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The human brain: rewired and running hot

Todd M. Preuss
Division of Neuropathology and Neurodegenerative Diseases and Center for Translational Social Neuroscience, Yerkes National Primate Research Center, Emory University, Atlanta, Georgia; Department of Pathology, Emory University School of Medicine, Atlanta, Georgia

Abstract

The past two decades have witnessed tremendous advances in noninvasive and postmortem neuroscientific techniques, advances that have made it possible, for the first time, to compare in detail the organization of the human brain to that of other primates. Studies comparing humans to chimpanzees and other great apes reveal that human brain evolution was not merely a matter of enlargement, but involved changes at all levels of organization that have been examined. These include the cellular and laminar organization of cortical areas; the higher-order organization of the cortex, as reflected in the expansion of association cortex (in absolute terms, as well as relative to primary areas); the distribution of long-distance cortical connections; and hemispheric asymmetry. Additionally, genetic differences between humans and other primates have proven to be more extensive than previously thought, raising the possibility that human brain evolution involved significant modifications of neurophysiology and cerebral energy metabolism.

Keywords

hominid; evolution; neuroimaging; genomics; cerebral metabolism

Introduction

Until quite recently, it has been impossible for neuroscientists to address in much detail one of the most fundamental questions in the life sciences—how do human brains differ from those of other animals? All we've known for sure is that human brains are freakishly large for a mammal of our body size. In most mammals, the portion of the skull devoted to eating is bigger than the part that houses the equipment for thinking, whereas the human brain box dwarfs the machinery of mastication. But what's in the box? What's in there that gives us the ability to think and act in specifically human-like ways? The allure of neuroscience surely depends on the conviction that there's something unusual about the human brain, yet neuroscientists have been unable to specify how the cells and the systems of connections that make up the brain were modified in human evolution.

The main reason for this failure is that neuroscientists have lacked the technical means to explore the human brain in anything like the detail with which they are able to study nonhuman species. For nonhuman species, we have had a range of powerful investigative techniques available to us, such as injecting chemicals into brain tissue to trace neuronal connections, a procedure considered unethical in humans. Such invasive techniques, it is important to note, are also out of bounds for studying rare and endangered species, such as chimpanzees, the animals most closely related to humans. Without the ability to compare

Correspondence: Todd M. Preuss, Ph.D. Yerkes National Primate Research Center, Emory University, 954 Gatewood Road, Atlanta, GA 30329 USA, tpreuss@emory.edu.

humans to chimpanzees and other great apes, we can say little about what's distinctively human about human brains.

Over the past 20 years, however, and particularly over the last decade, the means available for studying human brains, and for directly comparing humans to chimpanzees and other primates, have improved enormously. Of course, the continual refinement of noninvasive imaging techniques, and their application to nonhuman primates as well as to humans, has been very important. Functional magnetic resonance imaging (MRI) and positron emission tomography (PET) are the imaging techniques that have garnered the most attention, but perhaps the most important development in this area for students of human brain evolution is the introduction of diffusion-tensor imaging (DTI) and related techniques, which can be used to track white-matter pathways between gray-matter regions noninvasively (for a recent review, see Ref. [1]). Compared to conventional tract-tracing techniques, which involve making injections of chemical tracers into the brains of experimental animals, DTI has certain limitations: its resolution is relatively coarse, because under most circumstances it cannot track fibers into the gray matter, and it cannot distinguish between anterograde and retrograde connections. Yet DTI has made it possible to study the major fiber systems in human brains comprehensively and also to compare human fiber systems to those of other primates. Far less eye-catching, but nonetheless enormously important, has been the steadily increasing power of histological techniques for exploring the structure of tissue acquired postmortem, reflecting the proliferation of antibodies and other ligands available for probing the distribution of molecules in the brain. Older histological and histochemical techniques remain very useful, however. The value of all these techniques, and the value of the postmortem tissue to which they can be applied, has been multiplied by the introduction of antifreeze storage solutions that preserve tissue for years in a state suitable for immunohistochemistry and *in situ* hybridization, avoiding the degrading effects of overfixation [2]. A third source of new information about human brain evolution comes from genomics and comparative molecular biology, including techniques for identifying genes that underwent positive selection or expression changes in human evolution.

The upshot of these technical innovations is that the subject of human brain evolution, long something of a scientific backwater, has become a matter of keen interest, as reflected by a spate of recent books (e.g., Refs. 3–7). Different authors will, of course, have different takes on this subject. Here, I cast my account of current results in the light of hypotheses and expectations about human brain specializations that were posited before the advent of the new techniques just discussed.

Issues and evidence

Was encephalization accompanied by the expansion of association cortex?

There is no question that human brains are much, much larger than would be expected for a primate of our body size, and that most of this difference reflects an enlargement of the neocortex. Classically, it has been supposed that this enlargement resulted from a selective expansion of the higher-order association cortex of the frontal, temporal, and parietal lobes, relative to the primary sensory and motor areas (see, e.g., Refs. 8–11). With the application of structural neuroimaging techniques to the study of human brain evolution, this conclusion has been called into question [12]. The essence of the counterclaim is that association cortex —and prefrontal cortex, in particular—is no larger in humans than would be expected for an ape with a human-sized brain. More specifically, the claim is that if one were to plot the size of prefrontal cortex as a function of the size of the rest of the brain for anthropoid primates, human prefrontal cortex would fall within the expected size range. One can take issue with the methods employed by those who have adopted this view, for they have not measured prefrontal cortex size directly (something that is currently not possible to do using imaging

techniques), and have instead measured a morphology proxy for prefrontal cortex—the size of the entire frontal lobe or the size of the frontal cortex anterior to the precentral gyrus. Moreover, other authorities have affirmed the traditional view of association cortex expansion (e.g., Refs. 13–14).

Nevertheless, even if one grants for the sake of argument that humans have the expected amount of prefrontal cortex for a primate brain scaled up to human size, there is no getting past the fact that humans have a lot more association cortex in absolute terms than do chimpanzees or other great apes [15]. Human brains are about three times the volume of those of chimpanzees, and whereas the primary sensory and motor regions of humans are, in absolute terms, very similar in size to those of apes, humans have a much, much greater amount of association cortex (Tables 1 and 2) [15]. The same pattern holds for the sensory and association thalamic nuclei (Table 3). I suggest that the most straightforward interpretation of the data is that the primary areas maintained approximately ape-like sizes in human evolution, while association cortex underwent enormous expansion. The mere fact that the magnitude of association cortex expansion is (or might be) in line with what is expected from brain-size scaling might be taken to mean that association cortex expanded in a predictable manner (perhaps reflecting some conserved developmental processes), but it doesn't negate the fact that association cortex did expand. The result is that humans have a brain dominated by association cortex to an extent unmatched by any other primate, and this difference is likely to have profound implications for the internal organization of the cortex [6,16], for patterns of long cortical connections [17], and for cortical function.

Was the expansion of association cortex accompanied by the addition of new, human-specific areas to support human-specific functions?

This question has long been a matter of contention, with notable authorities lining up on both sides of the issue. To some, it has seemed that the enormous human brain, with its unique psychological functions, must contain human-specific areas [9,18,19]. Others, however, have failed to be convinced, arguing that humans have the same set of cortical areas found in our close primate relatives [11,20,21].

This important issue remains unresolved. It needs to be acknowledged, however, that at present, there is no compelling evidence that humans possess more cortical areas than do other primates, nor that human-specific functions require human-specific brain structures. The paradigmatic language areas of Broca and Wernicke provide a case in point. Although there is little doubt that in humans these areas are critically involved in language processing, and that language is a human specialization, there is nonetheless evidence that homologues of Broca's and Wernicke's areas exist in apes and monkeys, based on similarities in their location within the cortical mantle, in their histology, and in their other, non-linguistic functions, such as forelimb and orofacial movements and analysis of species-specific calls (see reviews in Refs. 22 and 23). Thus, the claim that Broca's and Wernicke's area evolved originally to support functions other than language, and then were "recruited" into a language-processing system (an old claim, in fact; see Ref. [24]), is defensible, and we should not conclude that human-specific functions require human-specific brain areas (see also Refs. 25 and 26).

Mapping studies of other brain regions also tend to identify a common complement of areas in humans and nonhuman primates. For example, if the cytoarchitectonic maps of Petrides and Pandya [27] are correct, each of the prefrontal areas of humans has a homologue in macaque monkeys, despite the much larger prefrontal region of humans. Similarly, mapping studies of extrastriate visual cortex using fMRI in humans and macaques identify an identical complement of visual areas [28], despite the expansion of extrastriate cortex relative to striate cortex in humans.

Recently, areas have been identified in human parietal cortex that have functional properties not found in monkeys. The human intraparietal sulcus (IPS) contains areas that are strongly activated when viewing three dimensional shape-from-motion stimuli; the same stimuli produce minimal activation in macaque IPS [29]. In general, IPS areas are much more sensitive to motion in humans than in macaques [30]. Similarly, humans possess an area in the left anterior inferior parietal lobule (i.e., the supramarginal gyrus; area PF or 7b) that is more strongly activated when human subjects view videos depicting tools being used to grasp or otherwise manipulate objects than when hands are viewed performing the same actions [31]. A comparable, tool-selective enhancement was not seen in the anterior inferior parietal lobule of macaques, even macaques with extensive training in tool use. It is possible, then, that humans possess new motion-selective and tool-use related areas in parietal cortex [29,31,32]. It might just as well be the case, however, that the functional differences observed between humans and macaques represent evolutionary changes in the functions of pre-existing areas. That evolution can effect these kinds of changes in visual areas is illustrated by the differences between humans and macaques in the functional properties of dorsal extrastriate areas V3 and V3A, with human V3A exhibiting greater sensitivity to motion, and V3 less so, compared to macaques [33]. We cannot settle the question of new areas without more complete cross-species mappings, so that the homologous areas shared by humans and non-humans are completely accounted for.

Although the data do not so far provide clear indication of human-specific cortical areas, it is the case that large regions of the cortex remain to be explored. Regions that appear to have been modified in human evolution, and may house new areas, include the cortex of the middle temporal gyrus, which is involved in semantic representation and is probably greatly enlarged in humans compared to other primates [34], and also the anterior and dorsal parts of insular cortex, a locus of self representation [35].

Are human brains more “lopsided” than those of other primates?

Human brains are highly lateralized functionally, the left hemisphere being dominant for language and motor control, and the right hemisphere dominant for visuospatial and attentional functions. Apes and monkeys, by contrast, do not exhibit the same degree of right-handedness as do humans at either an individual or population level, and while we know little about visuospatial representation in apes, monkeys do not show the same degree of lateralization as do humans [36]. Differences like these prompted Corballis to characterize the human species as “lopsided” [37] and Annett to postulate that humans underwent an evolutionary “right shift” in hand preference [38]. Hemispheric specializations have thus been regarded as key features of the human phenotype (see especially Refs. 5,39–41).

Despite the evidence for increased functional laterality, corresponding anatomical asymmetries have proven rather elusive. There are, to be sure, anatomical differences between human left and right hemispheres. The human brain has a kind of torque—the right frontal lobe protruding further interiorly than the left, and the left occipital lobe protruding further posteriorly than the right—and this has been advanced as part of a core specialization of humans [41]. There are, however, studies indicating that apes share this pattern [42,43], although direct comparison of humans and other hominoids does suggest that is more common and/or more pronounced in humans [44].

Given the uniqueness of human language, and strong left-hemisphere dominance for language, one might reasonably expect the human language areas to be more asymmetrical than their homologues in apes. Surprisingly, the planum temporale (the portion of the superior temporal lobe commonly identified with Wernicke’s area), which is larger on the left than the right in most humans [45], shows a very comparable asymmetry in chimpanzees

and other great apes [46,47], and area Tpt, the main cytoarchitectonic area on the planum temporale, is larger on the left than right in chimpanzees [23]. By contrast, a recent study in which Broca's area was delineated cytoarchitectonically indicates that this area, which is larger on the left than the right in humans, is not asymmetrical in size in chimpanzees [48].

At an even finer level of resolution, Buxhoeveden and colleagues [49] have reported an asymmetry in histology of cortical area Tpt, an architectonic territory that occupies the planum temporale and is often identified with Wernicke's area, with humans having more neuropil space between cell columns on the left than on the right; by contrast, no asymmetry was found in chimpanzees or macaques. Similar asymmetries, with higher neuropil fractions on the left than the right, are found in human motor and visual cortex (e.g., Refs. 50 and 51), however. This raises the possibility that the Tpt asymmetry reflects a human-specific, cortex-wide asymmetry [52] that is not specifically related to language.

The advent of diffusion-tensor imaging (DTI) has opened up new dimensions of organization for the analysis of asymmetries. One measure derived from DTI is the fractional anisotropy (FA) of brain voxels. FA is a measure of the propensity of water to diffuse directionally rather than randomly; differences in FA are thought to reflect differences in the microstructure of white matter—for example, the amount of myelin and the coherence of fibers. One can compare the FA of specific fibers tracts between hemispheres and across species. In a recent report, Li *et al.* [53] found that the corticospinal tracts of chimpanzees showed higher FA on the left than on the right, consistent with reports from humans. Work in progress, however, suggests that other tracts show marked differences between humans, chimpanzees, and macaques. For example, humans exhibit higher FA on the left than the right in the arcuate fasciculus (the tract that carries fibers between Wernicke's and Broca's areas), and the magnitude of asymmetry is greater in humans than in chimpanzees [54].

Was long-distance cortical connectivity modified in human brain evolution?

Cortical areas have extensive systems of long-distance connections; these connections link functionally related areas, and link the cortex to sensory and motor structures in the thalamus and brainstem. Prior to the development of robust methods to study fiber tracts noninvasively, few neuroscientists entertained the possibility that long-distance connectivity might differ in important respects between humans and other primates; Crick and Jones [18] and Deacon [17] are conspicuous exceptions. The only widely cited human specialization of connectivity came from evidence that humans, and not other primates, have direct cortical projections to brainstem nuclei involved in orofacial motor control, a projection thought to be related to language evolution [55,56]. This evidence, however, was obtained using silver staining for degenerating axons, a technique not considered to be very sensitive or reliable by modern standards.

The recent development of DTI and related *in vivo* fiber-tracking techniques makes possible systematic comparisons of human and nonhuman primate connectivity (Fig. 1). The first such study demonstrated differences in the composition of the arcuate fasciculus in humans, chimps, and macaques [34]. In humans, but not the other primates, the arcuate fasciculus carries not only fibers that interconnect Broca's area (in the posterior inferior frontal gyrus) and Wernicke's area (in the posterior superior temporal gyrus), but also fibers traveling between the inferior frontal lobe and areas in the middle and inferior temporal lobe that are known to represent word meanings.

Was the microstructure of cortical gray matter modified in human evolution?

Until recently, few would have taken seriously the possibility that cortical microstructure underwent important changes in human evolution. According to the doctrine of "basic uniformity" developed in the 1970s, the cortex of all mammals was thought to be composed of cell columns that were essentially unvarying across species in their cell number, cell types, laminar distribution of afferents and efferents, and intrinsic connectivity (see the reviews in Refs. 57 and 58). In this view, there is little room for human specializations at these levels of organization. While basic uniformity has enjoyed tremendous popularity, however, it simply cannot be squared with evidence from modern comparative studies that highlights the diversity of microstructural organization across mammalian species (reviewed in Refs. 57 and 58). At present, few studies have rigorously compared human microstructure to that of other primates. One area that has been studied in some detail, however, is the primary visual area (area V1; Brodmann's area 17; striate cortex), and this area exhibits a number of human specializations, particularly in the organization of layer 4A 59–61. The pattern of differences suggests modifications related to motion processing, changes that may underlie the human–macaque differences in the extrastriate and parietal motion-sensitive areas discussed above. Additional specializations of human cortex that have been documented include modifications of neuronal and glial phenotypes, 62–65 the horizontal spacing of neurons [66], and modifications of the laminar organization of afferents.67–69

Do human phenotypic specializations result from only a few genetic changes?

Since at least the mid-1970s, it has been understood that the amino-acid sequences of proteins, and the nucleotide sequences of the genes that code for them, are very similar in humans and chimpanzees—on the order of 98–99% similar [70]. The magnitude of similarity prompted King and Wilson [70] to conclude that evolutionary changes in gene expression, rather than changes in gene sequences, are the principal source of human phenotypic specializations. Gould [71] popularized this idea, and emphasized the possibility that a small number of expression changes acting early in development could have profound phenotypic consequences. Given this background, and the fact that there are few widely acknowledged specializations of the human brain and cognition other than encephalization and language, it is not surprising that when improved means to identify human genetic specializations became available, attention was focused on genes believed to be related to encephalization and language.72–74 The *FOXP2* gene has been especially appealing in this regard, as mutations of the gene result in language and cognitive deficits [75], it underwent positive selection in the human lineage [72], and it codes for a transcription factor that regulates the expression of numerous brain-expressed genes [76,77].

I certainly don't disparage the search for genes related to language or brain size, yet I fear that in focusing on these we've missed an important lesson of recent genomics research, specifically, that the genetic differences between humans and other primates have proven to be much more extensive than generally supposed [58]. While the protein-coding sequences of humans and chimpanzees are the same at about 98% of nucleotides, the overall DNA sequence similarity is more like 95–96% [78,79]. There are hundreds of genes, at least, that are differentially expressed in the brains of human and chimpanzees [80,81]. There are also hundreds of genes, at least, that were targets of positive selection in the human lineage subsequent to the human-chimpanzee divergence [82]. Gene duplications, deletions, and insertions, were common in the human lineage,83–85 in some instances resulting in the evolution of new genes and gene families (e.g., Refs. 86 and 87). There is also evidence of evolutionary changes in human protein chemistry not predicted by differences in genes (e.g., Ref. 88).

Comparisons of humans and nonhuman primates have, in short, yielded an embarrassment of molecular riches—embarrassing, because we currently know a lot more about human genetic specializations than we do about phenotypic specializations of the human mind and brain. Perhaps we should start thinking about genetics differently, and instead of focusing quite so much on identifying genes that influence known phenotypic specializations, use our knowledge of the genes to help us discover previously unknown human phenotypes [81]. Consider, for example, that we have genomic evidence suggesting that humans modified the expression and structure of genes related to synapse formation [89,90] and aerobic energy metabolism [91–93]. This suggests that human brains evolved so as to support higher levels of neural activity and plasticity than the brains of our closest relatives. Intuitively, this may seem unsurprising, but one would be hard pressed to identify a clear scientific claim for a human specialization of this kind, backed up by comparative phenotypic data. Such data may not be entirely lacking, however. While there are few modern data comparing brain metabolic rates between humans and nonhuman primates, those data that have been published from PET studies suggest that human brains in the awake state have rates of glucose consumption per unit of cortical tissue that are approximately equal in absolute terms to those of Old World monkeys in the awake state (e.g., Refs. 94 and 95). That shouldn't be—it is a well-established principle of physiology (Kleiber's law) that larger organs and organisms tend to use less energy per unit of tissue than do smaller ones. On this basis, we would expect the enormous brain of *Homo sapiens*, while using far more energy overall than that of apes and monkeys, to use less energy per gram of tissue. But the current evidence suggests this is not the case, and that human brains are running hot [89]. If true, this would likely have profound consequences for human psychology, neurophysiology, disease, and life history.

Conclusions

Neuroscientists are now in possession of powerful, noninvasive techniques for understanding the physical basis of the human mind. More than that, we can now determine what the human brain shares with that of other species, as well as what is distinctively human—that is, what we have evolved since our lineage parted ways with the lineage leading to our great-ape relatives. What is novel about this research, however, is not only the noninvasive methods employed, but also the strategy of comparative investigation. As valuable as studies of model species unquestionably are, if we want to understand how humans resemble and differ from other species, there is no substitute for studies that directly compare humans to other primates, and especially to our closest relatives, the chimpanzees.

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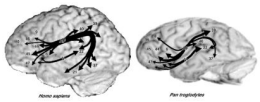

Figure 1.
Summary of results from a DTI study by Rilling *et al.* [34] comparing the organization of the arcuate fasciculus, a white-matter bundle conveying fibers between the frontal lobe and posterior cortex, in humans (*Homo sapiens*) and chimpanzees (*Pan troglodytes*). In both species, the arcuate fasciculus (AF) carries fibers between frontal language cortex, including areas 44, 45, and 47 (Broca's area), and posterior language cortex, including area 22 (Wernicke's area) and the inferior parietal lobule (areas 40 and 39). In humans, however, the AF carries fibers from middle temporal cortex (area 21) that represent word meanings. Fibers also pass between the temporal and frontal lobes via a ventral pathway (V), which is relatively prominent in chimpanzees and macaques (not shown).

Table 1

Absolute and relative sizes of primary motor area (area 4), prefrontal cortex, and other cortex in great apes and humans*

		Area 4 (cm^2)	Prefrontal (cm^2)	Other cortex (cm^2)
great apes	human	7.34 (65%)	181.40 (220%)	499.60 (149%)
	chimp	8.94 (79%)	52.84 (87%)	280.96 (84%)
	orang	13.57 (121%)	68.45 (113%)	389.22 (116%)

*Data from Blinkov and Glezer [8], Table 196. Values in parentheses represent species' values expressed as a percentage of the mean value of great apes (i.e., mean of chimpanzee and orangutan).

Table 2

Absolute and relative size of area striata (primary visual cortex; area 17) in humans and great apes *

		AS volume (ASV) (cm^3)	neocortical volume (NV) (cm^3)	ASV as % of NV	ASV as % of mean great ape ASV	NV as % of mean great ape NV
	human	20228	1006525	2.0%	136%	321%
great apes	chimp	14597	291592	5.0%	98%	93%
	orang	15185	341444	4.5%	102%	107%

* Data from Frahm et al. [96].

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Table 3

Absolute and relative numbers of neurons in thalamic nuclei in humans and great apes*

		Sensory relay			Motor/Premotor
		visual	auditory	somato-sensory	
		LGB	MGBp	VB	VL
	human	2.07 (102%)	0.87 (107%)	1.69 (147%)	3.31 (165%)
great apes	chimp	2.17 (107%)	0.91 (113%)	1.23 (107%)	2.06 (103%)
	gorilla	1.88 (93%)	0.71 (87%)	1.07 (93%)	1.84 (97%)

		Association and limbic			
		MD	PUL	LD	AP
	human	7.57 (312%)	10.11 (202%)	0.41 (272%)	1.19 (309%)
great apes	chimp	2.50 (103%)	5.45 (109%)	0.15 (99%)	0.39 (100%)
	gorilla	2.35 (97%)	4.56 (91%)	0.15 (101%)	0.38 (100%)

* Data from Armstrong [97]. Values represent the numbers of neurons × 10^6; values in parentheses represent species values expressed as a percentage of the mean value of great apes (i.e., mean of chimpanzee and gorilla).

Abbreviations: LGB - lateral geniculate body; MGBp – principal nucleus of the medial geniculate body; VB – ventrobasal nucleus; VL – ventral lateral nucleus; MD – mediodorsal nucleus; PUL – pulvinar-lateral posterior complex; LD – lateral dorsal nucleus; AP – anterior principal nucleus.