and connectivity, which are likely to be major topics in the future of brain research (Van Essen, 1997; Sporns *et al.*, 2002; Schenker *et al.*, 2005).

Conclusion

This analysis was aimed at assessing the allometric component and the major pattern of covariation within the primates subcortical brain morphology. Considering the present sample, size variation account for more than 76% of the shape variation. Nevertheless, the allometric vector is discontinuous when humans are included. The allometric variation could be largely influenced or even mimicked by a phylogenetic component that must be further investigated. Furthermore, each group shows genus-specific traits that must be considered both in terms of structural and functional changes, mostly taking into account the relationship with the cranial counterpart.

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