The Structure of the Human Brain

Precise studies of the size and shape of the brain have yielded fresh insights into neural development, differences between the sexes and human evolution

John S. Allen, Joel Bruss and Hanna Damasio

If you lived in the 19th century, your entire character—attributes such as ambition, tenderness, wit and valor—might have been judged by the size and shape of your skull. This practice, called phrenology, was developed by Franz Joseph Gall and Johann Spurzheim in Vienna during the early 1800s. Adherents claimed different mental "faculties" were localized to different parts of the brain, and these regions would be bigger if you possessed the traits in abundance. Phrenologists also believed the brain determined the shape of the skull, so they reasoned an external examination of the cranium would detect regional brain development. This led to the popular (and not inaccurate) characterization of phrenology as the "science" of bumps on the head.

We are right to be skeptical of these early explorations of brain size and its functional correlates. However, there was a nugget of truth in the phrenological view of world: Brain structure is a fundamental aspect of neuroscience because brain functions take place in specific combinations of brain regions. In complex animals, the size and shape of the brain reflect a host of evolutionary, developmental, genetic, pathological and functional processes that interact to produce an individual organism.

Because many factors influence neural structures, the study of brain volume, or volumetrics, has the potential to offer insights from many perspectives. In an evolutionary context, studies of brain volume across species can link anatomical, behavioral and ecological data. Species that have unpredictably large or small brains are useful for studying the forces of evolution that influence brain size. For example, Katharine Milton at the University of California, Berkeley has suggested that fruit-eating primates have a higher brain-to-body mass ratio than leaf-eating primates because locating widely dispersed, seasonally available fruit makes greater cognitive demands than finding more convenient foods, such as leaves. Volumetrics can also illuminate developmental patterns within and across species, which in turn suggest how evolution might be constrained by implicit rules of neurological growth. The study of neurological diseases also depends on a systematic analysis of brain size and shape. For instance, some children with autism have atypically large brains, and Alzheimer's disease causes progressive brain atrophy. In both cases, the pathological processes that underlie these conditions manifest as changes in brain volume. So volumetric studies are both a means to understanding brain function and an end in themselves.

Tools of the Trade

Neuroanatomy has undergone a revolution in the past 30 years. The leap became possible with the introduction of new imaging technologies such as x-ray computed tomography (CT, also called CAT scanning), magnetic resonance imaging (MRI) and positron emission tomography (PET). With these tools, scientists can view the structure and activity of the living human brain in unprecedented detail. For the structural and volumetric study of the brain, CT and MRI have been of critical importance.

Computed tomography is the older technology. It uses the variable absorption of x rays by different brain components to visualize structures inside the skulls of living subjects. A single CT image is the product of thousands of individual measurements, which are made as the x-ray source swivels in a full circle around the head.

Unlike CT, MRI does not use x rays, relying instead on powerful magnets to momentarily align the nuclei of hydrogen atoms in body tissues, most of which are within water molecules. When the magnet is turned off, the infinitesimal spinning (or resonating) nuclei fall back to a normal state, releasing energy in the form of radio waves. The frequency of these waves provides a measure of local hydrogen concentration, which varies according to tissue type, such as bone or fat. This produces a very fine-grained map—often as good as a postmortem analysis. The technique clearly distinguishes gray matter (mostly neuronal cell bodies), white matter (mostly nerve fibers insulated by fatty myelin, plus supporting cells) and cerebrospinal fluid or CSF (the liquid that fills the spaces within and around the brain). In addition, individual MR scans can be stacked to form a virtual three-dimensional model, then resliced along any plane or angle.

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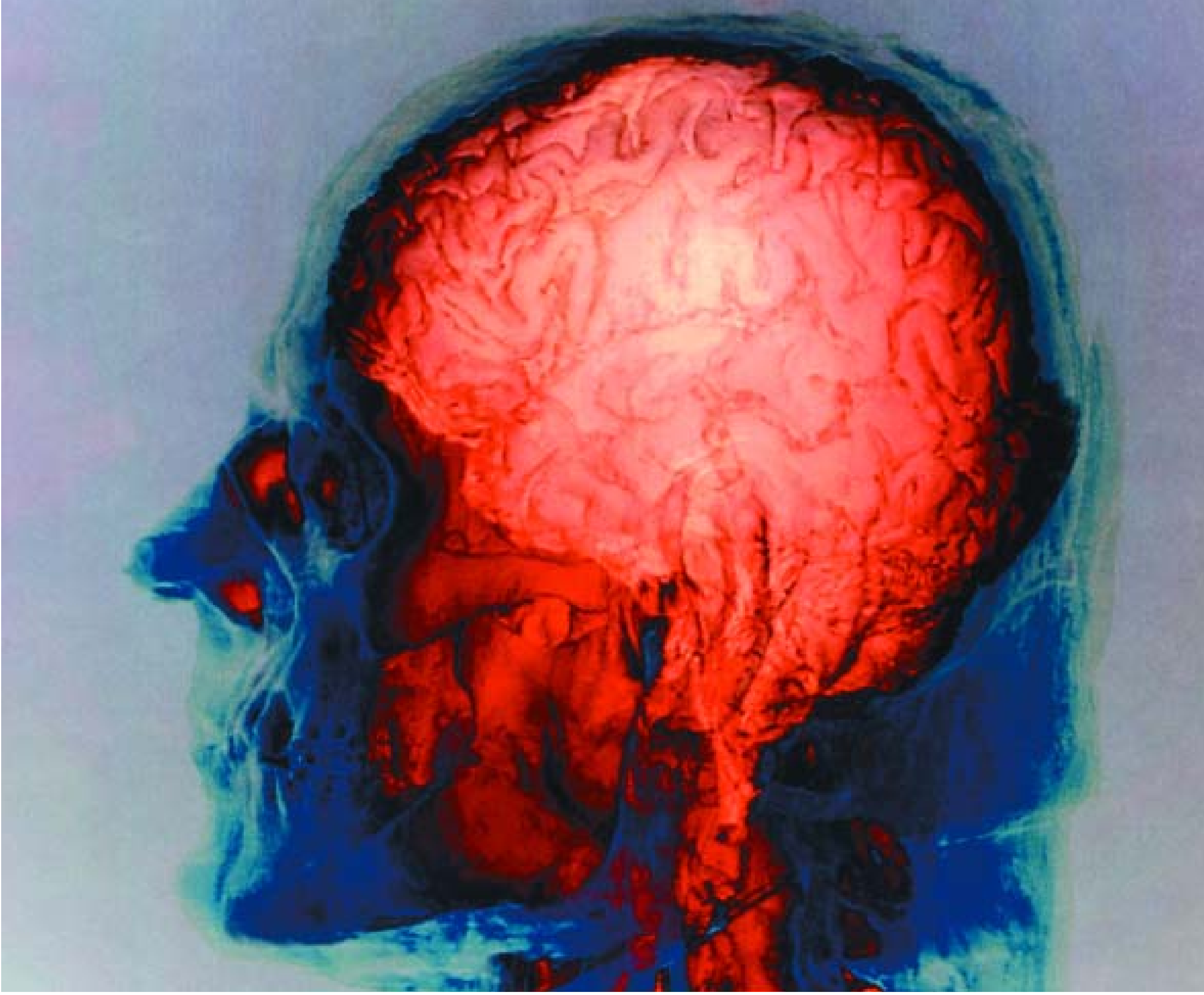

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Figure 1. Computed tomography (CT) and magnetic resonance imaging (MRI) allow unprecedented access to the living human brain, as seen in this colored, three-dimensional scan, which combines images from both techniques. The neuroanatomical study of the size and shape of the brain—long relegated to the autopsy table—has been tremendously invigorated by these advances.

Draw the Line

The process of dividing the brain into different regions is known as *parcellation*, and there are many ways to do it depending on the goals of the investigators and the methods available. MRI parcellation uses visible anatomical landmarks, such as the sulci (folds) and gyri (bulges) on the surface of the brain to create "regions of interest" or ROIs. They can include broad structural divisions—for example, the temporal, parietal and occipital lobes—as well as smaller structures such as the hippocampus or corpus callosum. The locations of specific brain activities, when they are known, can also guide anatomical parcellation.

A three-dimensional MR scan is made from a series of separate, contiguous images. A typical high-resolution analysis might have a slice thickness of 1.5 millimeters, meaning that an average brain would be compiled from more than 100 sections. Specialized image-processing software can then "extract" the brain from the skull and visualize it as a solid object. It can be sliced in any plane, rotated or resized to match a standard model. At this point, ROIs can be defined by marking the boundary limits of the structure on the surface of the brain. These marks are then transferred to "coronal" slices (parallel to the plane of a person's face) to define the region on each image. The ROI volume (area multiplied by slice thickness) from each section is summed to give an overall value. The studies mentioned in this article, like others in the field, were done through a laborious process of manually tracing ROIs onto each image. Several methods are currently being developed to automate this painstaking process, but to date none exists that can match the precision of hand tracing with expert knowledge of anatomy.

One of the most useful aspects of an MR scan for imaging neural structures is that it sharply defines gray matter, white matter and cerebrospinal fluid. Many research groups are studying the relative gray:white composition of var-

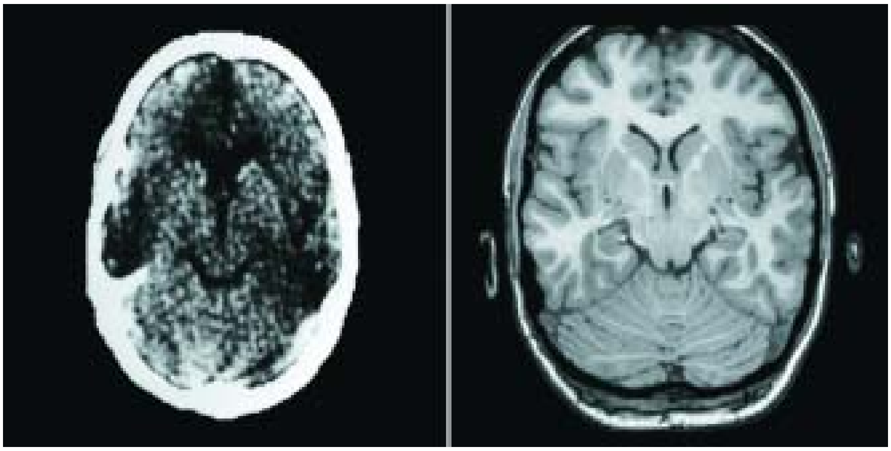

Figure 2. Although computed tomography (CT or CAT, *left*) scans were revolutionary when introduced in the 1970s, magnetic resonance imaging (MRI, *right*) provides a much more detailed view of the brain and its substructures. This technique clearly differentiates gray matter, white matter and cerebrospinal fluid (which appears black) with high resolution. The CT and MRI scans are from different subjects. (Photographs courtesy of the authors.)

ious structures, aided by automated methods (which do work well for this purpose) for segmenting MRIs into these categories.

Genes and Brains

Genetic processes underlie the development and evolution of the brain, and several research teams are studying the genetics of human brain volume and structure. One strategy is to use MRI to look at the brain volumes of identical and fraternal twins. The studies indicate that human cranial capacity is a strongly inherited trait, and most of the variation in total or hemispheric volume can be explained by genetic factors. In one report, by William Baaré and his colleagues at the University Medical Center of Utrecht in the Netherlands, genes accounted for the large majority of brain volume differences: 90 percent for the brain as a whole, 82 percent for gray matter and 88 percent for white-matter.

However, two major neuroanatomical features appear to be free of strong genetic control. In the same paper, Baaré stated that the lateral ventricles—CSF-filled cavities inside the brain—were only mildly influenced by heredity. A separate study by Alycia Bartley and her colleagues at the National Institute of Mental Health explained how patterns of sulci and gyri were more similar in monozygotic (identical) twins than in dizygotic (fraternal) twins. Interestingly, siblings from both groups were still very different from each other, especially in the smaller sulci. Thus, while overall volumes of major brain sectors are under strong genetic control, smaller regions may be more responsive to environmental influence. These insights into the relative contributions of genes and environments to this phenotype are useful in framing another area of volumetrics research—the evolution of the modern human brain.

Lobe Row over Low Brows

Scientists have debated for decades the hypothesis that frontal lobe expansion accelerated during hominid evolution. When we compare our own high foreheads to the low brows of our closest living kin (the chimpanzee) and extinct cousins (the Neandertals), the idea seems obvious. In terms of brain functions in which parts of the frontal lobe play a critical role, language, prediction and judgment represent important cognitive differences between us and other animals. So the idea that the frontal lobe expanded disproportionately during hominid evolution makes intuitive sense.

The equation of a big frontal lobe with intelligence is also embedded in the popular imagination. The 1955 science-fiction movie *This Island Earth* featured three intelligent species: humans, Metalunan aliens (similar to humans but more advanced, with unnervingly large foreheads) and the menacing but highly advanced Zagons. The mutant alien brains of the Zagons had apparently become so large that they literally burst through their foreheads. The implicit notion in this hierarchy is that brain size is linked with mental acuity. More specifically, the increasing size of the foreheads (especially in the human-like Metalunans) highlights a belief that cognitive ability is tied to the frontal regions. But is this assumption true?

Several recent studies have turned the tools of neuroimaging to the issue of relative frontal lobe expansion during hominid evolution. Our colleague Katerina Semendeferi, now at the University of California, San Diego, used MRI to compare the proportional size of the frontal lobe in people and other primates. She found that the frontal cortex (gray matter) and the entire frontal lobe (including gray and white matter) had very similar relative proportions in humans, orangutans, gorillas and chimpanzees. In these four species the frontal lobe as a whole comprised between 33 and 36 percent of the total volume of the cerebrum, and the frontal cortex made up 36 to 39 percent of the cerebral gray matter. Although the human brain is approximately three times larger than the brains of the great apes, regression analyses of the data indicated that the proportion of the frontal lobe is not greater than expected for an ape with our size brain. By contrast, our brain proportions *are* different than those of a

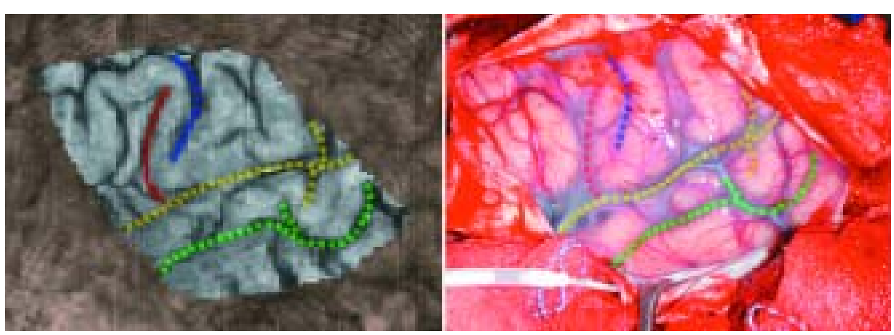

Figure 3. A three-dimensional MR image *(left)* renders the living brain at least as accurately as the view during an actual surgery *(right)*. Major sulci (folds) within the surgical window are indicated with yellow for the Sylvian fissure, green for the superior temporal sulcus, and blue and red to mark two parts of the precentral sulcus. (Photographs courtesy of the authors and Matthew Howard, University of Iowa Hospitals and Clinics.)

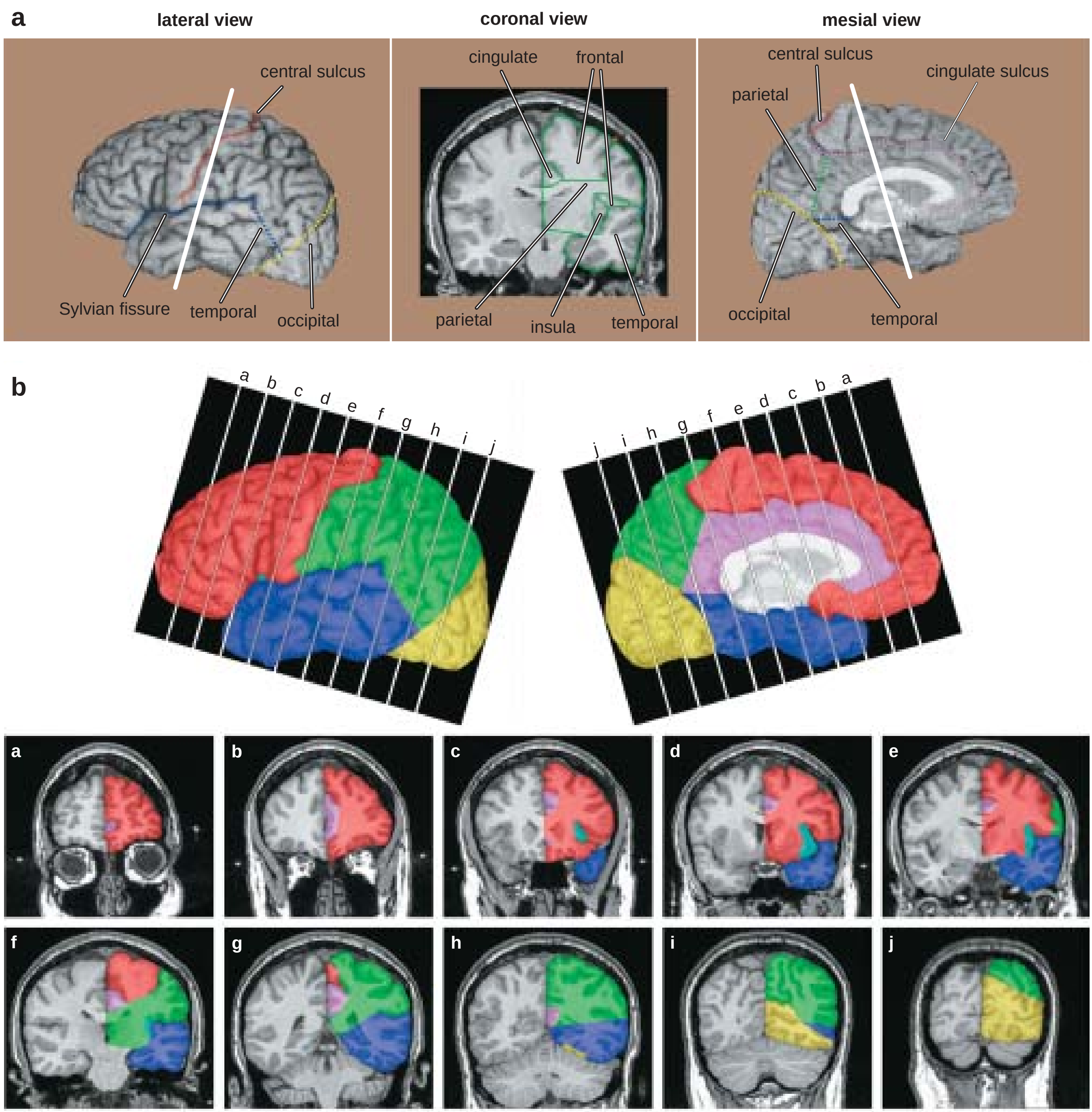

Figure 4. The process of dividing an MR scan into regions of interest is known as *parcellation*. It proceeds in two steps, which are shown in *a*. Analysts first identify sulci and other landmarks on the outer and inner surfaces of the three-dimensional model of the whole brain. In the second step, they manually trace so-called "regions of interest" onto computer-generated, coronal slices. The heavy white line indicates the coronal plane. Part *b* shows a brain on which the major lobes and the cingulate gyrus are color coded. Ten coronal sections (*a* through *j*) are shown below, representing fewer than 10 percent of all the hand-traced slices. The frontal lobe is colored red; the temporal is blue, parietal is green, occipital is yellow, and cingulate is purple. (Photographs courtesy of the authors.)

"lesser ape" (the small-bodied gibbon) and two monkey species (rhesus macaque and cebus monkey), which have significantly smaller frontal lobes.

Semendeferi suggests the evolution of a proportionally larger frontal lobe happened after the human and great ape lineage split off from the other anthropoid primates (20 to 25 million years ago), but before the divergence of hominids during the late Miocene (5 to 10 million years ago). Therefore, frontal lobe expansion is not a recent development in humans. She offers several hypotheses about the evolutionary origins of brain enlargement and cognitive change in the hominid line. These traits may have arisen from cortical reorganization within small subsectors of the lobe, enriched connectivity between selected regions, regional changes in cytoarchitecture or some combination of these features. The evidence from comparative anatomy supports all three possibilities.

Lobal Forming

Our most recent work on proportionate volume also relates to the debate over frontal lobe expansion. We found

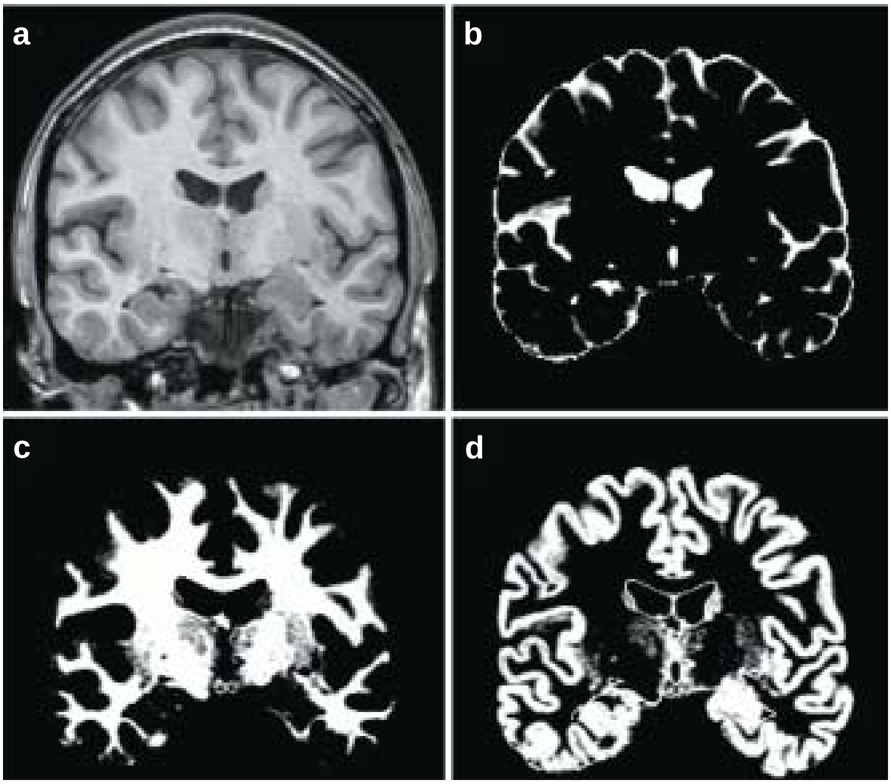

Figure 5. Automated segmentation of MR images is a valuable tool for determining the volume of different types of tissue in the brain. An original MRI is shown in *a*, followed by computer-generated images of the cerebrospinal fluid *(b)*, white matter *(c)* and gray matter *(d)*. (Photographs courtesy of the authors.)

that variation in total brain size is much greater than variation in the proportions of the major lobes. In other words, people vary more in brain size than in how the major regions of the brain are apportioned. This is strikingly evident when we compare men and women. Although men have larger brains, the proportions of the major lobes are similar. In both sexes, the frontal lobe comprises about 38 percent of the hemisphere (ranging from 36 to 43 percent), the temporal lobe 22 percent (ranging from 19 to 24 percent), the parietal lobe 25 percent (ranging from 21 to 28 percent), and the occipital lobe 9 percent (ranging from 7 to 12 percent). (Note that these values differ slightly from those of Semendeferi because of a parcellation scheme in this study that includes more of the white matter core.)

Comparing frontal- and parietal-lobe volumes has added another twist to the story. As we expected, people with large frontal lobes also have large parietal lobes, since they both reflect large overall brain size. However, after controlling for overall dimensions, we found that there was a highly significant, negative correlation between frontal and parietal lobe volume: People with larger frontal lobes had smaller parietal lobes and vice versa. We concluded that this inverse relation probably reflects genetic rather than environmental factors, because the boundary between these lobes, the central sulcus, appears early in the developing brain, and its course and position are strongly influenced by inheritance.

The negative correlation indicates that frontal lobe expansion during hominid evolution likely would have come at the cost of a smaller parietal lobe. And the contraction of the parietal lobe makes little sense from a cognitive standpoint. After all, association cortices in the parietal lobe serve many important language functions, and tool use, a hallmark of hominid cognitive evolution, depends on the connections between parietal and frontal lobes. Thus it is possible that there could have been selection *against* relative frontal lobe expansion if it compromised the functions of the parietal lobe. In light of this evidence, the frontal lobe probably grew at the same time as other major regions of the cerebrum during the past 2 million years.

A third perspective on frontal lobe evolution comes from a CT study of the skulls of several hominid fossils from the past half-million years. Fred Bookstein at the University of Michigan and his colleagues compared the skulls of our extinct hominid cousins with those of modern human beings. Archaic members of genus *Homo* are characterized by cranial capacities that equal or exceed those of modern *Homo sapiens sapiens.* However, the bones of the cranium and face are very thick and strong, and most specimens have large brow ridges and some degree of mid-facial prognathism (protruding nose), which together give the impression of a low, sloping forehead. But despite these external differences, Book-

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Figure 6. Along with a cast of humans *(left)*, the classic science-fiction movie *This Island Earth* (1955) features representatives of two advanced alien species—a toweringly browed Metalunan *(center)* and a menacing Zagon *(right)*. The film embodies the popular notion that big brains, particularly a big frontal lobe, convey intelligence.

stein *et al.* showed that the inside of the cranial vault was identical by using a statistical method known as Procrustes analysis. This strategy uses a series of floating intervals between fixed anatomical landmarks to standardize the measurement of size, position, orientation and, ultimately, shape. (Procrustes was the highwayman of Greek mythology who forced each victim to fit the same terrible bed—stretching or axing the unfortunates as necessary.) The authors determined that the interior shape of the frontal bone (and presumably the shape of the frontal lobe itself) had not changed over the past 500,000 years—despite substantial changes in the external morphology of the face.

Sex in the Brain

Postmortem and MRI studies show that on average, men's brains are larger than women's brains, even after correcting for body size. This dimorphism is unlikely to be a recently evolved trait, as other primates have similar patterns. But size is not the only difference. It turns out that women tend to have a higher proportion of gray matter than men.

We recently published a pair of papers that examined differences in brain structures of men and women. On average, male brains (mean 1,241 cubic centimeters) were about 12 percent larger than female brains (mean 1,100 cubic centimeters), although there was significant overlap between the two groups. This dissimilarity did not seem to involve sex-specific differences in hemispheric volume, as the majority of men and women had larger right hemispheres. In general, sex differences for each of the major lobes of the brain reflected those of the brain as a whole. However, the occipital lobe, which processes visual information, was less sexually dimorphic than other regions.

Our segmentation of the brain into gray and white matter revealed that women have a mean gray:white ratio of 1.35 compared with 1.26 for men. This higher ratio in women appears to be caused by less white matter rather than more gray matter. Men had, on average, 9.3 percent more gray matter than women, but the increase in white matter volume was almost twice as big—17.4 percent. When we analyzed the covariance in this data set, the ratio difference disappeared with white-

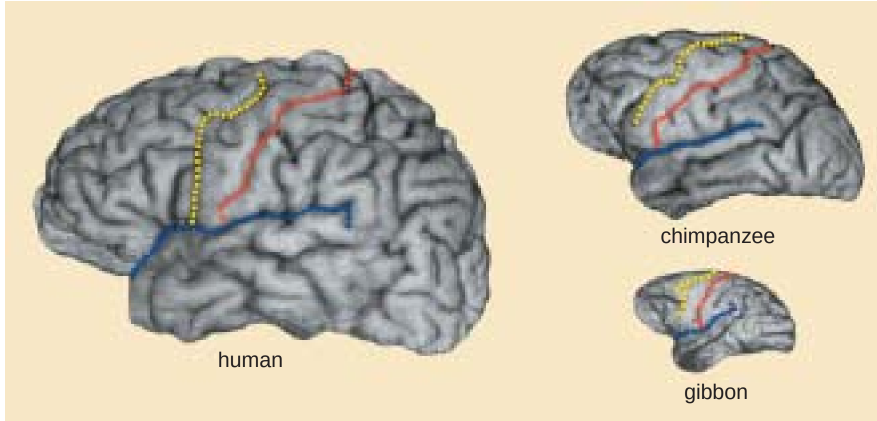

Figure 7. Human brains are substantially larger than those of chimpanzees, but the major sectors of the brains occupy similar proportions—despite differences in the way those structures are used. However, the relative proportions of human and chimp brains are different than those of a "lesser ape," the gibbon. The precentral sulcus is marked in yellow, the central sulcus in red and the Sylvian fissure in blue. The brains are presented at approximately the same scale. (Photographs courtesy of the authors and Katerina Semendeferi, University of California, San Diego.)

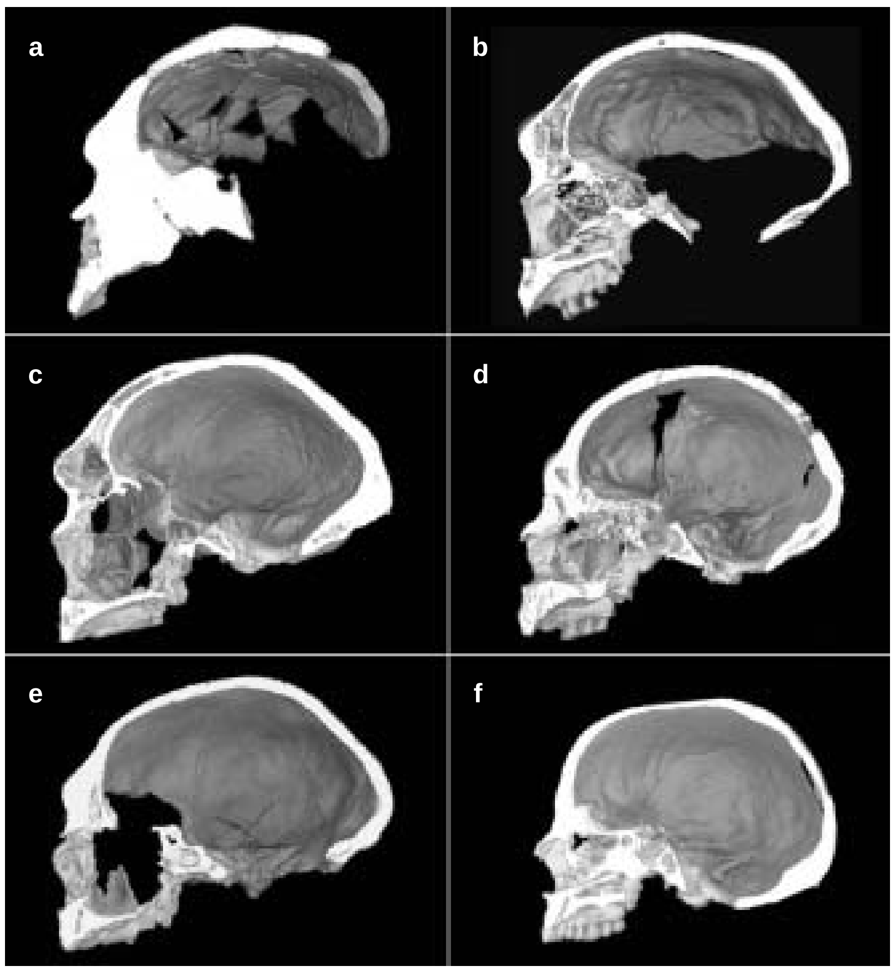

Figure 8. Despite the differences between fossil skulls from early hominids, the inner curve of the front of the cranium is nearly identical, suggesting the shape of the frontal lobe has not changed in recent hominid evolution. The oldest, *a*, is the so-called Bodo skull, an example of *Homo heidelbergensis* from about 600,000 years ago. The Kabwe *(b)* and Petralona *(c)* specimens are *H. heidelbergensis* skulls from more than 200,000 years ago. The Atapuerca skull *(d)* is a 300,000-year-old "proto-Neandertal" and the Guattari fossil *(e)* a "classic" example of *Homo neandertalensis* at 50,000 years old. Panel *f* shows a modern human (*Homo sapiens sapiens*). (Reprinted from Bookstein *et al*. 1999, by permission of Wiley-Liss, Inc.)

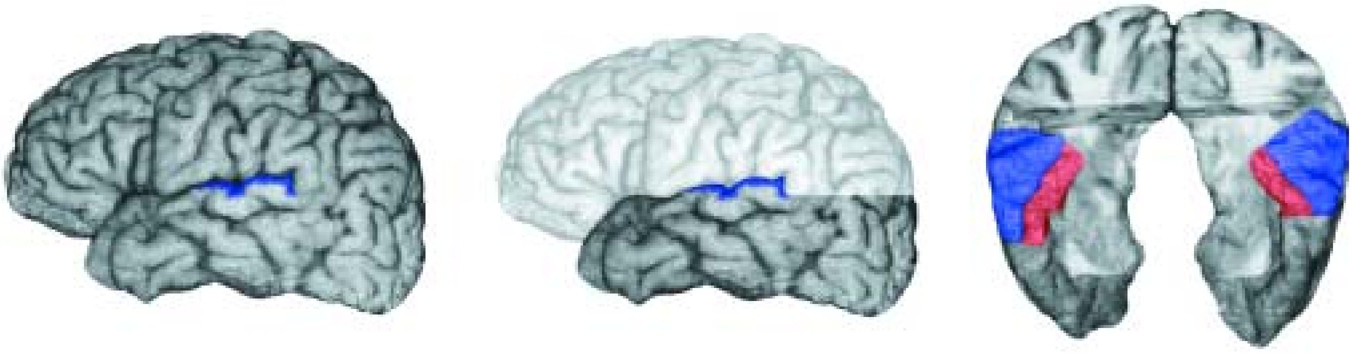

Figure 9. Investigators can manipulate MR images to visualize "hidden" structures on the cortical surface of the brain. In a lateral view *(left)*, Heschl's gyrus *(red)* is obscured, and the planum temporale *(blue)* is barely visible along the lower edge of the Sylvian fissure. Removing the frontal and parietal lobes *(center)* exposes these areas on the upper surface of each temporal lobe *(right)*. (Photographs courtesy of the authors.)

matter volume normalized. This analysis indicated that the variability in white-matter volume had the most influence on sex differences.

Of all brain structures, the corpus callosum has probably drawn the most attention over the years for putative differences between the sexes. This large band of white matter connects the right and left hemispheres, and early research suggested that it might be larger in women than men. However, the current generation of studies has found the opposite to be true—it is actually larger in men, reflecting the greater overall size of male brains. In our ongoing studies, we observe that the corpus callosum is about 10 percent larger in men; however, it constitutes a significantly greater percentage of the total white matter in women (2.4 percent versus 2.2 percent).

This detail suggests an explanation for why men have a greater proportion of white matter. In MR images, most white matter includes myelinated axon fibers, glial cells and blood vessels. By contrast, the white matter of the corpus callosum is mostly just fiber tracts. Therefore, if the callosum is an index of the axonal fraction of white matter, then men may have more non-axonal components (glia, blood vessels) in the overall makeup of their white matter. In other words, the "excess" white matter in men (underlying the lower gray:white ratio) probably doesn't represent a big step up in the connectivity of male brains.

Dispelling an Old Cliché

What do these differences in brain volume tell us about the way that male and female brains actually work? When the sexually dimorphic corpus callosum was first suggested in the early 1980s, many scientists speculated that the "larger" band in women meant they had a greater degree of communication between the two hemispheres. This idea seemed to support the cliché that in women, the "emotional" right side and the "analytical" left side were more "in touch" with each other. Of course, we now know that women do not have larger corpus callosa than men. This fact doesn't preclude greater functional connectivity between the hemispheres (as the stereotype would have it), but there is no anatomical evidence for the claim.

On average, the brains of men and women differ by more than 100 cubic centimeters, or about two and a half golf balls. Should we expect this difference to have direct cognitive effects? Not necessarily, for several important reasons. First, although the sex difference in brain volume is present after correction for body size, some of the variation *can* be attributed to a person's physical dimensions. In a careful MRI study (in which equal attention was paid to both brain and body size parameters), Michael Peters of the University of Guelph and his colleagues found that the difference in brain volume between the sexes dropped by two-thirds after height was included as a covariate.

Next, volume differences between the sexes are distributed fairly evenly throughout the major lobes of the brain; there is no "sex-specific" region that accounts for an undue share of the difference in total brain volume. This diffuse pattern indicates that it will be difficult to find a functional sex difference that correlates with differences in total brain volume. Furthermore, a similar pattern of sexual dimorphism is seen in several other primate species: the human sex difference in brain volume evolved before the profound changes in brain size and cognition that occurred during hominid evolution.

Although we have argued against a strong functional explanation for sexual dimorphism in total brain volume—indeed, it may reflect primate ancestry rather than cognitive adaptations—we do not suggest that there are no structural-functional differences in brain anatomy between men and women. Rather, we would expect the changes to exist in more subtle ways—particular regions or networks of the brain that are associated with specific behaviors (for example, visual-spatial tasks) that exhibit sexual dimorphism.

The Mark of Silence

Heschl's gyrus (HG) is a small structure on the top of the temporal lobe, buried within the Sylvian fissure. It is important because it marks the approximate position of the primary auditory cortex—the place in the brain where sound is initially processed. But how would HG develop in people who had never heard sounds in their lives?

The examination of HG in deaf individuals is related to a series of now-classic animal studies that proved the requirement for sensory information during critical periods of neural development. When the animal's sensory input was blocked (by covering one eye, for example), the brain structures that normally received those projections failed to develop. Obviously, such experiments cannot be conducted in people, so we have little direct information on sensory deprivation and the development of the human brain. With this in mind, we collaborated with Karen Emmorey at the Salk Institute to record gray and white matter volumes of HG in hearing and congenitally deaf individuals using high-resolution MRI.

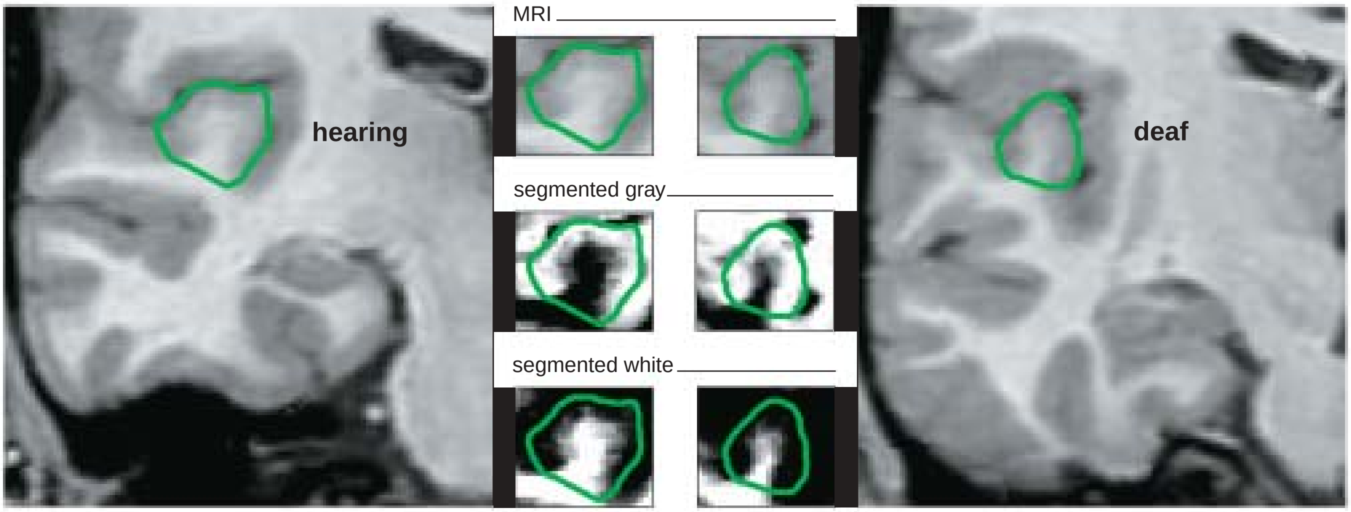

Figure 10. Congenitally deaf people have less white matter than do controls in Heschl's gyrus, the primary region for processing sound. Heschl's gyrus is outlined in green. The original MRI has been segmented into separate gray-matter and white-matter images for comparison.

We measured the volume of HG and other regions in the brains of 25 congenitally deaf individuals and 25 age- and sex-matched controls. One of these areas, the planum temporale, borders HG and is involved with secondary processing of sound. This structure is one of the most reliably asymmetric parts of the human brain, being larger in the left hemisphere than the right. In fact, many scientists once thought that the asymmetry might have evolved with spoken language. However, a similar pattern also exists in chimpanzees, so hemispheric language functions must have developed within the context of preexisting lateralization (at least in this area).

The planum temporale proved to be the same in deaf and hearing subjects, indicating that the structure of this region is not critically influenced by sensory input. However, HG did change: The gray:white ratio was significantly higher in deaf subjects compared to hearing controls. This increase was caused by a reduction in white matter volume, as the amount of gray matter (after normalization) varied little between deaf and hearing subjects. We speculated that the auditory deprivation from birth might have led to a combination of less myelination, fewer connections with the auditory cortex and the gradual decay of unused axonal fibers. This part of the brain is not dead—it responds to nonauditory stimuli, according to functional imaging studies. But our results do indicate that exposure to sound may influence the anatomical development of this primary sensory region.

Mind the Gap

Given the complexity of the subject matter and the number of issues that need to be addressed, the volumetric study of the human brain is still in its infancy. We have not yet ascertained the full scope of human-brain variability, and more normative research is necessary. And despite the fact that MRI has been used in hundreds of studies of schizophrenia, Alzheimer's disease and autism, quantitative volumetric data is not yet a standard component of clinical diagnoses. We anticipate the next generation of higher-resolution MRI studies will add even more analytical power to further elucidate the links between brain structure and function.

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