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Review

What Are the Synergies between Paleoanthropology and Brain Imaging?

Antoine Balzeau [1,2,*] and Jean-François Mangin [3]

[1] PaleoFED Team, UMR 7194, CNRS, Département Homme et Environnement, Muséum National d'Histoire Naturelle, Musée de l'Homme, 17, Place du Trocadéro, 75016 Paris, France
[2] Department of African Zoology, Royal Museum for Central Africa, 3080 Tervuren, Belgium
[3] Baobab Research Unit, CEA, CNRS, Neurospin Department, Université Paris-Saclay, 91191 Gif-sur-Yvette, France; jean-francois.mangin@cea.fr
* Correspondence: abalzeau@mnhn.fr

Abstract: We are interested here in the central organ of our thoughts: the brain. Advances in neuroscience have made it possible to obtain increasing information on the anatomy of this organ, at ever-higher resolutions, with different imaging techniques, on ever-larger samples. At the same time, paleoanthropology has to deal with partial reflections on the shape of the brain, on fragmentary specimens and small samples in an attempt to approach the morphology of the brain of past human species. It undeniably emerges from the perspective we propose here that paleoanthropology has much to gain from interacting more with the field of neuroimaging. Improving our understanding of the morphology of the endocast necessarily involves studying the external surface of the brain and the link it maintains with the internal surface of the skull. The contribution of neuroimaging will allow us to better define the relationship between brain and endocast. Models of intra- and inter-species variability in brain morphology inferred from large neuroimaging databases will help make the most of the rare endocasts of extinct species. We also conclude that exchanges between these two disciplines will also be beneficial to our knowledge of the *Homo sapiens* brain. Documenting the anatomy among other human species and including the variation over time within our own species are approaches that offer us a new perspective through which to appreciate what really characterizes the brain of humanity today.

Keywords: brain-endocast correspondence; paleontology; interdisciplinarity; artificial intelligence

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1. Introduction

The brain is important to us as humans beings. Its anatomy contributes to the biological definition of our species, *Homo sapiens*, but is also important to discuss evolutionary patterns along the last 7 millions years of human prehistory. It is also the center of all our thoughts, the tool we even use to study it. It has long been considered unique in its functioning and in its morphology compared to all other living beings. Technical progress and the multiplication of diverse approaches means that we are learning more about the biology and the functioning of our brain. However, an approach combining neuroimaging and paleoanthropology opens up new perspectives, as it could help us to better understand the characteristics of the *Homo sapiens* brain by integrating its variability over time. Studying related human fossil species closely will also allow us to better characterize what makes our brain unique and the evolutionary development of these specificities. This perspective, in light of our knowledge of past human behavior, will also allow us to better appreciate the mysterious functioning of our brain.

Paleoanthropology seeks to understand the evolution of the human brain by studying the shape of skull fossils [1]. For this reason, the first historical milestone of interest for this paper is phrenology, a nineteenth century endeavor to link personality traits with the morphometry of the bumps of the scalp, building upon the hypothesis that the extent of

these bumps is related to the extent of underlying brain convolutions [2]. Phrenology was fiercely criticized but very influential in its time. It was, however, rapidly considered as a pseudo-science and is not difficult to invalidate with modern imaging methods. For instance, it was shown recently that scalp curvature is not related to brain gyrification [3]. However, very few such studies have been carried out on the links between cortical morphology and the internal interface of the skull, which gives rise to the endocasts of paleoanthropology [4]. This is an important topic addressed in this study. It should be noted that despite the lack of scientific methodology behind the work of phrenologists, they were among the first to hypothesize the idea of "functional specialization" or "segregation", which is central to our current understanding of the brain's organization [5].

Towards the late 19th century, functional specialization was made more concrete thanks to the advent of clinical neuropsychology, based on the observation of the consequences of brain damage. For instance, this strategy was used by Paul Broca to show that different areas of the brain are responsible for articulation and the understanding of speech [6]. Clinical neuropsychology and paleoanthropology share a weakness, however: they have to make do with the samples that nature offers them and extrapolate the rest, even if the sample distribution is not optimal. In this paper, we discuss the possibility of improving the extrapolation performed in paleoanthropology by taking into account the models established in the world of modern neuroimaging regarding the intra-species variability of brain morphology.

At the beginning of the 20th century, the spatial heterogeneity of the microscopic organization of the cortex was highlighted in 2D brain sections observed under the microscope, giving rise to several major maps partitioning the cortex according to the distribution of cell types (cytoarchitectony [7]) or the myelination of cortical layers (myeloarchitectony [8]). Despite their importance for modeling the organization of the human cortex, these mappings are currently still inaccessible in vivo. They have only been achieved in 3D for about ten postmortem brains, each with its own idiosyncrasies [9]. In this sense, this particular field of neuroimaging shares with paleoanthropology the scarcity of samples from which a representative model of the brain of a species and its variability must be inferred.

During the last forty years, functional imaging has revolutionized brain research, allowing major advances in the understanding of brain regionalization and its anatomical characterization. Moreover, it is now possible to access huge databases of *Homo sapiens* brains combining morphological and functional imaging, but also maps of large axonal bundles whose evolution is probably key to the acquisition of certain abilities [10]. The study of the relationships between the inter-individual variability of morphological features and that of fiber bundles or functional areas could probably contribute to the interpretation of the differences observed between the endocasts of ancient species. The largest current database, UKbiobank, which will soon include 100,000 brain images but also an exhaustive map of the genome for each subject [11], and the progress of paleogenomics [12], now make it possible to study the impact of genes inherited from our ancestors on our brain structures [13,14]. There are now also very large databases on brain development [15,16], which will allow studies associating ontogeny and phylogeny. Finally, there is a major interest in the neuroimaging of non-human primates, which should also create synergies between neuroimaging and paleoanthropology [17–19].

Paleoanthropology and the Evolution of the Brain

In prehistoric sciences, the archaeological and paleontological record is scrutinized to explore directly several facets of past human populations. The available biological information obtained on fossil specimens is crucial to explore human variation and evolution but also to try to trace some relationships with past behaviors. Indeed, the anatomy of humans may provide some clues about this last aspect, though it is difficult to interpret [20–23]. The question of the available evidence related to brain anatomy for ancient humans is necessarily the first restriction and a crucial challenge for such studies. The debate about the potential interpretation of anatomical traits in terms of past functions is also important. In

this context, the rich anatomo-functional correlations observed with modern neuroimaging can be inspiring.

There is a huge body of research, spanning over a century, about the anatomical asymmetries of the extant human brain and those traits are still widely studied for their functional, physiological and behavioral implications [24]. However, the comparison with fossil hominins is complex for various reasons. Moreover, the question of the date of appearance of particular anatomical traits, including brain asymmetries, in the hominid lineage is still widely debated [25–29]. Among the aspects considered at this interface, the combination of right frontal/left occipital protrusions, usually associated with the 'torque' pattern, has been studied on brain endocasts (the imprints left by the brain on the internal surface of the skull), from both recent humans and fossil hominins. The larger anterior/frontal and posterior/occipital projection (petalia) is coupled with another component, a larger lateral extension of the more projected hemisphere (lobar asymmetries). Globally, the most common pattern in humans is the combination of right frontal/left occipital protrusions, which is also associated with the well-known Yaklovian "torque" pattern of the human brain. Several other aspects of hominin brain evolution have been also investigated, such as the shape of the third frontal convolution, the development of the parietal lobes in fossil *H. sapiens*, or particular areas with supposed functional implications. The field of paleoneurology is now very active and more and more actors are concerned. Nevertheless, an important constraint on these approaches is that the link between the structure of the brain and the information available on the endocast is not yet fully understood, whereas the possible peculiarities of the different human species must be addressed by this proxy.

In addition to this pronounced interest for the brain anatomy of our predecessors, there has been a new focus on our own particularities. This is why the study of the observed specific anatomical traits and structural asymmetries of the brains of living humans is of major importance as they are considered as an anatomical substrate of functional asymmetries in *H. sapiens*. Indeed, a new field of research is emerging in which these data are considered in comparison with those of great apes and fossil hominins, to understand the structural basis of modern human cognition and to investigate potential interpretations of the brain anatomy of fossil hominins.

In this paper, we contextualize the most recent improvements in neuroanatomy in the context of past studies of the human brain and of the brain endocast of our predecessors. In addition to detailing the current knowledge in "paleoneurology", we explore how up-to-date methodologies from different fields may help in the future to explore in more details the anatomy of the brain of other human species and to improve our deductions about their past behaviors.

2. A Synthesis on Past and Living Brains

Evolving Methodologies in the Study of Human Brain Morphology

The rise of computational neuroanatomy over the past 30 years has had a tremendous impact on the study of brain morphology. Previous methods were often cumbersome to implement, due to the manual delineation of structures they involved, not very reproducible, and often biased, due to a two-dimensional approach to quantification. For example, a gyrification index calculated in 2D was biased by the orientation of the slices used or by the large thickness of these slices at the early stages of MRI. Furthermore, as in paleoanthropology, each study led to the design of a specific ad hoc methodology, leading to huge difficulties when trying to synthesize research results, as can be observed, for instance, in the study of the asymmetry of the planum temporale [30].

The substantial requirements of neuroimaging research have led to the design of robust and automatic methodologies for brain morphology analysis. In spite of an abundance of proposed methodologies, Darwinian-style pressure has selected a small number of software packages (SPM, Freesurfer, FSL) that are sufficiently simple to be used by more than a thousand research teams using MRI in one way or another. This de facto standardization

of the analysis of brain anatomy has largely contributed to the success of the field and is linked to the emergence of a paradigm a la Kuhn that is difficult to escape without loss of credibility. The software is based on a powerful idea: "let's align brains with a template brain before comparing them".

Voxel-Based-Morphometry (SPM, FSL), born in the 1990s, encompasses methods that practice this alignment in 3D ("non-linear warping") [31]. They include approaches that work point-by-point but also ROI-by-ROI, with the ROI also being defined in the template space. VBM is a versatile technique that can be used for the cortex and for subcortical structures. The feature to be compared across subjects is a kind of grey or white matter density supposed to be a proxy for local tissue volume. A specific branch is dedicated to asymmetry studies, which usually involve the use of a specific symmetric template. The tools used in this area have generated much discussion [32,33]. The main issue lies in the fact that there is no clear ideal alignment across brains with varying morphologies (Figure 1), particularly with respect to the cortical folding that is supposed to be partially printed in endocasts [34].

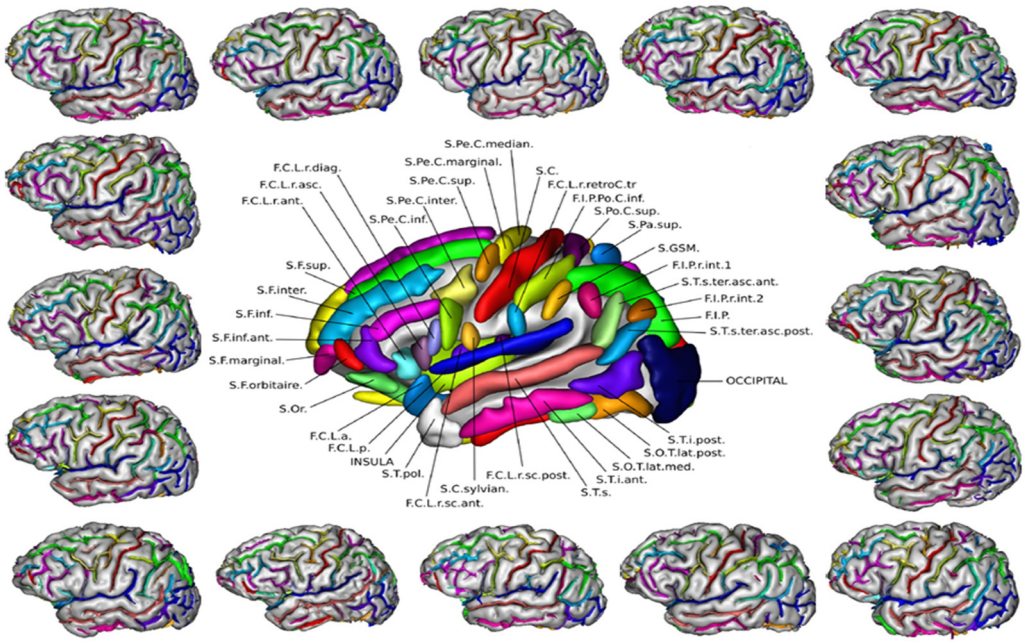

Figure 1. A nomenclature of cortical sulci applied to 16 different brains to illustrate the variability of the folding pattern.

The template used is usually an average brain in order to overcome the bias induced by the idiosyncrasies of specific brains. At the onset of VBM, this template was fuzzy because of the poor alignment of the folding patterns across the brains to be averaged; however, thanks to methodological advances, average brains are now very similar to actual brains but with regularized folding patterns (see Figure 2). The choice of the template, however, still raises questions: should it be adapted to the study population, should it be blurred to reflect variability, or should it resemble a real brain? Should it be symmetrical or asymmetrical? Should it be age-specific?

Surprisingly, geometric morphometrics, which is the mainstream strategy in paleoanthropology [35] has not been successful in neuroimaging. One could look for a technical explanation but this lack of interest is probably mainly linked to sociological phenomena. The rare use of geometric morphometrics in neuroimaging can be explained by the "winner takes all" phenomenon. The usual computational neuroanatomy methods are based on the concept of spatial normalization forged for functional imaging, the modality at the origin of the neuroimaging boom. There was probably no room for a radically different vision based on landmarks, all the more given that landmarks are difficult to define unambiguously in

the human brain. The fate of geometric morphometrics in the world of neuroimaging is that of all methods that have sought to deviate from the paradigm of their field.

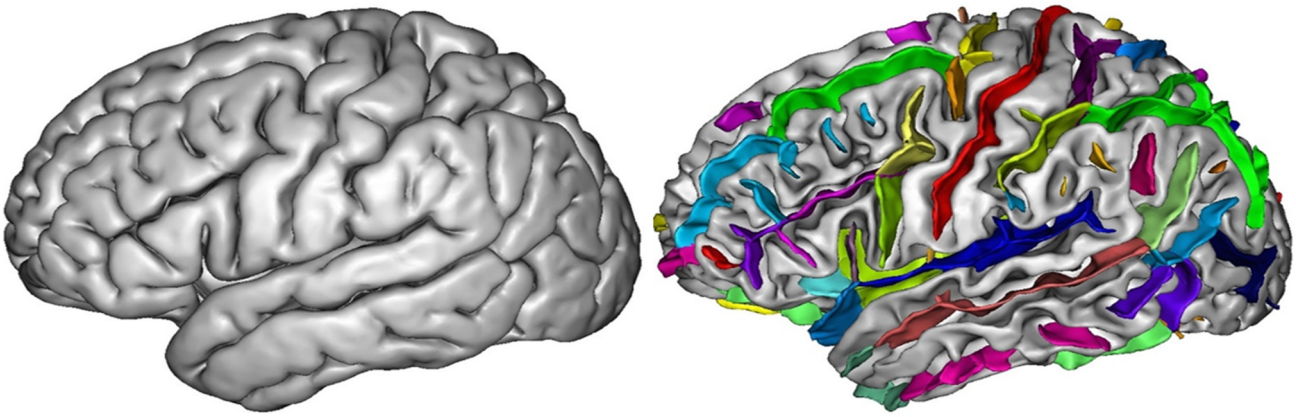

Figure 2. The ICBM 152 realistic template of the MNI (McGill University, Montreal), resulting from the averaging of 152 different brains, and its regularized sulci, with the nomenclature of Figure 1.

Surface-based morphometry (Freesurfer, CIVET) is very similar to VBM in spirit, but is dedicated to the cortical surface, which is inflated and mapped to a sphere before being aligned across subjects [36]. It was designed to simplify the alignment of large sulci and to quantify parameters with real anatomical meaning: the thickness of the cortex or the surface area of a convolution. Because this approach is more computationally complex, there are far fewer tools available than for VBM. It would be interesting to compare this surface-based strategy with methods that seek to align endocasts, i.e., surfaces with the trace of certain furrows. The major difference is that the neuroimaging approach unfolds the cortex, whereas the endocast approach can only manipulate the external part of the cortical surface. Morphometry of the shape of the cortical sulci (length, depth, etc.) can also be performed using brainVISA, whose output is illustrated in Figures 1 and 2 [37].

3. Virtual Anthropology and Paleoneurology

The use of imaging methodologies in paleoanthropological studies appeared to be of great benefit as early as the mid-1980s [38,39]. Among their first applications, the determination of endocranial volume aroused wide interest. Indeed, the resolution of the tomographic data was of the order of a millimeter, thus complicating the detailed study of fine character, but being well suited to overall quantifications of large structures. Fortunately, the technique has largely progressed, as has its application to the human fossil record. The term "virtual anthropology" has been proposed to name this emerging field [40]. Imaging facilities are now considered one of the classic techniques in the toolbox of paleoanthropologists (Figure 3). However, although they are very important, providing important possibilities, they also feature limitations.

Imaging data allows more robust studies. Fossils, of course, can only be studied by methodologies based on X-rays. MRI approaches are not applicable to our dry specimens, which are composed of highly mineralized and fossilized bones. It has recently been demonstrated that X-ray methodologies, when used at adapted settings for the classic study of fossils, have no influence on the preservation of the structure of the fossil and that they do not cause damage to the preservation of ancient DNA [41]. However, they have some effect on ESR dating [42]. These aspects have to be considered. Imaging methodologies play a crucial role in the preservation of our heritage. Moreover, thanks to this approach, the samples to be analyzed in the context of the study of human evolution may be much larger. From a methodological point of view, it is much easier to improve and test any protocol and methodologies may be more easily repeated. These aspects are particularly important as the original fossils are housed all over the (ancient) world. Nevertheless,

progress is still expected in the way we share the imaging datasets. Among technical limitations are those related to the size of the datasets and the necessary informatics environment to manage the analyses. The resolution is now potentially very high, allowing very precise analyses. Fortunately, computers and software have also progressed. In addition, paleoanthropologists could rely on the massive computational infrastructures that are currently emerging to support neuroscience research. For example, the virtual models of endocasts scattered all over the world could be gathered on Ebrains (https://ebrains.eu/, accessed on 11 October 2021), the platform resulting from the European flagship Human Brain Project, and give rise to synergies with other communities.

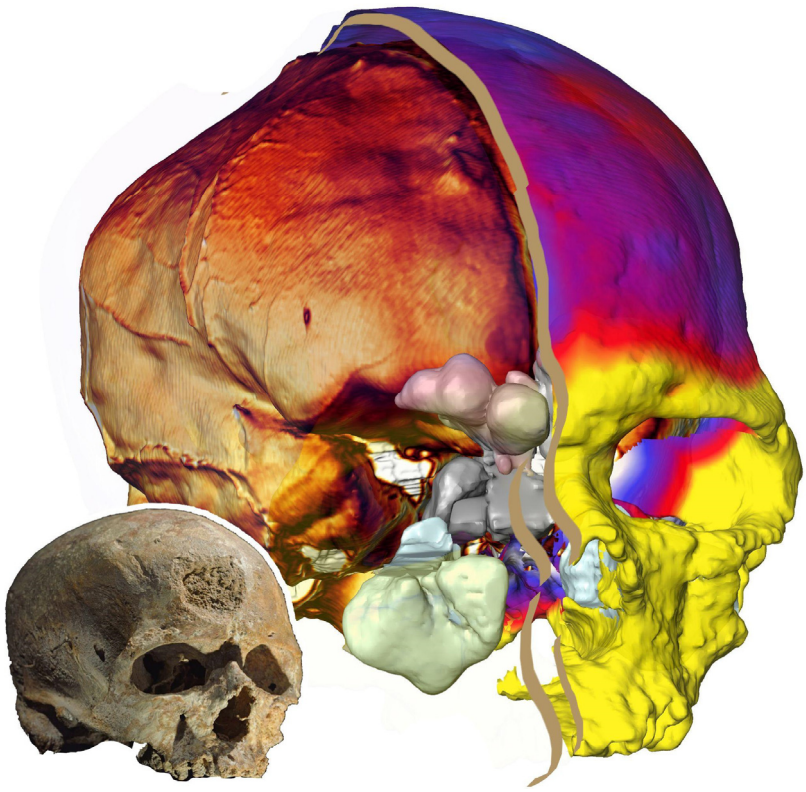

Figure 3. The original skull of Cro Magnon 1: 3D reconstruction of the endocranial cast (in orange) of the paranasal pneumatization and of the right half of the skull, on which are shown variations in bone thickness (thinner areas are in white and blue, intermediate areas in purple, and thicker areas are in red and yellow).

In fact, the main concern in "virtual anthropology" is probably an unexpected aspect. Virtual models may be reconstructed with mirror images, from templates obtained on comparative samples, or by estimation of the missing areas. As such, the new "virtual" fossils are not real reflections of the original specimens. It is, of course, particularly important to remove distortions related to post-mortem alterations, but it is crucial to keep a detailed record of all the modifications made to a model. For example, none of the *H. neanderthalensis* specimens analysed in a study of the evolution of the brain [43] preserve this anatomical area. The study is by itself interesting and important in a comparative perspective but raises some questions about the interpretation of the results that could be obtained beyond this particular context. The extreme and tautological case is when a reconstructed model is used as an essential milestone in a systematic approach.

3.1. Does the Endocast Reflects the Brain?

Paleoneurology is a fascinating topic, dealing with anatomical and biological aspects of past humans and, in addition, potential behavioral implications. The field is, of course, highly debated, for multiple reasons.

The main reason relates to the complex nature of the material that researchers analyze. Indeed, the soft tissues that constitute the brain never fossilize. Scientists only have to deal with the shallow imprints of the convolutions that the brain forms on the internal surface of the skull. This incomplete reflection of the brain is named the (brain) endocast. The brain presses on and leaves marks on the inner surface of the skull throughout a person's life. This was true for the humans who lived a few million years ago, but also for all of us. The phenomenon is particularly intense during the period of accelerated growth of the brain, and therefore of the cranial box which surrounds it, during the first years of life. The whole process is intertwined, so that the shape of the adult skull is reminiscent of the moment of peak brain development. The behavior of the skull can be described as that of a morphological black box, retaining information that later makes it possible to reconstitute its original contents. Therefore, when a fossil skull is discovered, its inner surface is molded, either physically or virtually, using imaging methods, to reconstruct its endocast. This model represents the preserved imprints of the external surface of the brain. However, the correspondence between these limited records of convolutional patterns and details of the surface of the brain remains to be demonstrated in modern humans. A few pioneer studies have considered this problem [4,44]. Moreover, it is necessary to develop new tools for the automatic and reliable determination of the endocranial sulci [45].

In the context of the PaleoBRAIN project, financed by the ANR, we are conducting a direct investigation of the correlation between the shape of the brain and that of the intracranial cast within a sample of modern humans using MRI (for Magnetic Resonance Imaging) acquisitions, including some with a specific sequence that allows the characterization of bone tissues. The comparison of morphometric data and anatomical traits between the brain and the endocast will be performed using state-of-the-art quantification methodologies. But our large dataset could probably also be used to refine the methodology dedicated to the sulcus detection in the endocast. Current methodologies use differential geometry to detect sulci as ravine or crest lines [4,44]. A key component in the design of such robust detectors is the amount of local smoothing performed before detection, which is usually tuned to the scale of the features to be detected. The T1-weighted MRI of our dataset can be used to define the ground truth using the sulci detected by the Brain VISA software. Subsequently, the optimal smoothing can be estimated using an inverse problem framework. Thanks to the large dataset, we can probably afford to include the estimation of regularized spatial variations of the optimal amount of smoothing, which may help to achieve a more consistent sulcus detection throughout the endocast. This could help to overcome some of the weaknesses observed in the superior part of the brain [4]. Once we have acquired a better understanding of the reliability of the endocast-based definition of the folding pattern within our own species, we will be able to use this model to address the shape of the brain/endocast in well-preserved fossil hominin specimens.

This project will also contribute to answering a key question about the evolution of the human brain. In many studies, the endocast is analyzed with distances characterized at maximal points of extension, maximal length or maximal width, or that correspond to intracranial points, such as endobregma or endolambda, for example [27,46], or with 3D methodologies that consider the surface as a whole [47,48]. These methodological approaches are justified by the complex nature of the material. Indeed, gyri and sulci are difficult to identify on the endocast (Figure 4). In this context, there is little information available about variations in the global size of the different lobes and their relationship with each other between hominin species.

In a previous study [28], we demonstrated clear differences in brain organization when considering the relative contribution of the different lobes to the surface of the complete endocast. Asian *H. erectus* specimens show a significantly smaller relative size of the parietal and temporal lobes than all other samples of the genus Homo. This field of research could benefit from the recent revival of interest in the study of the laws of allometry that govern the relative variations of the various cerebral structures, linked to the large databases of modern brain images [49].

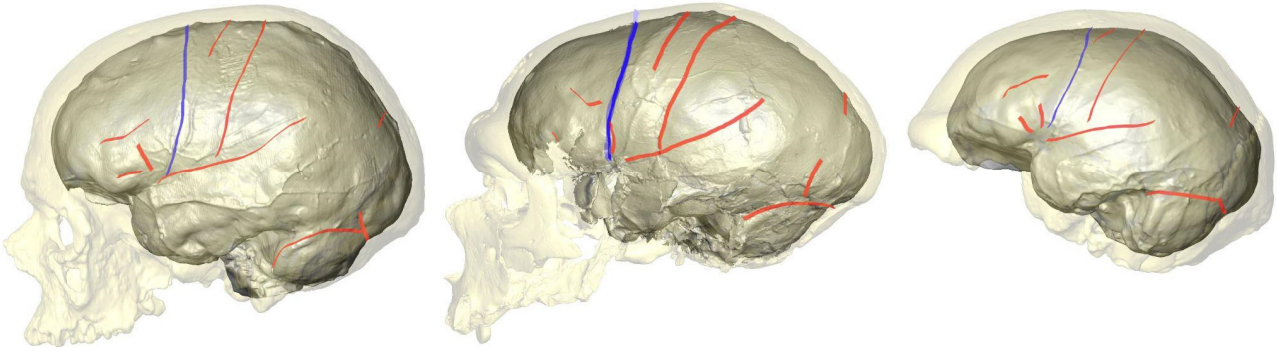

Figure 4. Comparison between the position of the main sulci of the endocranial surface (in red) and the shape and position of the skull, including the course of the coronal suture (in blue) in Cro-Magnon 1, an Upper Paleolithic *Homo sapiens*; La Chapelle-aux-Saints 1, an *Homo neanderthalensis*; and Sambungmacan 3, an *Homo erectus*.

Moreover, *H. neanderthalensis* and fossil *H. sapiens*, which have the largest endocranial volume of all hominins, show different brain structures (Figure 4). These results illustrate that differences existed in the structure of the brain in addition to the well-known variation in size during human evolution. An important contribution to this topic will be to improve our ability to determine the location of the sulci and gyri on fossil hominin endocasts. To do so, a better knowledge of the anatomy and characteristics of hominids is necessary [50,51], together with a better knowledge of the brain–endocast relationship in living humans. Finally, it is fundamental to obtain a more generalized and simplified access to high-resolution endocranial data for fossil specimens. Indeed, this material is so complex that multiple appreciation by the few researchers dealing with paleoneurological information would certainly enhance our capacity for anatomical determination. It would also certainly help to minimize potential conflicting interpretations, which are very frequent in this small field of research.

3.2. What Can Be Deduced about a Species' Folding Pattern from a Few Samples?

The very high intra-species variability of the cortical folding of Homo sapiens, illustrated by Figure 1, is a major difficulty for modern brain mapping. It should also warn us about the risk of over-interpretation inherent in the small number of samples available in paleoneurology. The idiosyncrasies of a specific brain are not necessarily representative of the folding pattern of its species. The amount of intra-species variability is species dependent. In great apes, it is less than in humans but still significant, especially in the frontal lobe. In baboons or macaques, it is almost non-existent. In species with a variable folding pattern, the match between the folds of an individual and its nomenclature can be difficult to establish and leads to confusion, especially when only an endocast is available [1,52]. In modern humans, the large sulci described in anatomical books are often split into pieces and reorganized into unusual folding patterns that are difficult to decipher (see Figure 5) [53]. Notably, these phenomena occur in the general population without developmental pathologies.

The mysteries hidden behind the variability of cortical folding have led to the emergence of a multidisciplinary community that aims to understand these variations and their meaning. It associates biologists, who focus on the developmental phenomena that are at the origin of cortical folding (spatially heterogeneous neurogenesis, spatially heterogeneous chronology of synaptic development, etc.) [54], and physicists, who model the mechanical phenomena that result from these growth heterogeneities [55]. This new community also includes anatomists, who study the links between folding and the organization of cortical areas and fiber bundles [56], and computer scientists, who geometrically model the variability observed in the general population, and the specificities of developmental pathologies [34,57]. In our opinion, the progress made by this community could contribute to a better exploitation of the scarce data observed in the endocasts of the folding of extinct species. A better understanding of the rules driving cortical folding dynamics would

provide insight into the architectural changes at the origin of the changes observed across species in endocasts. Endocasts are used as a proxy of the folding pattern, but the folding pattern is only a proxy of architecture, which is even more difficult to reverse-engineer. Current efforts for cracking the code behind folding patterns could contribute, for instance, to the discussion around the third frontal convolution when comparing sapiens, great apes, and extinct hominids. Joint modelling of folding variability and of functional variability will help to understand which features of the folding pattern can be used as landmarks of key cytoarchitectonic areas (see Figure 6) [58].

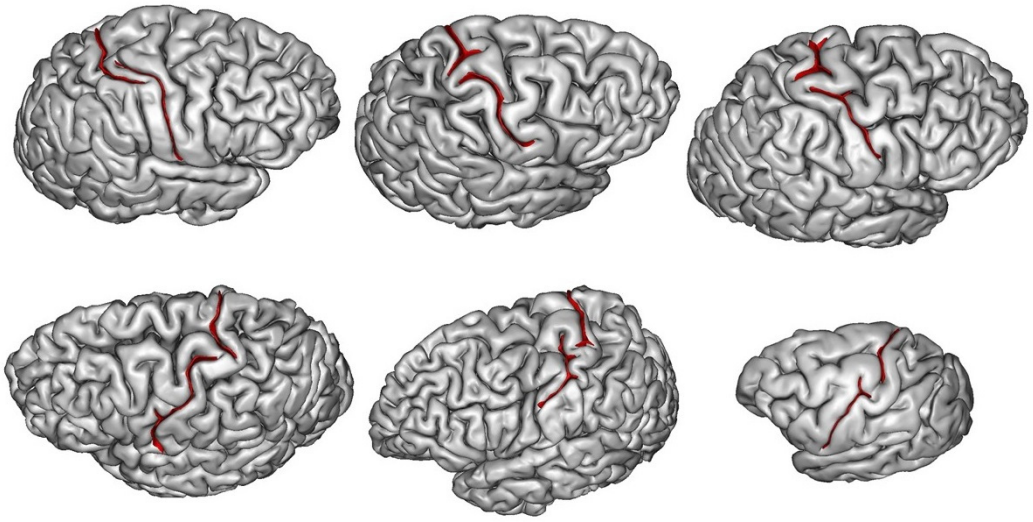

Figure 5. The hemispheres of five *Homo sapiens* and one chimp, with interruption of the central sulcus, which hosts sensorimotor areas (0.5% of occurrence). This kind of interruption is frequent in associative areas and leads to folding configurations that are difficult to decipher, which can be observed here in the frontal lobes.

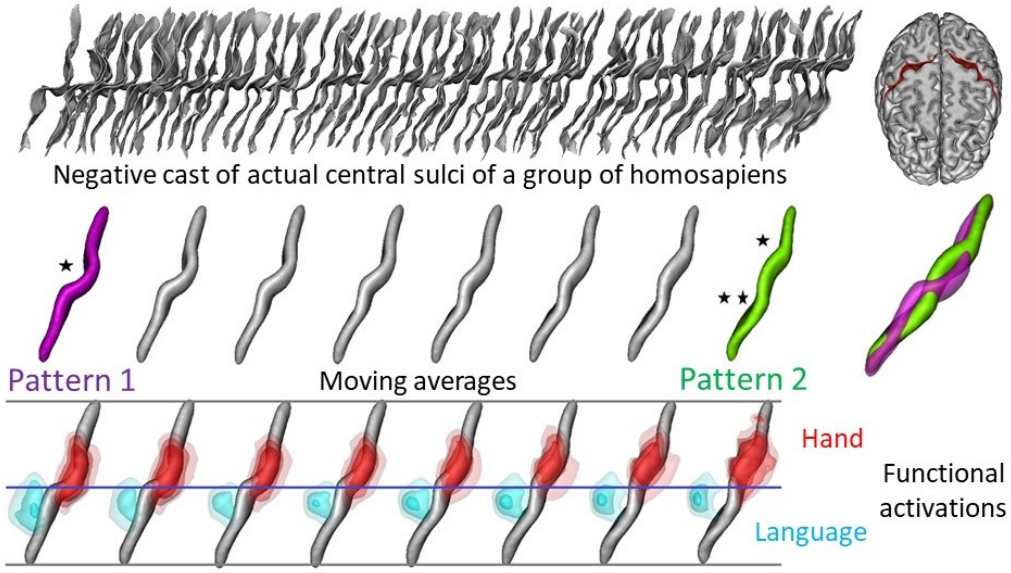

Figure 6. Machine learning can be used to model the variability of folding patterns. Here, the variability of the shape of the central sulcus is projected into a one-dimensional manifold representing the transition between a single knob and a double knob pattern. Functional mapping performed along this manifold shows that the two different folding patterns correspond to different localizations of functional areas along the central sulcus.

3.3. How Are Brain Asymmetries Quantified in the Hominin Fossil Record?

The number of brain structural asymmetries observable on endocranial casts and, consequently, in fossil specimens is limited due to several factors, which are of course related to the specificity of our material, which concerns only the external surface of the brain. By chance, features on the brain and endocast for which bilateral variation studies are possible are among the most consistent features available for cross-taxa studies on large samples. One important limiting point needs to be considered. Indeed, the difficulty in defining structural parameters and in establishing left-right homologies makes studies of brain asymmetries complex. Moreover, gross anatomical asymmetries of selected pairs of points may reflect combined asymmetries in brain subregions. The quantification of surface morphology, distance, or volume of discrete anatomical areas may not fully express real bilateral variation if their pattern of asymmetry is defined in reference to global anatomical brain areas. For example, previous works have proposed the quantification of the volume or regional surface areas of endocasts in hominin fossils [28,59,60].

Another limitation is that the methodologies employed in most previous studies of cerebral or endocranial asymmetries involved qualitative assessment or a simple index of bilateral traits and did not analyze departures from symmetry and different patterns of asymmetry (i.e., fluctuating and directional asymmetry, antisymmetry) in efficient and adapted ways [61]. It has indeed been shown that the brains of extant hominids demonstrated high levels of fluctuating asymmetry, allowing pronounced developmental plasticity and therefore making brains highly evolvable [62]. The quantification and analysis of the morphology—including the asymmetries—of the endocranial cavity need further development. Currently, the most advanced computational tools used in analysis of bilateral shape asymmetries rely on the standard framework of landmark-based morphometrics [63,64]. In this context, in addition to homologous landmarks between shapes for population studies, one must define homologous landmarks between the two sides of each shape under study. Analyses can then be carried out by using slight modifications of the linear distance-based [65] or superimposition [66–69] methods. However, we identified methodological problems underlying the theory and its application to the assessment of bilateral asymmetries [48,70,71]. Moreover, a limited set of landmarks is likely to be inadequate to capture the shape of intricate anatomical structures, or that of structures with few obvious salient features, such as brain endocasts. New methodological improvements are therefore necessary to better characterize and quantify bilateral asymmetries [72,73]. A specific methodology has been developed and tested on the endocast of the Cro-Magnon 1 fossil [28]. This approach is promising as it allows for an independent characterization of the asymmetries without referring to the potential global asymmetry of the object that is analyzed. New approaches based on machine learning could also be a source of inspiration. They allow us, for example, to establish the asymmetry of folding patterns without requiring the definition of homologous landmarks across subjects and hemispheres. For instance, the double-knob configuration of the central sulcus, depicted in Figure 6, is more frequent in the left hemisphere [74]. These new approaches could contribute to the old question of the language-related asymmetry of the third frontal convolution, which is difficult to tackle because of the large intraspecies variability of the related folding patterns [75].

3.4. The Complex Definition of Brain Features and of Their Application to the Fossil Record

A general problem concerns the lack of homogeneity in the definition of brain asymmetries and of the methods used to quantify them. For example, one of the most studied brain asymmetries on brain endocasts concern the petalias. LeMay [76,77] initially considered the antero-posterior projection of the frontal and occipital lobes, respectively. By contrast, later studies generalized the term 'petalias' to a wide range of anatomical traits. Some studies indeed referred to bilateral differences in the lateral extension of the posterior area of the frontal lobes [78], to other anatomical areas of the brain, and even to volumetric variations between hemispheres [79–83]. It is therefore difficult to compare data obtained on petalias if studies do not consider the same brain features. Nevertheless, it was largely accepted

that this pattern of asymmetries appeared with early Homo [27,78,84] and is more common in right-handed individuals [77,78,85–89]. Based on an original methodology applied to the largest samples ever used, we demonstrated a shared specific pattern of protrusions of the frontal and occipital across all hominids, including extant African great apes, modern humans, and hominin fossils [21,73]. These asymmetries are a topic of debate in non-human primate brain studies [76,79,80,90–92] and paleoanthropology [25,26,78,84,93–95] because of their relationship with handedness and other specific aspects of human cognition. Similar results were obtained recently by an independent team [48]. *H. sapiens* appear to have more asymmetrical petalias than other extant great apes, but a shared pattern is observed, suggesting that a globally asymmetric brain is the ancestral condition. A recent study questioned this observation [96]. However, this is a good example of differences in the definition of the anatomical traits that are analyzed. These authors measured the bilateral variation in lateral extension of slices of the brain. This trait is not directly comparable to our analyses of the 3D position of the occipital poles [29] or to the 3D displacement between the left and right corresponding anatomical area. Another good illustration of the problem is Broca's area, whose extension is defined differently according to authors [97]. This functional area is impossible to characterise on brain endocasts. However, we conducted a comparative study on the size, shape, and position of the third frontal convolution in great apes, *H. sapiens*, and hominin fossils [29]. The neuroanatomical asymmetries as quantified in our work show a pattern that is different from what was previously accepted based on qualitative data. Our main finding was a shared pattern of asymmetry in Broca's area in all hominins and Pan paniscus, as well as an increase in the size of this area during human evolution. We also identified that Pan troglodytes and Pan paniscus have differences in their asymmetry patterns in the third frontal convolution. This topic is of great interest for future research. More generally, brain and endocranial studies have to rely on a clear definition of the anatomical features that are analyzed and an effort to use similar protocols will certainly enhance the reproducibility of our studies.

3.5. How to Grow a Hominin Brain?

The knowledge of ontogenetic patterns in fossil human species is scarce [98–101] and, to date, no information is available about the evolution of brain lateralization during growth and development. Both *H. neanderthalensis* and *H. sapiens* have enlarged brains compared with other hominins, but their respective organizations and morphologies are different, each of the two species having "grown" large brains through specific evolutionary processes. Much remains unknown about what these processes are, and how they are rooted in the hominin evolutionary tree. In the case of *H. neanderthalensis*, although some changes in gross cerebral morphology during childhood are documented, researchers have presented conflicting results concerning how their endocranial growth patterns relate to those of other primates. While the post-natal Neandertal ontogenetic trajectory is deemed closer to that of chimpanzees than to that of *H. sapiens* by some researchers, emphasizing a unique globularization phase in *H. sapiens* [101], others find that the mode of cerebral growth is largely similar in *H. neanderthalensis* and *H. sapiens*, emphasizing instead the characteristic morphologies of each species at birth, and refuting the idea of the derived nature of the post-natal cerebral growth trajectory in *H. sapiens* [102]. Nevertheless, these studies only consider the global shape of the internal surface of the skull. Additionally, available data addressing cerebral growth do not provide enough details, so that much of "how" the Neandertal brain grows remains unknown (e.g., do the contributions of the different lobes to total brain volume remain stable throughout infancy and childhood?).

We previously demonstrated that the two species have distinct brain organizations [103], but this important biological aspect has not yet been considered in the study of brain growth in *H. neanderthalensis*. The emergence of large databases on the brain development of sapiens, and to a lesser extent of extant non-human primates [104], could contribute to these debates.

3.6. Brain Endocast and Function

The question of the relationship between brain shape and function in hominins has been explored in previous studies [105]. According to their authors, they "show that Neanderthals had significantly larger visual systems than contemporary anatomically modern humans (indexed by orbital volume) and that when this, along with their greater body mass, is taken into account, Neanderthals have significantly smaller adjusted endocranial capacities than contemporary anatomically modern humans." For the authors, these results had implications for interpreting variations in brain organization in terms of social cognition. Indeed, larger visual systems would have implied smaller adjacent anatomical areas, including the parietal areas related to social skills. Their final conclusion was that the extinction of *H. neanderthalensis* was due to weaker social cognition compared to modern humans. This study suffered from methodological limitations. The main problem was that they were improperly interpreting data mostly derived from the research of one of the authors of this paper [103]. These authors considered that our data for the external extension of the occipital lobe were directly related to the size of the visual cortex. However, such a direct interpretation was not demonstrated. Moreover, they did not measured any anatomical areas on the endocasts of *H. neanderthalensis* or of contemporary *H. sapiens*. All those approximations make any interpretation in terms of behaviors impossible.

This example should not prevent us from analyzing morphological variation among hominins species and exploring functional and behavioral implications. However, this needs to be undertaken on a solid anatomical framework, particularly in the context of interspecies comparisons, and with more caution for the evaluation of the potential link between brain anatomy and suspected function.

4. Perspectives for Future Studies of the Evolution of the Human Brain

4.1. The Future of Neuroimaging

The world of neuroimaging is in perpetual development, constantly fed by technological advances and new concepts aimed at deciphering the organization of the human brain. However, large parts of the brain's functioning remain misunderstood. Despite the wealth of knowledge accumulated on its development, the incredible efficiency of its learning processes remains a mystery; it is probably very different from deep learning. Unlocking the secrets of its evolution still seems to be an unattainable goal, given the limited information available to paleoanthropologists. However, the possibility of almost unlimited advances in technology probably holds surprises for us. The last decade has given rise to extraordinary investments in this respect. The American "Brain Initiative" has thus generated science-fiction-like technologies for the "reverse engineering" of rodent brains: for example, the possibility of simultaneously recording the activity of a million neurons, or of mapping the synaptic connectivity between a large number of neurons. The possibilities for the non-invasive exploration of the human brain are much more limited, but the rise of brain imaging raises many hopes. Large shared research infrastructures dedicated to the exploration of the brain are being created, in the spirit of what happened in physics in the middle of the last century. These infrastructures will house outstanding scientific instruments, unique in terms of sensitivity or resolution, built to open up new "discovery spaces". Moreover, the most important discoveries made with these instruments are often those that had not been foreseen in the initial scientific dossier. For example, the French CEA has decided to exploit the expertise of its physicists, who were behind the magnets at CERN in Geneva, to design a new generation of MRI. The 11.7 Tesla magnet located at Neurospin in the southern suburbs of Paris should, for example, make it possible to zoom in vivo to study the functioning of the brain at the true scale of the organization of its cortex into cortical layers and columns. These deep phenotyping initiatives are complemented by major international phenotyping initiatives to understand the genetic basis of the human brain, which will probably provide important insight into the evolutionary events at the origin of our brains. Molecular analysis of humans, archaic hominins, and non-human primates has allowed the identification of chromosomal regions, showing

evolutionary changes at different points of our phylogenetic history, which may be related to the evolution of the endocast-based clues about the cortical folding patterns [106]. The coming decades may see the emergence of a better understanding of the evolution of the genetic building plan behind the human brains [107].

4.2. Endocast Side

Variation is an important concept in paleoanthropology. Paleoneurological approaches try to identify as precisely as possible intraspecific variations, as well as diagnostic features, between species. In turn, the initial mainstream paradigm in brain mapping involved canceling out morphological variability to allow comparative analysis of the functional maps across subjects and experiments. Neuroimaging, however, has widened its scope during the last decades to the modeling of intersubject variability, in order to tackle the discovery of biomarkers of pathology or the stratification of populations of patients. Furthermore, neuroimaging is now widely used to understand brain development and to compare primate species. It is time to consider cross-fertilization with paleoneurology, which has evolved in a niche built upon geometric morphometrics, which has prevented synergies. Broadening our knowledge of brain variability in our species by including a long time dimension will be of great help in defining the brain anatomy of *H. sapiens*. It also opens up perspectives for understanding how our brain works.

One original and exciting perspective will be to reconstruct a fossil hominin brain. A recent study [108] was the first to attempt the reconstruction of a *H. neanderthalensis* brain by deforming a population average brain for modern humans into the shape of the endocast of a reconstituted Neandertal. However, this approach does not consider the differences in brain structure between these species, such as those that we documented [103]. The different approaches detailed here, aiming at the collection of better information on the brain/endocast correspondence in living humans, developing new tools of automatic determination of the sulci on the endocasts, and enlarging our knowledge of fossil hominin variation thanks to a better availability of high-quality endocranial surfaces, will make it possible to obtain more satisfactory results.

Modern Artificial Intelligence could even play a role in the cross-fertilization between paleoneurology and neuroimaging. Provided that dedicated MRI sequences can deliver consistent proxies of endocasts on a large scale, deep learning could be trained to transform endocasts into standard representations of the cortical surface used in the mainstream neuroimaging field. Transfer learning could be tested on extant non-human primates and applied to extinct species in case of success.

5. Conclusions

It undeniably emerges from this perspective that paleoanthropology has much to gain from interacting more with the field of neuroimaging. Improving our understanding of the morphology of endocasts necessarily involves studying the external surface of the brain and the link it maintains with the internal surface of the skull. A fundamental perspective is to describe more fossils among more species in order to better understand the evolution of the human brain. Our discipline must also work towards better data accessibility. This will reinforce the quality of the comparisons and the repeatability of the work on the complex material that is the endocast. This will also contribute to a better definition of the traits that are analyzed. This aspect will be greatly improved by the contribution of neuroimaging, which will allow us to better define the relationship between brain and endocast. Finally, the exchanges between these two disciplines will also be beneficial to our knowledge of the *H. sapiens* brain. Documenting the anatomies of other human species and including the variation over time within our own species are approaches that offer us a new perspective through which to appreciate what really characterizes the brain of humanity today.

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