CHAPTER 11

Human brain evolution writ large and small

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Abstract: Human evolution was marked by an extraordinary increase in total brain size relative to body size. While it is certain that increased encephalization is an important factor contributing to the origin of our species-specific cognitive abilities, it is difficult to disentangle which aspects of human neural structure and function are correlated by-products of brain size expansion from those that are specifically related to particular psychological specializations, such as language and enhanced “mentalizing” abilities. In this chapter, we review evidence from allometric scaling studies demonstrating that much of human neocortical organization can be understood as a product of brain enlargement. Defining extra-allometric specializations in humans is often hampered by a severe lack of comparative data from the same neuroanatomical variables across a broad range of primates. When possible, we highlight evidence for features of human neocortical architecture and function that cannot be easily explained as correlates of brain size and, hence, might be more directly associated with the evolution of uniquely human cognitive capacities.

Keywords: pyramidal neuron; cortical area; chimpanzee; great ape.

Human brain evolution writ large

The most obvious and distinctive evolutionary specialization of the modern human brain is its exceptionally large size. Although elephants and whales have larger brains than humans, allometric scaling analyses have demonstrated that humans are the most encephalized of all mammals (Jerison, 1973; Martin and Harvey, 1985), with a brain that is more than three times larger than would be expected for a primate at the same body mass (Holloway, 1979). This disproportionate

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growth of the brain in the human lineage is a relatively recent phenomenon, having increased dramatically in the past 2.5 million years (Falk et al., 2000; Holloway et al., 2004). Although it is apparent that large brain size is a hallmark of human cognitive and cultural evolution, consensus is lacking on the selection pressures driving encephalization. Among the hypotheses put forward, it has been proposed that the complexity of social interaction, with a greater focus on cooperation and learning from others (Boyd et al., 2011), as well as deception (Byrne and Whiten, 1988), might have played a role.

While difficult to test, these hypothesized causes of encephalization are appealing because they attempt to explain the evolutionary benefits associated with such a prominent feature of human neuroanatomy. Given the high energetic costs of growing and maintaining neural tissue (Aiello and Wheeler, 1995; Chugani and Phelps, 1986), it is reasonable to conclude that there must be decisive fitness benefits associated with increased investment in brain mass beyond what is minimally necessary for a given body size. Indeed, it has been demonstrated across taxa that there is a trade-off between relative brain mass and other metabolically expensive tissues, as well as the extent and timing of life history stages (Barrickman et al., 2008; Barton and Capellini, 2011; Deaner et al., 2002). Some have proposed that encephalization (Jerison, 1973) or greater total numbers of neurons (Herculano-Houzel, 2011) can be taken as a satisfactory, or singular, explanation for our cognitive capacities. Among primates, correlations have been found between relative brain size and an enormously diverse range of variables, including exercise capacity (Raichlen and Gordon, 2011), the total amount of visual input as measured by the size of the optic canal (Kirk, 2006), the extent of stereoscopy as indicated by the degree of orbital convergence (Barton, 2004), behavioral innovation (Reader and Laland, 2002), sociality (Shultz and Dunbar, 2010a), and executive function (Shultz and Dunbar, 2010b). The adage, “a theory that explains everything really explains nothing” seems apt.

To some extent, explaining human cognitive uniqueness as merely a by-product of encephalization, absolute brain size, or total numbers of neurons reflects the infancy of studies in evolutionary neuroscience. If the goal is to understand the distinctive neural bases of the specific behavioral abilities that are unique to humans, then how can any unitary variable explain such a multifaceted suite of characteristics? Although still a source of debate, there appears to be a growing consensus that human cognition is most unique in (1) the representational understanding of one’s own and other’s mental states, such as beliefs, desires, and goals—that is, “theory of mind” or “mentalizing”—and (2) syntactically ordered symbolic communication in the form of language (Hauser et al., 2002; Herrmann et al., 2007; Suddendorf et al., 2009). Even if brain size can be understood as a major contributor to human cognitive uniqueness in these respects, it would still be necessary to learn more about how this single large variable translates to smaller-scale differences that can be interpreted in terms of the development of connectivity, the integration and signaling of neurons, and the flow of information within the central nervous system. Further, advances from modern behavioral neuroscience and clinical neuropsychology show that dramatic differences in behavior, including social cognition and language, can be mediated by subtle microstructural and molecular changes in brain organization (Arnold and Breedlove, 1985; Craig and Halton, 2009; Donaldson and Young, 2008; Robinson and Becker, 1986; Rosenzweig and Bennett, 1996), most often in the absence of any major difference in brain size.

At present, however, we have only a rudimentary understanding of the anatomical, functional, and energetic consequences of increased brain size or encephalization in human evolution. In large part, this is because only a few studies have yet probed the differences between human brains
and those of our close relatives, the great apes, in any detail. Consequently, many questions remain unanswered. For example, the extent to which particular modifications of neuronal morphology and cell type distributions regularly scale up with increases in brain size is poorly known; it is unclear whether all regions of the cerebral cortex tend to increase in size at the same rate, or if there are particular areas that grow disproportionately in correlation with brain size evolution; and it has not been determined how the connectivity of the cerebral cortex varies with brain size. While theoretical models exist to predict some of these scaling regularities across mammals (Kaas, 2000; Striedter, 2005), the absence of sufficient comparative data from hominoid primates precludes clear assessment of whether human neural organization is largely determined by increased brain size, or alternatively, whether certain features have emerged as departures from allometric expectations.

Within this framework, we will discuss changes in neocortical architecture in the evolution of the human brain. Specifically, we will review evidence for microstructural modifications of neocortical structure as reflected in cellular distributions and neuronal morphology, and we will consider their implications for energetics. Other excellent recent reviews discuss the allometric scaling of larger anatomical components of the brains among humans and other primates (Rilling, 2006; Schoenemann, 2006).

### Scaling regularities and the human brain writ small: Cellular distributions and morphology

One way of exploring how the human brain differs from other primates is to determine whether features of neocortical architecture deviate from predictions derived from other smaller-brained primates, with the aim of identifying scaling regularities and evolutionary specializations (de Sousa et al., 2010a; Rilling, 2006; Rilling and Insel, 1999b; Rilling and Seligman, 2002; Semendeferi and Damasio, 2000; Semendeferi et al., 1998, 2001, 2002; Sharma et al., 2010; Sherwood et al., 2004, 2005a,b, 2006, 2007, 2010). In many ways, after taking overall brain size into account, comparative evidence indicates that human neuroanatomy is not unexpected. For example, it has been shown that the total number of neurons in the neocortex of humans closely matches expectations for a primate of the same brain size (Azevedo et al., 2009), that total neocortical white matter and corpus callosum size are predicted by scaling (Bush and Allman, 2003; Rilling and Insel, 1999a), and that the frontal cortex of humans is not any larger than expected for brain size (Bush and Allman, 2004; Semendeferi et al., 2002). Human neocortical architecture at the histological level may also be examined from the perspective of allometric scaling. For example, the ratio of glial cells to neurons and the proportion of different subtypes of inhibitory GABAergic interneurons in the dorsolateral prefrontal cortex (Brodmann’s area 9) of humans have been shown to be explained by scaling predictions (Sherwood et al., 2006, 2010). Thus, at present, scaling exponents have been calculated for a number of macro- and microscopic neocortical variables, including neuron number and density, cortical thickness and surface area, white matter volume, number of brain areas, number of synapses per neurons, synaptic density, cell soma size, and axon diameter (for review see Changizi, 2001). Accordingly, many anatomical characteristics of the human brain are likely to be closely intertwined with an increase in overall size. Table 1 summarizes results from several studies that have examined whether human neuroanatomical structure is predicted by allometric scaling equations derived from smaller-brained primates.

While scaling regularities may reflect underlying biophysical, computational, or biochemical laws that operate to maintain functional equivalence across variation in brain size (as is probably the case for increases in white matter and
Table 1. Percent difference from allometric predictions for various neuroanatomical variables in humans

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent difference from allometric prediction</th>
<th>Independent variable used in the prediction</th>
<th>Nonhuman species used in the prediction equation</th>
<th>Human sample size</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volumes of structures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neocortex (gray and white matter)</td>
<td>+9%</td>
<td>Brain</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Rilling (2006), data from Rilling and Insel (1999b)</td>
</tr>
<tr>
<td>Frontopolar cortex (area 10)</td>
<td>+6%</td>
<td>Brain</td>
<td>Hominoids</td>
<td>n=1</td>
<td>Holloway (2002), data from Semendeferi et al. (2001)</td>
</tr>
<tr>
<td>Primary visual cortex (area 17)</td>
<td>−121%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>−6%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Striatum</td>
<td>−69%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>−39%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Lateral geniculate nucleus</td>
<td>−144%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>−20%</td>
<td>Brain</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Rilling (2006), data from Rilling and Insel (1999b)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>−14%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Medulla</td>
<td>−74%</td>
<td>Brain</td>
<td>Primates</td>
<td>n=1</td>
<td>Holloway (2002), data from Stephan et al. (1981)</td>
</tr>
<tr>
<td>Trigeminal motor nucleus</td>
<td>−17%</td>
<td>Medulla</td>
<td>Primates</td>
<td>n=5</td>
<td>Sherwood et al. (2005a)</td>
</tr>
<tr>
<td>Facial motor nucleus</td>
<td>+3%</td>
<td>Medulla</td>
<td>Primates</td>
<td>n=5</td>
<td>Sherwood et al. (2005a)</td>
</tr>
<tr>
<td>Hypoglossal nucleus</td>
<td>+24%</td>
<td>Medulla</td>
<td>Haplorhines</td>
<td>n=4</td>
<td>Sherwood et al. (2005a)</td>
</tr>
<tr>
<td><strong>Cellular organization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glia-neuron ratio in DLPFC (area 9)</td>
<td>−5%</td>
<td>Brain mass</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Sherwood et al. (2006)</td>
</tr>
<tr>
<td>CB-ir interneuron density in DLPFC (area 9)</td>
<td>−40%</td>
<td>Total neuron density</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Sherwood et al. (2010)</td>
</tr>
<tr>
<td>CR-ir interneuron density in DLPFC (area 9)</td>
<td>−35%</td>
<td>Total neuron density</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Sherwood et al. (2010)</td>
</tr>
<tr>
<td>PV-ir neuron density in DLPFC (area 9)</td>
<td>−43%</td>
<td>Total neuron density</td>
<td>Anthropoids</td>
<td>n=6</td>
<td>Sherwood et al. (2010)</td>
</tr>
<tr>
<td>Number of TH-ir neurons in locus coeruleus</td>
<td>+3%</td>
<td>Medulla vol</td>
<td>Catarrhines</td>
<td>n=4</td>
<td>Sharma et al. (2010)</td>
</tr>
<tr>
<td>Number of ChAT-ir neurons in nbM</td>
<td>−126%</td>
<td>Neocortex vol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−110%</td>
<td>Brain mass</td>
<td>Anthropoids</td>
<td>n=2</td>
<td>Raghanti et al. (2011b)</td>
</tr>
<tr>
<td></td>
<td>−104%</td>
<td>Neocortex vol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DLPFC, dorsolateral prefrontal cortex; CB, calbindin; CR, calretinin; PV, parvalbumin; ChAT, choline acetyltransferase; ir, immunoreactive; nbM, nucleus basalis of Meynert.

All variables represent volumes unless otherwise indicated. All percent differences between observed and predicted values are based on contemporary species data, not independent contrasts. We include percent differences only from studies where this value was calculated and reported. Other scaling analyses have also examined whether humans are within the 95% prediction intervals generated from nonhuman data, but do not calculate a percent difference between the observed and predicted values. We excluded those studies from this table.
In fact, recent studies examining dendritic morphology across different cortical areas indicate that pyramidal cell size may depend more on regional specializations than solely on brain size (Elston et al., 2001). In particular, it has been shown that some features of dendrites (i.e., dendritic spine density), but not others (i.e., branching patterns, cell size, and total spine number), correlate with overall brain size (Elston et al., 2001). Moreover, examination of regional differences in the pyramidal cell phenotype of humans and nonhuman primates has revealed substantial variation across cortical areas, with peaks of branching complexity and spine density typically observed in the prefrontal region (Fig. 1; Elston, 2000; Elston et al., 2001; Jacobs et al., 2001). As greater dendritic branching and higher spine densities allow sampling and integration of a larger number of inputs from neighboring cells, these regional differences may reflect functional

Fig. 1. Morphology of layer III pyramidal neurons in a human and a chimpanzee as revealed by Golgi impregnation. (a) Tracing of a neuron from primary motor cortex (area 4) in a human. (b) Tracing of a neuron from frontopolar cortex (area 10) in the same human individual as in (a). (c) Photomicrograph of a neuron in frontopolar cortex (area 10) of a chimpanzee. In the human, note the greater extent of dendritic branching in the region of the prefrontal cortex as compared to the primary motor cortex. Tracings of human neurons modified from Jacobs et al. (2001). Scale bar=100μm.
differences in neuronal computational power (Elston, 2000; Elston et al., 2001; Jacobs et al., 2001). Interestingly, when compared to macaque monkeys, the closest human relative yet examined for comparative studies of pyramidal morphology, the prefrontal cortex of humans exhibits a greater degree of branching complexity as well as spine density and total spine number (Elston et al., 2001, 2006). By contrast, pyramidal neurons of the primary visual cortex do not demonstrate as much species-specific variation among primates (Elston et al., 2006). Comparative studies of neuropil in the neocortical gray matter (which is primarily occupied by dendrites, axon, and synapses) across hominoid primates also show increased neuropil selectively in the frontopolar cortex of humans (Semendeferi et al., 2011). Taken together, these data support the suggestion that increased connectivity within the prefrontal cortex is an evolutionary specialization of the human neocortex (Elston, 2003). Because there is not a significant correlation between the fraction of neuropil in the neocortex (as measured in areas 4, 10, 13, 17, and 18) and brain size in hominoids (de Sousa et al., 2010b; Sherwood and Hof, 2007), the evidence for increased connectivity in the human prefrontal cortex may be an evolutionary change that cannot be accounted for by models of scaling.

One possibility that needs further testing, however, is whether regional differences in dendritic morphology straightforwardly reflect variation in neuronal density and neuropil fraction across cortical areas. As shown by a recent study of galagos, macaques, and baboons, neuronal density varies up to five times within species, with the highest density being observed in the primary visual cortex (Collins et al., 2010). Moreover, interpreting the functional implications of structural differences may be further complicated by the fact that, although cell morphology does not correlate with cortical area size, increasing or decreasing the dimension of neurons may have different impacts on small or large areas (Kaas, 2000).

The neuroanatomy of cognitive specializations: Comparing cortical area size and neurotransmission between humans and apes

In addition to investigations of scaling regularities that might account for the evolution of human brain organization, other analyses that make the narrow comparison of neocortical areas between humans and our close relatives, the great apes, also provide important insight. Although such comparison would ideally incorporate data from a greater number of primate species to examine brain size-related correlations, this is not always practical. Nonetheless, these studies provide an essential step to locate changes in the brain which might relate to the recently evolved cognitive specializations of humans by focusing on particular cortical areas that are known to be involved with language and cognition. Broca’s area and Wernicke’s area in the left hemisphere, for example, are principal nodes in a network that is strongly activated during language processing (Friederici et al., 2006). Regions of the medial prefrontal cortex and along the posterior superior temporal sulcus have been consistently found to be involved in “theory of mind” tasks (Saxe, 2006). Identifiable homologues exist in other primates for all the basic circuitry that is employed for language function and “theory of mind” in humans (Petrides and Pandya, 1994, 2002; Petrides et al., 2005; Preuss and Goldman-Rakic, 1991a,b). Therefore, understanding the neural basis for the origin of these functions requires examining how evolution has modified these regions or their connections in humans.

One important characteristic of the functional control of language in humans is that it is strongly lateralized to the left hemisphere in most people (Toga and Thompson, 2003). This functional dominance is associated with certain anatomical asymmetries, such as an increased size of the planum temporale on the left (Geschwind and Levitsky, 1968; Toga and Thompson, 2003). To examine the coevolution of the brain and language, Broca’s area (area 44 and area 45) and
Wernicke’s area (the posterior part of area 22; also called area Tpt) in chimpanzees have been studied using magnetic resonance imaging, histological data, and associated behavioral information (Hopkins et al., 2008, 2010; Schenker et al., 2010; Sherwood et al., 2003a, 2010; Spocter et al., 2010). Using cytoarchitecture to define cortical areas, it has been shown that humans and chimpanzees are similar in showing a population-level bias toward leftward asymmetry of Wernicke’s area (area Tpt) volume (Specter et al., 2010). By contrast, Broca’s area (area 44 and area 45) of chimpanzees does not display human-like lateralization (Schenker et al., 2010).

In addition, when the size of these cortical areas is compared between humans and chimpanzees, it is evident that Wernicke’s area has increased in size only proportionately with overall neocortex in human evolution, whereas Broca’s area has increased in size to a substantially greater extent (Table 2; Fig. 2). In fact, of the cortical areas measured for their volume in both humans and chimpanzees so far, area 44 in the left hemisphere displays the greatest enlargement in humans. These results allow us to speculate that the uniqueness of human language function may depend more critically on modifications to the processing capacity of the inferior frontal cortex for syntax, lexical retrieval, and other hierarchically ordered information but is built upon more ancestral functions of the superior temporal cortex (area Tpt) in phonological processing.

At present, only a small number of regions in both humans and chimpanzees have been measured for their size based on cytoarchitecture (Table 2). Interestingly, from the cortical areas that have been compared, a similar pattern of disproportionate regional expansion seems to also characterize differences in the size of cortical areas between human and macaques, as well as the heterogeneous growth of the cerebral cortex that occurs over the course of postnatal development in humans (Hill et al., 2010; Fig. 2). This suggests that the difference in cortical area sizes that evolved in humans after branching from the rest of the ape lineage may be an extension of common scaling trends across primate phylogeny that are mediated by conserved developmental mechanisms (see Chapter 4). More detailed parcellations and volumetric comparisons of the temporal cortex and inferior parietal cortex in apes are warranted and may provide insight into additional cortical modifications that have contributed to the evolution of human language and other cognitive functions.

In addition to clarifying which regional size differences appear to be most significant in human brain evolution, recent research has also revealed human-specific changes to the microstructure of connections and distributions of

### Table 2. Comparison of fold-differences in the sizes of neocortical areas between humans and chimpanzees

<table>
<thead>
<tr>
<th>Structure</th>
<th>Human versus chimpanzee fold-difference</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>3.6</td>
<td>Holloway (1996)</td>
</tr>
<tr>
<td>Neocortical gray</td>
<td>4.0</td>
<td>Rilling and Insel (1999b)</td>
</tr>
<tr>
<td>Area 44 (left)</td>
<td>6.6</td>
<td>Amunts et al. (1999), Schenker et al. (2010)</td>
</tr>
<tr>
<td>Area 10 (right)</td>
<td>6.3</td>
<td>Semendeferi et al. (2001)</td>
</tr>
<tr>
<td>Area 45 (left)</td>
<td>6.0</td>
<td>Amunts et al. (1999), Schenker et al. (2010)</td>
</tr>
<tr>
<td>Area 45 (right)</td>
<td>5.0</td>
<td>Amunts et al. (1999), Schenker et al. 2010</td>
</tr>
<tr>
<td>Area Tpt (left)</td>
<td>4.2</td>
<td>Galaburda and Sanides (1980), Specter et al. (2010)</td>
</tr>
<tr>
<td>Area 44 (right)</td>
<td>4.1</td>
<td>Amunts et al. (1999), Schenker et al. (2010)</td>
</tr>
<tr>
<td>Area 6 (hemisphere unknown)</td>
<td>2.5</td>
<td>Glezer 1958*</td>
</tr>
<tr>
<td>Area Tpt (right)</td>
<td>2.0</td>
<td>Galaburda and Sanides (1980), Specter et al. (2010)</td>
</tr>
<tr>
<td>Area 17 (left)</td>
<td>1.8</td>
<td>de Sousa et al. (2010a)</td>
</tr>
<tr>
<td>Area 13 (right)</td>
<td>1.4</td>
<td>Semendeferi et al. (1998)</td>
</tr>
<tr>
<td>Area 4 (hemisphere unknown)</td>
<td>0.8</td>
<td>Glezer (1958)*</td>
</tr>
</tbody>
</table>

*All comparisons are based on volumes, except for the data from Glezer (1958) which provide surface area measurements.
neuron types. The supply of neurotransmitter afferents to the cerebral cortex, originating from subcortical neuron populations located in the basal forebrain and brainstem, plays a key role in the balance of excitation and inhibition underlying information processing in the neocortex. These neurotransmitters (e.g., dopamine, norepinephrine, acetylcholine, and serotonin) have diffuse termination zones and have long-term effects on the processing characteristics of postsynaptic cells by interacting with multiple G-protein-linked receptor subtypes. Severe psychiatric disturbances in human patients have been shown to correlate with abnormalities in the synthesis, transport, and metabolism of these neuromodulatory systems (for review see Briand et al., 2007). By using immunohistochemical staining to identify individual axon fibers in combination with stereologic quantification, it has been shown that the extrinsic supply of serotonergic, dopaminergic, and cholinergic axons to the prefrontal cortex has been selectively altered in

Fig. 2. Maps illustrating the disproportionate expansion of the neocortex in human evolution and development. (a) Fold-difference in size of cortical areas between humans and chimpanzees. Values were taken from Table 1 and overlaid on Brodmann’s map of the cerebral cortex. All data are from the left hemisphere except where only right hemisphere or unknown were available. (b) Fold-difference in surface area of cerebral cortex between humans and macaque monkeys expressed relative to the total neocortical size difference between species, modified from Hill et al. (2010). Right hemisphere is shown. (c) Fold-difference in surface area of cerebral cortex between neonatal and adult humans, modified from Hill et al. (2010). Right hemisphere is shown.
humans and chimpanzees as compared to macaque monkeys (Raghanti et al., 2008a–c). In both humans and chimpanzees, a greater axonal length density of fibers that are immunoreactive for these neurotransmitters innervates prefrontal cortex (areas 9 and 32) in a layer- and species-specific manner (Fig. 3). Because these neurotransmitter systems are involved in behavioral flexibility, attention, and learning, it is tempting to speculate that this evolutionary shift might contribute to some of the cognitive abilities that are exclusively shared between ourselves and the great apes, such as increased behavioral inhibition, enhanced attention to the gaze of others, greater social tolerance, diffusion of social learning through regional traditions, and a capacity for self-awareness (Barth et al., 2005; Beran and Evans, 2006; Boesch, 1993; Evans and Beran, 2007a,b; Suddendorf and Whiten, 2001).

Notably, comparative allometric scaling analyses have revealed that the subcortical neuron populations that provide neurotransmitter innervation to the prefrontal cortex do not show a corresponding relative increase in humans, despite the enlargement of human cerebral cortex. Surprisingly, for both the locus coeruleus (supplying norepinephrine) and the nucleus basalis of Meynert (supplying acetylcholine), the human subcortical neuron populations actually are smaller than expected relative to brain size and neocortical volume in comparisons involving large samples of nonhuman primates (Table 1; Raghanti et al., 2011b; Sharma et al., 2010). Taken together, these results indicate that modifications in the anatomy of these neurotransmitter systems in human evolution involved alterations in terminal axon patterns, independent of correlated changes in numbers of neurons in the basal forebrain nuclei themselves.

Additional studies focusing on intrinsic sources of neurotransmitters within the cortex have also revealed that there is a significant degree of variability in both the density and distribution of cortical neurons immunoreactive for various

Fig. 3. Tracings of axon fibers immunoreactive for tyrosine hydroxylase (TH), a marker for dopamine, serotonin transporter (SERT), a marker for serotonin, and choline acetyltransferase (ChAT), a marker for acetylcholine, in dorsolateral prefrontal cortex (area 9) of macaque monkeys, chimpanzees, and humans. Images modified from Raghanti et al. (2008a–c). Scale bar=250μm.
neurotransmitters among primates. As with neurotransmitter-immunoreactive axons, these populations of cortical neurons are also selectively targeted in human neuropathologies (Fukuda et al., 1999; Marui et al., 2003; Nihei and Kowall, 1993). Tyrosine hydroxylase-immunoreactive neurons are found sparsely in the cerebral cortex of several mammals; however, humans are the only species that possess these neurons distributed throughout the entire cerebral cortex, with the highest densities occurring in the dorsolateral prefrontal cortex and anterior cingulate cortex (Benavides-Piccione and DeFelipe, 2007; Kohler et al., 1983). However, while present in the siamang, these cells are conspicuously and consistently absent among the great apes (chimpanzee, bonobo, gorilla, and orangutan), indicating that this neurochemical phenotype has independently evolved in humans (Raghanti et al., 2009). It is unclear why this biochemical expression pattern has reemerged in humans, after having been previously lost from the great ape lineage.

Neuropeptide Y-immunoreactive cortical cells are another class of neurons that are present in human and nonhuman primates, including the great apes. As with the neuron populations expressing tyrosine hydroxylase, there are species-specific patterns of variation, but quantitative analyses do not reveal anything unique about their densities or distributions in humans (Raghanti et al., 2011a).

The emergence of neuronal specializations for social cognition: VENs

Another interesting feature of the hominoid cerebral cortex is the presence of VENs (Fig. 4; Allman et al., 2010; Nimchinsky et al., 1995, 1999; Seeley et al., 2012; von Economo, 1926). VENs are projection neurons located principally in layer V of the anterior cingulate and frontoinsular cortices and, in more limited numbers, in the superior frontal cortex (area 9; Fajardo et al., 2008). Current data suggest that VENs represent a specialized neuronal type with a characteristic morphology that evolved only in a restricted number of species, most likely from a population of pyramidal neurons present in ancestral mammals (Butti and Hof, 2010; Butti et al., 2011). VENs, which are especially numerous in the hominoid lineage, are particularly

Fig. 4. von Economo neurons (VENs) as revealed by Nissl staining from layer V of anterior cingulate cortex in great apes and humans. (a) human, (b) chimpanzee, (c) bonobo, and (d) gorilla. Scale bar=100μm.
vulnerable in neuropsychiatric conditions in which social and emotional skills are characteristically affected. Moreover, recent evidence on the neurochemical profile, morphologic features, and laminar and regional distribution of VENs suggests that the functional specificity of this neuronal population could be critically involved in autonomic regulation.

VENs are generally larger than layer V pyramidal neurons and their somatic volume is strongly correlated with the encephalization quotient, unlike that of pyramidal cells (Nimchinsky et al., 1999). In adults, VENs are more abundant in the right hemisphere (Allman et al., 2010), possibly reflecting asymmetries in the organization of afferents from the autonomic nervous system (Craig, 2005). Their densities, however, are low in all species in which they occur, representing only a few percent of the total number of pyramidal neurons (Allman et al., 2010). VENs have been shown to be enriched in nonphosphorylated epitopes of neurofilament proteins, similar to large pyramidal neurons (Nimchinsky et al., 1995), and to express several markers such as dopamine D3 receptor, vasopressin 1a receptor, activating transcription factor 3, interleukin-4 receptor α chain, neuromedin B, gastrin-releasing peptide, and disrupted on schizophrenia-1, in higher levels than neighboring pyramidal cells (Allman et al., 2010, 2011; Stimpson et al., 2011).

The function of VENs remains poorly understood. Nonetheless, it is interesting that VENs are affected in a number of neuropsychiatric illnesses that present impairments of social and communication skills, emotionality, morality, and self-awareness. They are severely lost in the behavioral variant of frontotemporal dementia and in agenesis of the corpus callosum (Kaufman et al., 2008; Kim et al., 2012; Seeley et al., 2006), exhibit decreased densities in schizophrenia (Brüne et al., 2010), and show abnormal cortical distribution and increased number in young children with autism (Santos et al., 2011), as well as increased densities in suicide victims with psychosis (Brüne et al., 2011). The specific localization of VENs in cortical areas in which information on the physiological state of the body is used to guide behavioral choices (Craig, 2009), their involvement in diseases in which social conduct is dramatically affected, their richness in markers such as bombesin-related peptides, and their position in a layer characteristically sending subcortical projections (Brodal, 1978; Glickstein et al., 1985) suggest a role for VENs in cortico-autonomic pathways, supporting the original intuition of von Economo (1926) on the involvement of VENs in autonomic function. The fact that they have also independently emerged in other large-brained social mammals, such as elephants and whales (Butti et al., 2009; Hakeem et al., 2009; Hof and Van der Gucht, 2007), strongly suggests that their development is mediated by mechanisms related to brain size scaling.

Energetics and microstructural changes in human neocortical evolution

Kleiber’s law states that the mass-specific energetic cost of an organ declines with increases in total mass (Kleiber, 1961). Accordingly, because the energy required for the maintenance and development of neural tissue is correlated with the overall mass of the brain, greater metabolic efficiency of the human brain would be predicted because of its large size. However, contrary to this expectation, recent comparative studies of gene expression indicate that the human cerebral cortex is characterized by an upregulation of RNA transcripts involved in energy metabolism compared to the cortex of great apes (Caceres et al., 2003; Fu et al., 2011; Khaitovich et al., 2008; Preuss et al., 2004; Uddin et al., 2004). Moreover, the observation that genes coding for synaptic function are also highly expressed in human samples suggests that the human neocortex may be more metabolically expensive as a way to support its underlying cytoarchitecture and greater demand for synaptic signaling (Uddin et al., 2004). However, because these studies were performed
with homogenates of tissue, it is still unknown which cellular and biochemical modifications are especially responsible for the apparent increased mass-specific metabolic demand of human neocortical tissue.

Studies have found that the metabolic expense of the rodent brain is tightly correlated with neural activity associated with the most prevalent excitatory neurotransmitter in the brain, glutamate (Attwell and Laughlin, 2001; Sokoloff, 1977). Among the most energetically expensive aspects of neural activity are the depolarization of a neuron’s membrane potential following chemical stimulation at a synapse and presynaptic neurotransmitter release and recycling (Lennie, 2003). Together, these processes account for over 60% of the cost of neural activity and localize the majority of metabolic expense to the excitatory glutamatergic synapse (Raichle and Mintun, 2006). If it is assumed that the primate brain allocates energy in the same proportions to neural functions as the rodent brain, it would be expected that cortical regions with a higher density of excitatory synapses, or those regions more consistently stimulated by excitatory inputs, would be more energetically expensive to maintain throughout adulthood. Thus, greater metabolic requirement may be predicted in regions such as in the human prefrontal cortex and other association cortical areas, which have been shown to exhibit greater connectivity (Elston et al., 2006; Jacobs et al., 2001; Semendeferi et al., 2011).

Additionally, studies using radiolabeled glucose to track energy uptake in the brain have found evidence for a default mode network (DMN), a group of regions including the medial prefrontal and medial parietal cortices that are active even during times of cognitive “rest” (Raichle and Snyder, 2007; Raichle et al., 2001). Although similar patterns and high levels of activity have been found during rest in chimpanzees (Rilling et al., 2007) and macaques (Vincent et al., 2007), recent studies indicate that regions activated as part of the DMN in humans are the same regions that first exhibit the pathophysiology unique to Alzheimer’s disease, a uniquely human illness (Vaishnavi et al., 2010). If the consistently high levels of activation in the DMN predispose humans to neurological diseases not seen in other primates, a case for the uniqueness of neural activity and energy expenditure in the human lineage is stronger than ever. Thus, human neural connectivity and the biochemical processes involved in energy metabolism may set humans apart from other primates in a manner not readily predicted by brain size.

Conclusions

Only by examining the detailed architecture and function of the human neocortex in a comparative perspective will it be possible ultimately to uncover the neurobiological basis of human behavioral distinctiveness. It is to be expected that some modifications to neocortical organization will be consequences of overall brain-size expansion. Others features, however, may prove to have emerged independent of encephalization. The complexity of the human mind, of course, is not likely to be explained solely by either brain size or by statistical residuals from allometric scaling equations. Rather, the human brain phenotype is constructed dynamically in ontogeny through the interaction of uniquely modified genes that regulate neuronal proliferation (i.e., the size of parts of the brain), cell migration (i.e., the histological organization of the brain), cell adhesion, and axon guidance (i.e., connectivity), as well as the synthesis and turnover of chemicals involved in signaling and energy utilization (Gilbert et al., 2005; Konopka and Geschwind, 2010). Many exciting discoveries have already been made identifying genes that control these processes and which have undergone adaptive evolution in human descent (Dorus et al., 2004; Enard et al., 2002; Evans et al., 2004; Konopka et al., 2009; McLean et al., 2011; Popesco et al., 2006; Uddin et al., 2008a,b). The complexity with which these gene
networks are regulated through development and in response to environmental factors provides further opportunities for biocultural interactions to affect the phenotype and function of modern human brains. We are only now scratching the surface and beginning to reveal what makes the human brain phenotype truly special. This effort necessitates interdisciplinary comparative analyses involving a wide variety of molecular, histological, and imaging techniques that include data from our closest kin, the great apes.

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