

## Chapter 2

# Neuroscience and Human Brain Evolution

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**Abstract** Evidence from comparative neurobiological studies indicates that humans differ from other primates along several different dimensions of brain organization. Differences in cytoarchitecture, connectivity, and gene expression demonstrate that substantial remodeling of brain microstructure and molecular biology occurred during human evolution, and these changes are likely associated with cognitive specializations. The paleoneurological study of brain reorganization, however, has often been considered only on a larger scale, since the evidence from endocasts is limited to brain regions that can be detected from the traces left in the fossil record. Neuroscience offers a critical perspective on paleoneurology by investigating the microstructure and genetic mechanisms that might be responsible for brain reorganization. Recent findings suggest that neural tissue differs in its anatomical structure and molecular biology across primate species and is not uniform in its processing capabilities. Connectivity patterns can differ across species, producing selective enlargement of connected brain regions. Changes in patterns of innervation for various neurotransmitters may also occur on a microscopic scale, but can produce substantial changes in brain function and cognition. Furthermore, differential regulation of various transcription factors and genes can produce variation in the size of brain structures across primate species. Although the exact nature of brain reorganization related to the evolution of cognitive processing in humans remains to be fully defined, these findings indicate that it may have occurred through a number of different pathways. Further research in both neuroscience and paleoneurology is necessary to identify areas where brain reorganization likely occurred, along with the underlying mechanisms of evolutionary change in human brain structure and function.

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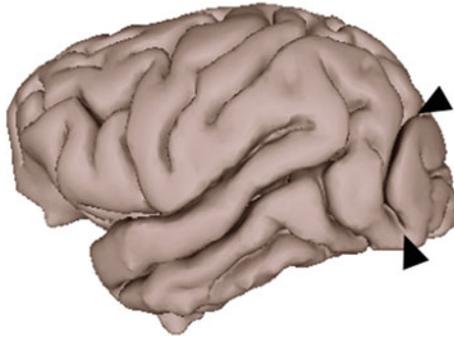
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## Introduction

Overall brain size has increased over evolutionary time in several mammalian lineages, and especially in primates (Jerison 1973, 1979; Shultz and Dunbar 2010). Scaled to body size, however, cranial capacity in the hominin lineage has increased even more dramatically than is typical of other primates, indicating that brain size has expanded in hominins significantly more than expected based only on body size increase (Jerison 1973; Hofman 1983; Hawks et al. 2000). Modern human brain mass, which is approximately 1,400 g on average, is about three times larger than in great apes, our closest living relatives. While cranial capacity displays clear evidence of enlargement in the hominin fossil record, the issue of when brain reorganization occurred is more difficult to determine. The term brain reorganization refers to changes in the structures of the brain that account for differences in function and behavior that are independent of variation in brain size (Holloway 2008).

The notion of concerted versus mosaic evolution as a means of reorganization has been addressed in reference to brain evolution across mammals. Concerted evolution can be defined as changes in structure that occur in a coordinated manner throughout the entire brain due to constraints on neural development, while mosaic evolution is the ability for specific systems or regions to change independently of one another. Finlay and Darlington (1995) proposed that the size of brain regions in mammals enlarge predictably based on absolute brain size. This is primarily due to a conserved order of neural development in mammals, which was shown to be correlated with the relative enlargement of different brain regions as brain size increased. These results suggest that adaptations for many behaviors in evolution likely involve enlargement of the whole brain, since modification of individual regions is most easily achieved by changing the duration of the entire brain's schedule of neurogenesis.

However, there are instances in which certain systems within the brain of particular species or lineages have been shown to increase in size independently of changes in overall brain size (Barton and Harvey 2000). For example, neocortical volume in primates is disproportionately large when compared to neocortical volume in insectivores, with primate neocortical volume nearly five times that of a similarly sized insectivore brain. These results suggest that neocortical enlargement in primates is associated with adaptation toward a different ecological niche, and shows that increased neocortical volume relative to brain size may be a part of



**Fig. 2.1** The lunate sulcus forming the boundary between the parietal and occipital lobes on the *left* hemisphere of a chimpanzee brain. The location of the lunate sulcus in hominin fossil endocasts has been highly debated

that adaptive grade shift. There is also evidence of an adaptive shift in primates toward a diurnal niche and increased reliance on vision, with the size of areas associated with vision negatively correlated with size of areas associated with olfaction. Hence, the evidence of brain reorganization in primates indicates that constraints may have resulted in overall concerted evolution among most brain structures, but these constraints did not preclude system-specific changes. For example, in anthropoid evolution, mosaic changes, such as the coordinated evolution of regions linked by a common system, affect neural diversity more than changes in relative brain size. Relative brain size only accounts for a small proportion of the variation seen in anthropoid brains, and underestimates the contribution made by the different neural pathways (Smaers and Soligo 2013).

With respect to the hominin fossil record, the discussion of brain reorganization has centered on whether changes in the relative size of cortical regions occurred prior to major brain expansion or whether these changes were primarily linked to allometric effects of cortical enlargement, with a longstanding debate concerning the position of the lunate sulcus (Fig. 2.1). Lunate sulcus position is important because it indicates the location of the parietal cortical areas important for sensorimotor integration, object manipulation, and attention (Bruner 2010), in relation to the primary visual cortex in the occipital lobe (Holloway 2008). Comparative data from volumetric measurement across hominoid primates indicates that the modern human primary visual cortex is significantly reduced and that the position of the lunate sulcus provides a reasonable approximation of primary visual cortex size (de Sousa et al. 2010). In ape endocasts, the lunate sulcus occupies a rostral, or more anterior, position than in modern human endocasts (Falk 1980). Therefore, a more caudally positioned lunate sulcus in an endocast would signal a shift in cortical reorganization toward a more modern human-like pattern of parietal expansion and occipital reduction.

Much of the debate regarding the position of the lunate sulcus has focused on australopithecines, from approximately 4 to 2.5 million years ago, particularly the Taung endocast of *Australopithecus africanus*. Whereas Falk (1980, 1983, 1985a, b, 1989) identifies the australopithecine lunate sulcus more rostrally in an ape-like position, Holloway (1981a, 1983, 1984, 1988, 1992), Holloway and Shapiro (1992), and Holloway et al. (2004) assert that the position of the lunate sulcus is more caudal, similar to modern humans. Because australopithecines have relatively small cranial capacities in the range of great apes, a rostrally positioned lunate sulcus would suggest that reorganization had not occurred in these species, and did not occur in the hominin lineage prior to brain enlargement. A caudally positioned lunate sulcus, however, would suggest that reorganization in the parietal and occipital lobes had occurred in these relatively small-brained species prior to brain enlargement in the hominin lineage (Holloway et al. 2004).

Recent fossil discoveries have provided further evidence for the possibility of reorganization in other regions of the cerebral cortex in hominins without an increase in brain size. The discovery of *A. sediba* from about 2 million years ago suggests the possibility that cortical reorganization had occurred prior to brain size enlargement in hominins. The endocast of *A. sediba* has a relatively small endocranial volume comparable in size to earlier *Australopithecus* species. However, the morphology of its orbitofrontal region is claimed to be more similar to that seen in later *Homo* (Carlson et al. 2011). Further complicating the debate is the endocranial morphology of the *H. floresiensis* specimen LB1. The position of the lunate sulcus in the LB1 endocast of *H. floresiensis* from 94,000 to 13,000 years ago has been identified in a more posterior modern human-like position and it displays other derived morphology of the frontal and temporal lobe similar to that of *Homo erectus*, even though it has an incredibly small cranial capacity of 417 cc (Falk et al. 2009).

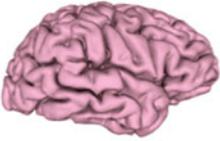
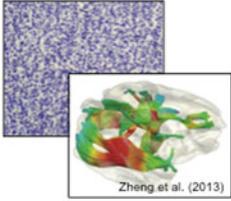
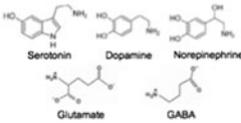
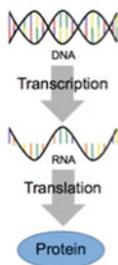
Relative sizes of the various lobes of the cerebrum have also been estimated to differ among hominin species with similar brain sizes, suggesting that changes can occur in a mosaic fashion without a change in overall brain size. Balzeau et al. (2012) examined the surface areas of the frontal, parieto-temporal, and occipital lobes relative to endocranial volume for *Homo* endocasts. Humans and Neandertals exhibited marked differences in relative lobe size despite similar endocranial capacities; Neandertals had relatively larger frontal and occipital lobes and a relatively smaller parieto-temporal lobe than humans. Evidence for parietal and cerebellar expansion in humans has also been demonstrated using geometric morphometrics techniques (GM). GM is based on the use of landmarks to define the shape of an object. Landmarks are biologically homologous loci across all specimens, and contain spatial data that can be separated according to size and shape information (Zelditch et al. 2004). The use of GM methods has transformed the field of paleoneurology, as it allows for a quantitative, rather than descriptive, study of shape changes among different specimens. Using GM, Neubauer et al. (2009) investigated the growth pattern of the endocranium throughout human development. The parietal and cerebellar regions of the cranial vault undergo pronounced expansion during early postnatal development. This pattern of globularization

during early development is not seen in chimpanzees, as humans and chimpanzees differ for their entire cranial growth trajectory (Neubauer et al. 2010). Although modern human and Neandertal crania both have relatively large endocranial capacities, they differ in both adult and developmental endocranial shape; Neandertals lack the early postnatal globularization phase seen in the human cranium, and develop along a trajectory that results in a more elongated cranial shape (Gunz et al. 2010, 2012). These results show that cranial growth trajectories have influenced the shape of the modern human brain, independently of changes in overall brain size (Bruner 2004).

Thus, there is considerable evidence to indicate that reorganization has occurred in parallel with brain expansion in hominin evolution. However, it is impossible to know the full extent of reorganizational changes in human brain evolution based solely on the fossil record. Although endocasts provide the only means of studying neural morphology of extinct hominins, the information they offer is limited to overall size differences, imprints of cerebral vasculature, the external convolutional morphology of well-preserved gyri and sulci, and changes in shape (Falk 2012). Although important information can be gained from such studies, they do not provide insight concerning changes that occurred in the microstructure, connectivity or molecular biology of the brain. Furthermore, modifications of internal structures, such as the basal ganglia, thalamus, and other deep nuclei cannot be examined from endocasts. Comparative neuroanatomical and genetic data across primates, therefore, is needed to reveal possible changes in microstructure, connectivity, and function that cannot be detected in endocasts (Fig. 2.2). The knowledge gained from such research has the potential to inform our interpretations of how the earliest hominins may have differed from the living great apes, and how later *Homo* may have evolved modern behaviors such as language.

## Reorganization in Structure

Recent findings have provided a better understanding of how regions of the human cerebral cortex have changed compared to other primates in terms of size and position. The frontal lobe has been identified as a region that is noticeably enlarged and widened in Neandertals and modern humans compared to other hominins (Bruner and Holloway 2010). It is notable that the primate frontal cortex (including primary motor cortex, premotor cortex, supplementary motor area, and prefrontal cortical areas combined) hyperscales relative to the rest of the neocortex and brain, with a steeper scaling exponent than what is observed in carnivores (Bush and Allman 2004). The human brain does not differ from other primates in this respect (Bush and Allman 2004), and the total frontal lobe is as large as expected for an ape of human size (Semendeferi and Damasio 2000; Semendeferi et al. 2002; Barton and Venditti 2013). Furthermore, the human frontal cortex, though absolutely larger in humans, occupies a similar proportion of the cortex as in nonhuman primates (Semendeferi et al. 2002). Thus, humans appear to follow

Structure	<p><b>Macrostructure</b></p>  <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Gross observation</li> <li>• Dissection</li> <li>• Magnetic Resonance Imaging (MRI)</li> <li>• Geometric morphometrics</li> <li>• Voxel-based morphometry</li> </ul> <p><b>Features:</b></p> <ul style="list-style-type: none"> <li>• Study of brain surface anatomy</li> <li>• Shape analysis</li> <li>• Gross anatomical scale</li> <li>• Limited to large regions</li> </ul>
	<p><b>Microstructure</b></p>  <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Histology</li> <li>• Diffusion Tensor Imaging (DTI)</li> </ul> <p><b>Features:</b></p> <ul style="list-style-type: none"> <li>• Finer anatomical scale</li> <li>• Reveals underlying cellular structure of brain regions</li> <li>• Can show connectivity between regions</li> </ul>
Molecular biology	<p><b>Neurotransmitters, receptors and other molecules</b></p>  <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Immunohistochemistry</li> <li>• Western blotting</li> <li>• Proteomics</li> </ul> <p><b>Features:</b></p> <ul style="list-style-type: none"> <li>• Use antibodies to stain neurons or glia</li> <li>• Identify specific cell types</li> <li>• Can identify cells that use specific neurotransmitters</li> </ul>
	<p><b>Genetics</b></p>  <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Comparative genomics</li> <li>• RNA-seq</li> <li>• PCR</li> <li>• Microarray</li> <li>• Transgenic/knockout organisms</li> </ul> <p><b>Features:</b></p> <ul style="list-style-type: none"> <li>• Allow for comparison of genetic material across species</li> <li>• Can show changes in gene expression</li> <li>• Reveals molecular differences in development</li> </ul>

**Fig. 2.2** Different levels of examining brain reorganization, with a description of methods discussed in this chapter. Macrostructure includes large, visible structures of the brain. Macrostructure is the only level that can be investigated in endocasts. Microstructure is the next level, and allows for the analysis of cytoarchitecture and connectivity between different brain regions. Molecular biology refers to neurotransmitters, receptors, genes, and other molecular components of the brain

an expected pattern of total frontal cortex enlargement for a primate of our brain size. More uncertainty surrounds the question of prefrontal cortex enlargement in human evolution. The granular prefrontal cortex of humans contains regions that are important for language, social cognition, abstract thinking, long-term planning, and other executive functions. The frontal pole region (area 10) has been measured based on cytoarchitecture across hominoid species and has been shown to be both absolutely and relatively larger compared to the rest of the brain in humans than in other apes (Semendeferi et al. 2001), though human area 10 is only approximately 6 % larger than expected for an ape of human size (Holloway 2002). Other studies of the whole prefrontal cortex have concluded that it is larger than expected by allometry in humans for both grey and white matter (Schoenemann et al. 2005a; Smaers et al. 2011; Sherwood and Smaers 2013).

Less is known about how reorganization may have affected other brain regions. The temporal lobe in humans is larger than expected for an ape brain of human size (Semendeferi and Damasio 2000; Rilling and Seligman 2002). Humans also have larger than expected temporal lobe surface area and white matter (Rilling and Seligman 2002). Enlargement of the temporal lobe may be due to adaptations for language, as it contains the auditory cortex and Wernicke's area, two regions important for language processing, along with other regions such as the middle and inferior temporal gyri that are active in phonological and lexical-semantic functions (Binder et al. 1997). The parietal lobe has been difficult to differentiate from other regions, as its boundaries are not easily identified. Semendeferi and Damasio (2000) showed that the occipito-parietal sector, which is the combined volume of the parietal and occipital lobe, is as large as expected for an ape brain of human size. Although the total volume of the occipito-parietal sector is not larger than expected in humans, more fine-grained reorganization in this region is evident in modern humans; the size of the parietal lobe appears to have become more rounded in modern humans compared to Neandertals (Bruner 2004, 2008; Bruner et al. 2011), while a comparative study including humans and apes showed that the size of the adjacent primary visual cortex in the occipital lobe is reduced in modern humans compared to hominoids (de Sousa et al. 2010).

In sum, reorganization of neocortical regions of the human brain beyond what is expected by allometry appears to be relatively subtle for most regions. Many additional significant reorganizational differences are seen in the microstructure and molecular biology of the human brain. Microstructure consists of smaller components that form the larger, visible structures of the brain, and includes cytoarchitecture and connectivity. Cytoarchitecture refers to the organization of neurons and glia within neural tissue. Connectivity involves the structure and pathways of white matter tracts that traverse the brain and connect different regions. These can be large pathways, such as the corpus callosum, or smaller ones that connect neighboring regions of tissue, such as the "U-fibers" that connect adjacent gyri in the neocortex. Brain microstructure is an important component of brain function and studies of comparative neuroanatomy have revealed key differences at this microscopic level between humans and nonhuman primates that may have resulted in unique aspects of human cognition.

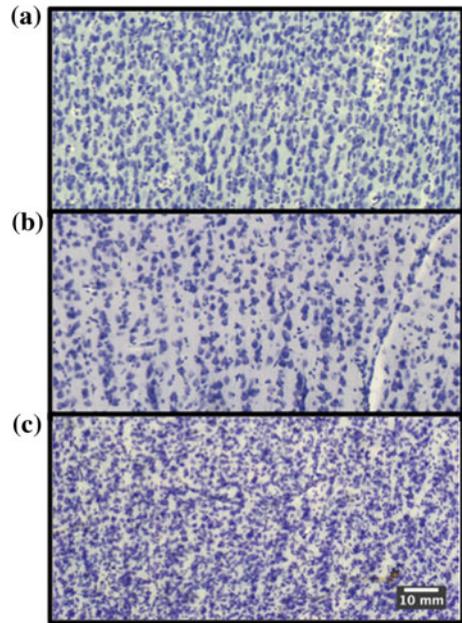
One major question concerning brain reorganization is whether one unit of neocortex has a uniform structure and functional processing capacity among species (Holloway 1968). Many models assume this is true, and propose that processing power of cortical tissue does not vary significantly along with brain size changes. The assumption that brains of different species are generally comparable on the basis of simple measures of size was bolstered by the influential publications of Jerison (1973) and Rockel et al. (1980). More recent evidence from comparative studies of the cytoarchitecture of the neocortex, however, indicates that the contents of 1 mm<sup>2</sup> of neural tissue may not be uniform across species. Cortical uniformity assumes that 1 mm<sup>2</sup> of cortex contains a constant number and density of neurons across species. In primate species, however, the average number of neurons under 1 mm<sup>2</sup> of cortex varies tremendously, with total surface area of the cortex increasing more slowly than neuron number (Herculano-Houzel et al. 2008).

Analyses of minicolumns throughout the neocortex also bring the hypothesis of cortical uniformity into question. Minicolumns are single-neuron wide vertical arrays that traverse the cortical layers, and are considered to be an important functional unit of the cerebral cortex (Buxhoeveden and Casanova 2002). Two measurements of cytoarchitecture, gray-level index (GLI) and horizontal spacing distance (HSD), have been used to quantify neuron organization in minicolumns of the primate neocortex. GLI is a measure of the percent-area of perikarya, or neuronal cell bodies, compared to neuropil (Schleicher and Zilles 1990; Semendeferi et al. 1998), while HSD indicates the amount of neuropil space separating minicolumns from each other horizontally (Semendeferi et al. 2011). Neuropil consists of dendrites, axons, synapses, glial cell processes, and vasculature (Spocter et al. 2012) and the amount of neuropil can be used to estimate interconnectivity of surrounding neurons (Wree et al. 1982).

Comparisons among humans, apes, and macaque monkey minicolumns throughout the neocortex show variability in neuron density, horizontal spacing, and amount of surrounding neuropil (Fig. 2.3). In the frontal lobe, there is proportionally more neuropil in humans than in great apes for Broca's area (Schenker et al. 2008) and the frontal pole (Semendeferi et al. 2001). The GLI value (i.e., space occupied by cell somata) is lowest in the human frontal pole despite being both absolutely and relatively larger than that of great apes, reflecting increased connectivity in the larger human brain (Semendeferi et al. 2001). HSD was also largest in the human frontal pole and was 30 % larger than in great ape species, likely related to more corticocortical integration and processing power (Semendeferi et al. 2011). The frontal pole region may have become more specialized in hominin evolution, with increasing neuropil space providing more processing capacity in this and other prefrontal regions, including the anterior region of the insular cortex (Semendeferi et al. 2001; Spocter et al. 2012).

Studies of microstructure in the temporal lobe have focused on the cortex of the planum temporale (PT). The PT is a region that is part of Wernicke's area and is associated with speech comprehension in humans (Hickok 2009). Cytoarchitectonic area Tpt is located in the posterior portion of PT, sometimes extending into adjacent regions of the parietal cortex (Galaburda and Sanides 1980; Galaburda and

**Fig. 2.3** Minicolumns in layer III of left area Tpt (Wernicke's area homologue) of a macaque (a), chimpanzee (b), and human (c). Magnification = 10x and scale bar = 10 mm for all photos



Pandya 1983). Humans are reported to have the lowest neuron density in this cortical region as compared to chimpanzees and macaques, with the least linear and widest minicolumns (Buxhoeveden et al. 1996). Despite lower neuron density, the core of human minicolumns is more compact than in chimpanzees and macaques. Lower neuron density indicates increased neuropil space and connectivity in humans. Despite a large size difference between chimpanzee and macaque brains, both have similar minicolumn neuron density and neuropil space (Buxhoeveden et al. 1996, 2001). This evidence suggests that the human neocortex may have increased minicolumn size associated with more input and output pathways for language processing (Buxhoeveden et al. 2001). Although one study concluded that humans show a leftward predominant asymmetry of minicolumn spacing and neuropil in the PT which was absent in chimpanzees (Buxhoeveden et al. 2001), a more recent study with a larger sample size failed to replicate this earlier finding and showed that neither humans nor chimpanzees display neuropil asymmetry (Spocter et al. 2012). Humans also show differences from chimpanzees in minicolumn morphology in the fusiform gyrus of the temporal lobe. In both species, the fusiform gyrus is involved in facial recognition. Humans have larger neurons and increased neuropil space in the fusiform gyrus than in chimpanzees, particularly in the left hemisphere. The asymmetry may be associated with a functional difference for the left FFA in humans (Chance et al. 2013).

In the occipital lobe, minicolumn width in the primary visual cortex is larger and more variable in humans than in chimpanzees and macaques, with a

corresponding increase in neuropil. As in the cortex of the PT, chimpanzees and macaques are similar in minicolumn width and variability despite a difference in size, suggesting increased processing power in the human primary visual cortex (Casanova et al. 2009). It is notable that such microstructural reorganization is evident in the human primary visual cortex, since in terms of volume, humans have a particularly reduced V1 as compared to what would be expected based on scaling for brain size (de Sousa et al. 2010). Additional histological evidence suggests that layer IVA of V1, which is involved in motion processing, has also been altered in recent human evolution (Preuss and Coleman 2002). Humans differ from anthropoid primates in the structure of the magnocellular pathway in the primary visual cortex, and differ from great apes in the organization of V1 (Preuss et al. 1999).

Humans also have astroglial specializations associated with minicolumn anatomy that are unique among primates. The primate neocortex contains astroglial cells with long processes that extend vertically across the cortical layers (Colombo et al. 1997, 2000; Oberheim et al. 2006; Sherwood et al. 2009). These astroglial processes are closely associated with pyramidal cell columns and are concentrated in layers II and III in most primates, suggesting a pattern of organization similar and complementary to cortical minicolumns (Colombo et al. 1999). Anthropoids, especially catarrhines, have a vertical, radial distribution of long interlaminar astroglial processes that form a palisade in the superficial cortical layers that may increase the functional capability of the cortical minicolumns by facilitating communication among them (Colombo and Reisin 2004). Compared with other cararrhines, humans have increased branching complexity of astroglial cells, which may contribute to synthesis of processing in cortical minicolumns (Oberheim et al. 2009).

Studies of minicolumns and corresponding astroglial organization demonstrates that the anatomical structures underneath  $1 \text{ mm}^2$  of neocortex is not constant across species, or even across the neocortex of a single individual. Although larger brains are expected to have decreased neuron density and increased neuropil (Jerison 1973), evidence from the diversity of minicolumn structure across mammals suggests that brain size alone may not be sufficient to explain this aspect of cortical microstructure (Raghanti et al. 2010).

## Reorganization in Connectivity

Major differences between humans and other primates, furthermore, may lie in patterns of connectivity among brain regions. White matter is especially important for connectivity as it contains tracts of axons (Schüz and Braitenberg 2002). However, white matter is impossible to assess using endocasts, and is most readily studied in brain tissue using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), a variant of MRI. Both MRI and DTI can be used to study white matter *in vivo*, and have been applied to the study of connectivity in humans

and nonhuman primates. DTI, however, has the added advantage of revealing specific white matter tracts (Rilling 2006). Evidence from MRI scans suggests that frontal lobe white matter may differ between humans and nonhuman primates. There is a general trend of whole brain neocortical white matter to increase disproportionately with gray matter in mammals (Zhang and Sejnowski 2000), and anthropoids exhibit different scaling patterns for frontal lobe and non-frontal lobe white matter (Smaers et al. 2010; Schoenemann et al. 2005a, b). This differential scaling results in a white matter to gray matter ratio in the prefrontal cortex that is greatest in humans (Sherwood and Smaers 2013). Primates also demonstrate hyperscaling of the left prefrontal cortex. Asymmetrical hyperscaling occurs in left prefrontal white matter volume compared to gray matter volume in apes and humans, but not in monkeys. Although apes and humans share this pattern of hyperscaling, the trend is taken to its extreme in humans (Smaers et al. 2011). Areas of the cerebellum that are connected with the expanded prefrontal cortex in humans have also enlarged compared to the same areas in capuchins and chimpanzees (Balsters et al. 2010), suggesting that other brain regions may have become relatively enlarged due to connectivity with the prefrontal cortex.

Zhang et al. (2012) investigated connectivity-based cortical landmarks identified in macaques, chimpanzees, and humans using DTI. These landmarks showed where white matter connectivity was similar or different across the three species. Areas with more common landmarks were considered more evolutionarily conserved, with fewer changes in patterns of white matter connectivity. Overall, there were 65 common landmarks and 175 differences across species. The most similarities were found in the frontal and occipital lobes and fewer were located in the temporal lobe. In the parietal lobe, the superior portion had more common landmarks, while the inferior portion contained more species differences. Although all regions showed some major differences, highly specialized regions in humans, such as Broca's and Wernicke's areas, showed a large change in white matter connectivity. These results suggest that connectivity has changed significantly across different regions during primate evolution, and may be linked with human-specific capacities such as language.

One of the major long-range white matter pathways in the primate brain is the superior longitudinal fasciculus (SLF). It is made up of four parts: three branches (SLF I, II, and III) and the arcuate fasciculus (Makris et al. 2005). The evolution of language capabilities may have influenced the connectivity between the frontal and temporal lobes in humans along the arcuate fasciculus. The arcuate fasciculus connects the frontal and temporal cortices, specifically Broca's and Wernicke's areas. The arcuate fasciculus is involved in higher order cognition including syntax and semantics (Rilling et al. 2012). DTI suggests that the human arcuate fasciculus has a different pattern of connectivity compared with that of chimpanzees and macaques. In humans, the portion of the arcuate fasciculus connecting the left frontal cortex to the middle and inferior temporal gyri is enlarged (Rilling et al. 2008). This portion of the arcuate fasciculus is specifically associated with speech prosody (rhythm and tone) and lexical-semantic (word meaning) processing in

humans (Glasser and Rilling 2008). The human arcuate fasciculus also exhibits a higher level of modification compared with the extreme capsule. The extreme capsule is a ventral white matter pathway that is associated with auditory processing and memory retrieval in macaques. In humans, the extreme capsule is involved in retrieval of verbal information. The arcuate fasciculus experienced the most change in the human lineage, suggesting a reorganization of processing capabilities in humans due to the evolution of language (Rilling et al. 2012).

Expanded tool-use and tool-making behaviors in modern humans may have also affected white-matter connectivity in the mirror neuron system. The mirror neuron system is comprised of frontal, parietal, and temporal areas that are active during observation and execution of hand and hand-object manipulation (Rizzolatti and Craighero 2004). Mirror neurons were first identified in macaques (Gallese et al. 1996; Rizzolatti et al. 1996), and their presence has since been extended into humans (Iacoboni et al. 1999; Gazzola and Keysers 2009; Keysers and Gazzola 2010). Using DTI, Hecht et al. (2013) investigated the connectivity of the mirror neuron system in macaques, chimpanzees, and humans, specifically connectivity among frontal area F5c in macaques/area 44 in chimpanzees and humans, the inferior parietal lobule (IPL), and the superior temporal sulcus. Connections among these regions fall along ventral (extreme/external capsule) or dorsal (inferior/middle longitudinal fasciculi and SLF III) pathways that are shared with language processing. The ventral pathway is associated with goal-directed observations, while the dorsal pathway is involved in extracting detailed information from observed actions. Macaques, chimpanzees and humans differ in the pattern of connectivity among these areas; macaques and chimpanzees exhibit more connectivity via the ventral pathway, though this pattern is less pronounced in chimpanzees, while human connectivity occurs primarily through the dorsal pathway. Connections between the IPL and the inferior temporal cortex are also smallest in macaques, larger in chimpanzees, and largest in humans. These connections link the IPL with regions in the temporal lobe associated with tool recognition, with stronger connections indicating that information concerning tool type can be more easily integrated with information about tool actions. Connections between the frontal and parietal mirror neuron regions extend furthest into the superior parietal lobule (SPL) in humans. The SPL is associated with attention and spatial tasks (Husein and Nachev 2007), indicating that the human mirror neuron system relies more on these functions than in chimpanzees and macaques. These results indicate that variation in the connectivity of the mirror neuron system in macaques, chimpanzees, and humans can be linked with differences in capacity for tool-use and tool-making. Chimpanzees and humans are better able to imitate observed actions than are macaques, while humans have increased capacity for imitation of highly detailed actions compared with chimpanzees.

Von Economo neurons (VENs) are large, spindle-shaped neurons with one large axon and one primary apical dendrite on the opposite end. They were first identified in the anterior cingulate cortex (ACC) and fronto-insular cortex (FI) of humans, then subsequently great apes as well (Nimchinsky et al. 1999). In humans, VENs have also been found in the dorsolateral prefrontal cortex (DLPFC)

(Nimchinsky et al. 1999; Fajardo et al. 2008). VENs are more numerous in humans than in apes (Allman et al. 2010, 2011), and also differ biochemically in humans (Stimpson et al. 2010). VENs have been found in the ACC, anterior insula, and frontopolar cortex of cetaceans (Butti et al. 2009), and the FI and ACC of elephants (Hakeem et al. 2009), though not in the same pattern as seen in great apes and humans. VENs have also recently been identified in the macaque anterior insula and ACC, though they were smaller than those in humans, chimpanzees and bonobos (Evrard et al. 2012). Neurons with VEN-like morphology have been observed in smaller numbers in other cortical areas throughout many mammals (Butti et al. 2013), but they appear to have a specialized cortical distribution in particular large-brained and social species.

Although the exact connectivity of VENs is not currently known (Fajardo et al. 2008), it is likely that regions containing VENs project to the frontal and insular cortices, along with regions in the limbic system (Allman et al. 2010). Based on their relatively simple morphology and thick axon, it has been proposed that VENs are responsible for rapid information transfer, while pyramidal neurons in these regions send information more slowly (Allman et al. 2011). VENs have also been implicated in social behavior based on their abundance in large-brained, social animals and evidence from human neurodegenerative and neuropsychiatric diseases (Allman et al. 2010, 2011). VENs are selectively diminished in fronto-temporal dementia and agenesis of the corpus callosum (AgCC) (Kaufman et al. 2008; Allman et al. 2011; Kim et al. 2012), and are overly abundant in autism (Santos et al. 2011). Reduction of VENs is associated with deficits in empathy, social awareness, and self-control in fronto-temporal dementia (Allman et al. 2011), and an increase in VENs might be associated with heightened introspection in autism (Santos et al. 2011). VENs may participate in monitoring the internal body state, information that guides empathically understanding the emotions of others (Stimpson et al. 2010). Changes in VEN distribution, number, connectivity and biochemical composition may be involved in increasingly sophisticated social behaviors, such as cooperation and imitation, that have arisen in human evolution.

## Reorganization in Molecular Biology

Molecular biology refers to the expression of neurotransmitters, receptors, and other molecular constituents in the tissues of the brain. Often these aspects of molecular biology are studied using immunohistochemistry, Western blotting or mass spectrometry for protein analysis, or various methods to examine gene expression. A large portion of reorganization may have taken place at the molecular level during human evolution independent of changes in brain size. For example, patterns of cortical innervation for dopamine, acetylcholine, and serotonin have been shown to differ among humans, chimpanzees, and macaques. Such phylogenetic differences in innervation for these neuromodulators may have widespread effects on attention and learning, and are evident in areas associated

with higher cognition, including the dorsolateral prefrontal cortex (area 9) and the dorsal anterior cingulate cortex (area 32) in the frontal cortex, whereas innervation in the primary motor cortex (area 4) is more similar among the three species (Raghanti et al. 2008a, b, c). Both humans and chimpanzees have an increase in dopaminergic afferents and serotonergic axons in areas 9 and 32 compared with macaques (Raghanti et al. 2008a, c). Humans and chimpanzees do not differ from macaques in cholinergic input in these areas, but instead exhibit clusters of cholinergic fibers not present in macaques (Raghanti et al. 2008b). Humans differ from both chimpanzees and macaques in the pattern of sublaminal dopaminergic innervation of layer 1 in both area 9 and area 32 (Raghanti et al. 2008c). These results suggest that the human frontal cortex underwent reorganization of neuromodulatory innervation compared with other primates that may not be directly associated with an increase in brain size.

Overall, gene expression appears highly conserved between the human and chimpanzee brain. However, there is more variability in gene expression among regions in human brains than among regions in chimpanzee brains. This could be influenced by the different environmental conditions from which chimpanzees and human brain samples are typically obtained for research, or may indicate that the human brain is more plastic in how genes are expressed due to a longer period of neural development (Khaitovich et al. 2004). Gene expression associated with neural development is delayed in humans compared to chimpanzees and macaques (Somel et al. 2009), and timing of the expression of genes associated with synaptic function in the prefrontal cortex is extended (Liu et al. 2012). The relationship between developmental gene regulation and synaptogenesis or myelination, however, is poorly understood. The brain also has fewer changes in gene expression than other tissues when comparing humans and chimpanzees, although acceleration of gene expression change is greater in the brain than in any other tissue (Khaitovich et al. 2005). Genes associated with the brain have thus accumulated more changes in the human lineage than in the chimpanzee lineage (Khaitovich et al. 2005). Most differences in gene expression in the evolution of the human brain involve up-regulation, or increased expression level, as compared to other primates (Cáceres et al. 2003; Khaitovich et al. 2004). Up-regulated genes in the human neocortex include those involved in energy metabolism, synaptic plasticity, cell growth, cellular maintenance, and protein targeting (Cáceres et al. 2003; Oldham et al. 2006; Babbitt et al. 2010; Liu et al. 2012).

There is also evidence that species differences in gene expression may be affected by epigenetic regulation. Patterns of DNA methylation differ between humans and chimpanzees (Zeng et al. 2012). DNA methylation is a means of silencing a gene's transcription, and is an epigenetic regulator of gene expression (Weber et al. 2007). Genes associated with neurological function have significantly lower levels of methylation in humans compared to chimpanzees, and are thus more active than in chimpanzees. Genes that are hypomethylated in the human brain are also more highly expressed than in chimpanzees (Zeng et al.

2012). Evidence from microRNA (miRNA), furthermore, shows differences between humans and nonhuman primates. miRNA is a non-coding RNA that is responsible for regulating transcriptional and post-transcriptional gene expression (Chen and Rajewsky 2007). miRNA associated with neurons and neural functions diverged significantly between humans and chimpanzees, and even more so between humans and macaques (Hu et al. 2011). miRNA has the fastest rate of human-specific evolutionary change in the brain, especially miRNA that regulates human-specific neural development.

Thus, the extensive amount of changes in gene expression between humans and other primates suggest that they may be associated with human-specific cognitive capabilities, and may have been involved in the relatively rapid evolution of phenotypic modifications in the human brain (Somel et al. 2011). One hypothesis is that an increase in physiological activity in the human brain may have increased energy demands, resulting in the up-regulation of many genes associated with metabolism (Oldham et al. 2006; Preuss 2012). There is also evidence that a shift towards slower neurodevelopmental rates occurred after the divergence of the Neandertal and human lineages (Liu et al. 2012), lending support to the notion that major changes in the human brain occurred independently of a change in overall brain size.

Two genes, *ASPM* (Abnormal Spindle-like, Microcephaly-associated) and *MCPHI* (Microcephalin), have been proposed to play a role in the evolution of human brain enlargement (Bond and Woods 2006). *ASPM* is a microtubule-associated protein in humans, and mutations in the *ASPM* gene result in microcephaly (Evans et al. 2004; Mekel-Bobrov et al. 2005). *ASPM* is likely involved in microtubule and spindle protein organization during mitosis (Bond and Woods 2006). *ASPM* evolution was accelerated in great apes, and was especially accelerated in hominin evolution due to strong positive selection (Evans et al. 2004). Despite evidence for strong selection in hominins, exactly how evolutionary changes in *ASPM* might have affected brain enlargement is still unknown (Evans et al. 2004).

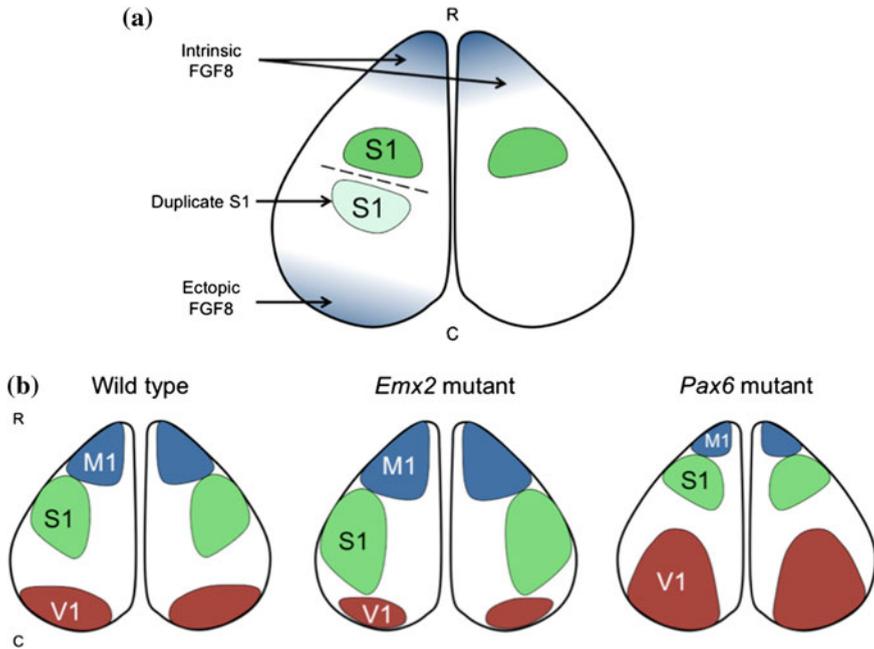
*MCPHI* is thought to regulate brain size, and evolved in the hominin lineage under positive selection (Evans et al. 2005). *MCPHI* is involved in DNA damage response, cell cycle control, and telomerase regulation. It is also associated with the control of progenitor cell division (Bond and Woods 2006). Haplotype 49, a member of haplogroup D is a form of *MCPHI* that is present in high frequency in modern humans (Evans et al. 2005). Haplogroup D arose in a lineage separated from modern humans for approximately 1.1 million years and entered the modern human lineage by 40,000 years ago (Evans et al. 2006). After entering the modern human lineage, haplogroup D swept to high frequency due to strong positive selection (Evans et al. 2005).

Recent analyses of both *MCPHI* and *ASPM* indicate less of a role in brain size than originally proposed. Montgomery et al. (2011) studied a larger range of primates and found that these genes along with two others associated with microcephaly, *CDK5RAP2* and *CENPJ*, experienced positive selection in all anthropoids with no further intensification in the human lineage. Furthermore,

*CENPJ* and *MCPHI* were not linked to brain size evolution among primates, while *CDK5RAP2* and *ASPM* had a positive relationship with neonatal brain mass and a weak positive relationship with adult brain mass across species. Changes in *ASPM* have also been linked with the evolution of smaller brains in primate species that have undergone body size reduction, such as callitrichids. Thus, *ASPM* appears to be involved in brain size changes in both directions (Montgomery and Mundy 2012). Furthermore, there is little evidence for the effects of *MCPHI* and *ASPM* on brain function. There does not appear to be an association between these genes and variation in human IQ, a common measure of intelligence (Mekel-Bobrov et al. 2007). This evidence suggests that primate brain size has a conserved genetic basis, but is also under more complex regulation than expected (Montgomery et al. 2011; Montgomery and Mundy 2012).

Further genetic evidence suggests that changes in transcription factors and genes associated with cortical region allocation may result in reorganization independent of changes in brain size. Most major brain structures and the basic layout of primary sensory and motor cortical areas are conserved across mammals (Krubitzer 1995). Despite this high degree of conservation, variation in the size of different cortical regions occurs between lineages through differences in genes and gene expression (Krubitzer and Kaas 2005). Many of the differences in gene expression occur through changes in transcription factors. Transcription factors are proteins that control the expression of genes by regulating how frequently DNA is transcribed into mRNA. Multiple transcription factors often work together to regulate one or a number of genes. Experimental genetic studies using mice indicate that transcription factors influence the size of cortical areas by regulating growth factor protein expression during neural development (Inoue et al. 1998; Bishop et al. 2000; O'Leary and Nakagawa 2002; Muzio and Mallamaci 2003). For example, the development of the boundary between the telencephalon and hippocampus involves a number of transcription factors that regulate growth. Wingless-INT (WNT) proteins define the edge of the telencephalon, or cortical hem, and form its boundary with the hippocampus throughout embryonic development (Grove et al. 1998). Telencephalon growth relies on signaling from fibroblast growth factors (FGFs) that are regulated by bone morphogenic proteins (BMPs), while signaling of WNTs in the cortical hem induces hippocampal growth (Fukuchi-Shimogori and Grove 2003; Shimogori et al. 2004). If BMP signaling is inhibited, up-regulation of *FGF8* results in a suppression of WNT proteins, and leads to reduced hippocampal size and an increase in area devoted to the telencephalon (Shimogori et al. 2004).

Changes in transcription factor regulation can also influence the location of cortical areas. *Emx2* and *Pax2* are transcription factors involved in the development of areas in the neocortex (Fig. 2.4). The developing neocortex has opposing gradients of *Emx2* and *Pax2* expression, with *Emx2* expressed more posteriorly and *Pax2* expressed more anteriorly. Loss-of-function mouse mutants for both *Emx2* and *Pax2* demonstrate that reduced *Emx2* expression shifts somatosensory areas anteriorly, while reduced *Pax2* expression results in the opposite effect (O'Leary and Nakagawa 2002). The growth factor *FGF8* is expressed in the



**Fig. 2.4** Changes in cortical organization of primary sensory areas based on expression of *FGF8*, *Emx2*, and *Pax6* in a mouse model. Addition of a posterior source of *FGF8* results in the duplication of S1 (a). *Emx2* loss-of-function mutants had primary sensory areas shifted posteriorly, while *Pax6* loss-of-function mutants had primary sensory areas shifted anteriorly compared to the wild type mouse. R = rostral, C = caudal. Adapted from O’Leary and Nakagawa (2002)

anterior developing neocortex and is involved in anterior/posterior neocortical patterning during development (Heikinheimo et al. 1994; Ragsdale and Grove 2001). Fukuchi-Shimogori and Grove (2001) showed that increased expression of *FGF8* in the anterior developing neocortex results in a posterior shift of cortical areas. Reducing *FGF8* expression anteriorly produces the opposite effect, and cortical areas are shifted anteriorly. The introduction of a second *FGF8* source in the posterior developing neocortex causes a duplication of the somatosensory cortex (S1). The completeness of the duplicated S1 is variable across individuals, although all duplications appear reversed in their organization. These results suggest that new sensory areas could have been added during primate evolution by changes in transcription factor regulation, or through modulation by a growth factor such as *FGF8*.

Evidence from embryonic mouse models also suggests that *FGF8* and *Emx2* along with *FGF17* regulate organization of the frontal cortex during development. Each of these growth factors is located in a specific region of the developing frontal cortex (Cholfin and Rubenstein 2007). *FGF17* knockout mice have a smaller dorsomedial frontal cortex, while the dorsomedial frontal cortex in *FGF8*

hypomorphic mice resembles the cingulate cortex. *FGF8* mutants also exhibit an underdeveloped orbital frontal cortex. In *Emx2* knockout mice, the dorsal frontal cortex is shifted ventrally, and the ventromedial orbital cortex and ventrolateral frontal cortex are expanded dorsally (Cholfin and Rubenstein 2008). Although these mutations result in embryos that are not viable, these results suggest that less drastic changes in growth factor expression may have resulted in changes in the organization of cortical regions. These studies demonstrate that the sizes of cortical regions are under the influence of cross-regulated genetic factors and can occur relative to one another independent of an increase in brain size.

A final example of a genetic change that is associated with brain reorganization in human evolution is *FOXP2*. A change in the *FOXP2* (forkhead box protein P2) gene in humans may have resulted in changes in speech and language independent of changes in brain size. *FOXP2* has been associated with human speech and language based on deficits from mutation or translocation (Enard et al. 2002). Human *FOXP2* has two different amino acids that alter its function and result in divergent transcriptional regulation in humans compared to chimpanzee *FOXP2* (Konopka et al. 2009). The changes in human *FOXP2* were likely selected due to their downstream effects on gene expression and regulation (Konopka et al. 2009). Human *FOXP2* has experienced strong selection during the last 200,000 years of evolution (Enard et al. 2002), and Neanderthals share the two amino acid changes in *FOXP2* with humans (Krause et al. 2007). Enard et al. (2009) showed that transgenic mice with two copies of the human *FOXP2* gene had altered behavior and microstructure of the striatum. Mice with human *FOXP2* substitutions had a different quality of vocalizations and changes in exploratory behavior and decreased dopamine concentration, along with increased dendrite lengths and increased synaptic plasticity in the striatum, an area associated with proper speech function in humans. This study suggests that *FOXP2* may affect the cortico-basal ganglia circuit involved in human speech and language, but does not produce changes in brain macrostructure or size.

## **How Does This Evidence Affect Our View of Hominin Brain Evolution?**

Recent evidence from comparative neurobiological studies indicates that humans differ from other primates, including our close relatives the great apes, along several different dimensions of brain organization, including the size of cerebral cortical regions, as well as microstructure and molecular biology. Differences in cytoarchitecture, connectivity, and gene expression indicate that human evolution has been characterized by substantial remodeling of brain microstructures that form the fundamental processing units of neuronal computation and likely are associated with modifications of cognitive capabilities. Genetic evidence has shown that reorganization of brain region size is possible without correlated

changes in overall brain volume, and has occurred within pathways associated with human language.

The field of paleoneurology itself has long influenced the question of brain reorganization. Paleoneurology largely involves the study of endocasts, and has been limited to analysis of larger brain regions that might be detected from the traces left in the fossil record. Consequently, within the field of paleoanthropology, brain reorganization has often been considered on this scale. The debate over the position of the lunate sulcus highlights this point of view. The debate largely focused on brain reorganization occurring in terms of the entire parietal and occipital lobes (Holloway 2008; Falk 2012) and only later considered corresponding changes in cytoarchitecture (Holloway et al. 2003). The discovery of the *H. floresiensis* endocast from the specimen LB1 challenged many assumptions concerning the relationship between brain size and reorganization. The volume of its virtual endocast was estimated at only 417 cm<sup>3</sup>, at the lower range of endocranial volume for extant chimpanzees and australopithecines (Falk et al. 2005), but came from a species associated with Oldowan-like stone tool technology, cut-marked bones, and evidence for the use of fire (Morwood et al. 2005; Moore et al. 2009). If *H. floresiensis* does, in fact, represent a new species of hominin, its small endocranial volume, coupled with stone tool manufacturing and use, raises the questions of whether neural tissue at a given brain size is equivalent in processing power across species, and what kind of neural reorganization may have taken place for such a reduced brain to maintain cognitive capabilities of larger brains (Conroy and Smith 2007).

Another major question that has been posed in paleoneurology is whether brain reorganization occurred in a global or mosaic fashion. Global brain reorganization in hominins was proposed in Dart's early interpretations of the Taung endocast based on *H. erectus*-like morphology in multiple brain regions (Falk 2009, but see Holloway et al. 2004). However, selective enlargement has been identified in the parietal region of *Homo*, with major changes in superior parietal lobule size compared to australopithecines, and changes in inferior parietal lobule size compared with extant great apes (Holloway 1981b). Further evidence for mosaic evolution can be seen in differences in late *Homo* frontal lobe morphology. Neandertals and modern humans exhibit lateral frontal lobe expansion in the region of Broca's area that is not linked with the overall enlargement of the brain (Bruner and Holloway 2010). Mosaic brain evolution is also evident in morphological changes between Neandertal and modern human endocasts with selective expansion and globularization in the modern human parietal lobe (Bruner 2004, 2008, 2010; Bruner et al. 2003, 2011). Despite morphological evidence that mosaic changes may have occurred in hominin brain evolution, possible mechanisms for such evolutionary changes remained unknown.

Recent findings in neuroscience help to address such questions by investigating the microstructure and genetic mechanisms that might be responsible for brain reorganization. It is now known that neural tissue differs in its anatomical structure and molecular biology across species. Recent evidence also indicates that changes in patterns of connectivity can influence processing, and may produce isolated

enlargement of the connected brain regions. Furthermore, changes in patterns of innervation and receptors for various neurotransmitters may occur on a small scale, but can produce important changes in function and cognition. Genetic evidence shows that changes in regulation for various transcription factors and genes can produce differences in size and location of cortical regions across species, and suggests that mosaic evolution was not only possible during hominin brain evolution, but also probable.

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