

CHAPTER 9

# Human prefrontal cortex: Evolution, development, and pathology

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**Abstract:** The prefrontal cortex is critical to many cognitive abilities that are considered particularly human, and forms a large part of a neural system crucial for normal socio-emotional and executive functioning in humans and other primates. In this chapter, we survey the literature regarding prefrontal development and pathology in humans as well as comparative studies of the region in humans and closely related primate species. The prefrontal cortex matures later in development than more caudal regions, and some of its neuronal subpopulations exhibit more complex dendritic arborizations. Comparative work suggests that the human prefrontal cortex differs from that of closely related primate species less in relative size than it does in organization. Specific reorganizational events in neural circuitry may have taken place either as a consequence of adjusting to increases in size or as adaptive responses to specific selection pressures. Living in complex environments has been recognized as a considerable factor in the evolution of primate cognition. Normal frontal lobe development and function are also compromised in several neurological and psychiatric disorders. A phylogenetically recent reorganization of frontal cortical circuitry may have been critical to the emergence of human-specific executive and social-emotional functions, and developmental pathology in these same systems underlies many psychiatric and neurological disorders, including autism and schizophrenia.

**Keywords:** primate; frontal lobe; autism.

## Introduction

The frontal lobe and the portion of it occupied solely by association cortex, the prefrontal cortex (hereafter PFC), are eternally popular areas to

research in human brain evolution due to their functional attributes. The PFC comprises several Brodmann areas (BAs) anterior to the primary motor and premotor cortex (Fig. 1). The PFC is involved in higher-level cognitive processes grouped under the term of “executive functions” in humans, including mostly dorsolateral areas, like BA 9, 10, and 46 (Baddeley, 1992; Fuster, 2000a; Jurado and Rosselli, 2007), as well as in

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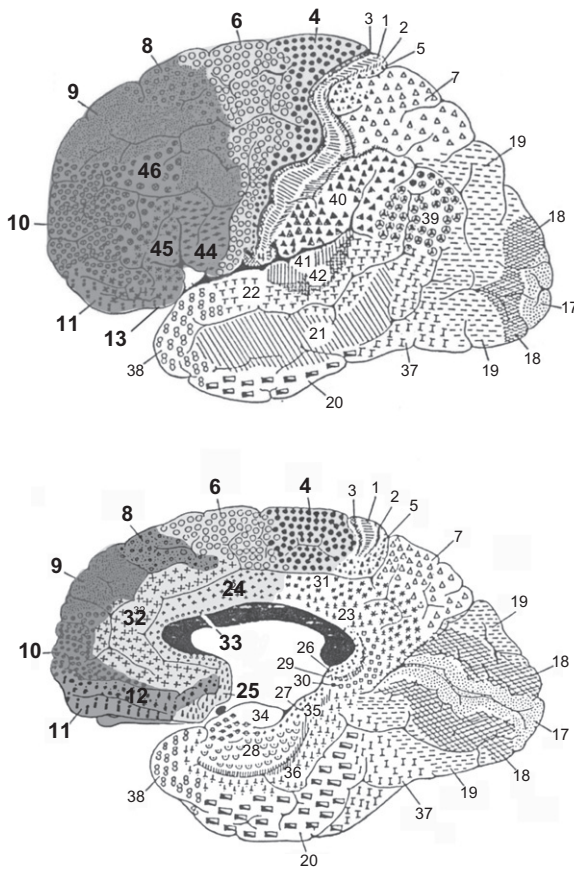


Fig. 1. Diagram of the human brain modified from Brodmann (1909) that illustrates the frontal lobe (all shaded regions rostral to the central sulcus), including the prefrontal cortex (only the darker gray shaded regions) and the anterior cingulate. According to Brodmann's classification scheme, "frontal region" included areas 8, 9, 10, 11, 12, 44, 45, 46, and 47 (of which 44, 45, and 47 he termed "subfrontal"); "precentral region" included areas 4 and 6; and anterior "cingulate region" included areas 24, 32, 33, and 25. Area 13 was at first identified by Brodmann only in nonhuman primates, not humans. It has subsequently been identified in humans as part of the orbital prefrontal. Interestingly, the term "prefrontal" was used by Brodmann only for orbitofrontal area 11 located in the rostroventral part of the frontal lobe. Contemporary use of the term prefrontal cortex refers usually either to all areas demarcated here as part of the frontal lobe, with the exception of the motor/premotor cortex (BA 4 and 6), BA 44, and BA 24, or to areas located only in the dorsolateral frontal lobe, mostly BA 9, 10, and 46. Another use of the term prefrontal is increasingly found in the imaging literature, where the term usually refers to areas "anterior to the genu of the corpus callosum."

language (mostly BA 44/45), emotional processing, and sociality (mostly BA 47, 10, 11, 13 in the orbitofrontal cortex; Beer et al., 2003; Fellows, 2007a,b; Habib et al., 1996; Stone et al., 1998). Executive functions include the organization of input from diverse sensory modalities, the maintenance of attention, the monitoring of information in working memory, and the coordination of goal-directed behaviors (Jurado and Rosselli, 2007; Miller, 2001; Miller and Cohen, 2001; Muller et al., 2002). Together, these abilities would have been necessary for navigating both the complex social groups and unpredictable, dangerous environments of our hominin ancestors. Thus, the capacities enabled by the PFC, while most are not exclusively human, are certainly a crucial aspect of what we think of as "human" in cognition. One of the most fundamental problems to be solved by any animal (Fuster, 2001a), human, or otherwise, living in a complex and ever-changing world, is how to make sense of this setting. There is variation in the environment, as well as in discernable patterns; navigating both the variation and the patterns are things at which humans excel and are activities largely subserved by the PFC.

Although the frontal lobe as a whole has not been differentially enlarged across human evolution (Semendeferi and Damasio, 2000; Semendeferi et al., 1997), there is increasing evidence for its reorganization, as some regions with known functional correlates are either bigger or smaller in the human brain than expected when compared with the same region in great apes. It is also increasingly important to look at microstructural differences in histology, given that humans do not stand out when gross measures such as whole frontal lobe volume are employed. In this chapter, we discuss comparative structural and microstructural work on the human PFC, including stereology, magnetic resonance imaging (MRI), minicolumn analysis, and diffusion tensor imaging (DTI), concentrating on the question of whether, and if so, in what ways the

human PFC or any of its subdivisions differ from other primates, in particular, the apes.

A comparative exploration of PFC microstructure is all the more necessary given both that the PFC is one of the last regions of the brain to mature, based on most indices of development (Fuster, 2002), and that neurons in areas that develop later in life have more complex dendritic trees than those that mature earlier, such as primary somatosensory and primary motor cortex (Jacobs et al., 2001; Travis et al., 2005). Brain development is on the whole unusually prolonged in the human species, beginning *in utero* in the third gestational week and continuing well into adolescence. The evolutionary trade-off that arose between large brains and bipedality, and the ensuing difficulty with childbirth, led to the secondarily altricial state of the human newborn (Rosenberg and Trevathan, 1995) and thus an uncommonly lengthy period of brain maturation. Interestingly, the most markedly late-developing regions of the PFC, on the lateral aspect, are those involved in executive functions (Fuster, 2002).

The PFC is also affected in a number of conditions and disorders; its late maturation makes it particularly susceptible to disruption (Bradshaw and Sheppard, 2000; Dumontheil et al., 2008; Ghika, 2008). Some have also hypothesized that the brain regions that were most recently developed or altered in the course of human evolution, including prefrontal association cortex, are predominantly the site of disorders (Ghika, 2008). Here we discuss the impact of autism and schizophrenia on the PFC and frontal lobe in terms of histological and microscopic studies. Dorsolateral PFC, an especially late-developing region, exhibits abnormalities in both autism and schizophrenia, which is further characterized by abnormalities in medial frontal cortex.

Despite this chapter's focus on the anatomy of the PFC, we recognize that no region of the brain operates as a separate and monolithic entity; discussing the role of the PFC necessarily implies a role for other brain regions with which it shares extensive interconnections, including the basal

ganglia, thalamus, brainstem, hippocampus, amygdala, and other neocortical regions (Ghashghaei and Barbas, 2002; Thorpe and Fabre-Thorpe, 2001). In addition to its intrinsic connections with other areas of the PFC, allowing access to emotional responses and other information, the lateral PFC is connected to occipital, temporal, and parietal cortices, and thus synthesizes visual, somatosensory, and auditory information at a high level of processing (Miller and Cohen, 2001). It receives input from other limbic structures by way of other prefrontal cortical regions. Further, even as we discuss the functional specialization of the major subdivisions, we appreciate the existence of extensive connections between these subdivisions (Barbas and Pandya, 1989; Wagner et al., 2001); while the orbital and medial regions of the PFC are thought to be involved in the processing and regulation of emotional behavior, and the lateral PFC is differentially implicated in language and the executive functions more traditionally associated with the PFC (Fuster, 2001b), it is well established that emotion plays an important role in many of the cognitive processes grouped under the term executive function, and vice versa (Bechara et al., 2000).

## Development

The first brain structure to arise is the neural tube, which is formed in the third week of gestation from progenitor cells in the neural plate (Stiles and Jernigan, 2010). Neuron production begins in the sixth week. From gestational weeks 13 to 20, neuronal count increases exponentially in the neocortical part of the telencephalon (Dobbing and Sands, 1973), with  $5.87 \times 10^9$  neurons at 20 weeks in the cortical plate and marginal zone (Samuelsen et al., 2003). Although it had traditionally been thought that all of neuronal proliferation and migration occurs by mid-gestation (Rakic, 1988; Sidman and Rakic, 1973), newer cell counts reported for mid-

gestation brains are less than half the  $19\text{--}23 \times 10^9$  neurons in the average adult human brain (Pakkenberg and Gundersen, 1997). Thus, it seems parsimonious to suggest that neurogenesis continues after mid-gestation (Shankle et al., 1999). Another study found that many regions of the cortex reached their peak cell density between 28 and 38 weeks (Rabinowicz et al., 1996). The future white matter in the intermediate zone also experiences a significant degree of growth from 13 to 20 weeks, with cell number increasing by 380% during this time period. Neurogenesis then slows to a linear rate of increase from gestational week 22 to birth, with total neuron number increasing to about  $30 \times 10^9$  cells in full-term infants.

The chief external landmarks of the PFC, its primary sulci (superior frontal, inferior frontal, and precentral), develop during gestational weeks 25–26 (Stiles and Jernigan, 2010). In dorsolateral and lateral PFC, basic features of the dendritic arbors of pyramidal neurons emerge during gestational weeks 17–25 (Mrzljak et al., 1988). From weeks 26 to 34, layer III and V dendrites continue to mature, as spines develop, basal dendritic length increases, and interneurons differentiate in layer IV (Mrzljak et al., 1992). At birth, total brain weight is about 370g (Courchesne et al., 2000).

During early childhood, the brain quadruples in size and grows to roughly 90% of the adult volume by age 6 (Courchesne et al., 2000; Knickmeyer et al., 2008). The initial periods of rapid neurogenesis and synaptogenesis subsequently give way to a period of pruning and neuronal death to manage the overproduction of these components. Throughout childhood and adolescence, brain development is characterized by both growth and then decline in gray matter volume, and increases in white matter volume. During this period of brain development, dorsolateral and medial PFC expands nearly twice as much as some other regions, including medial occipital and insular cortex (Hill et al., 2010). Converging evidence from diverse methodologies

has established that the frontal lobe, in particular, much of the PFC, matures late relative to much of the remainder of the cortex (Fig. 2). Regions of the temporal cortex, which, like the PFC, are higher-order association areas that also integrate diverse inputs from sensorimotor and other lower-order regions and develop late as well.

Cortical thickness is a useful gauge of overall maturity in developmental studies, since it is a composite measure that includes neurons, axons, dendrites, synapses, and glia. Prenatally, cortical thickness increases linearly throughout the entire brain as a function of age (Rabinowicz et al., 1996). If cortical thickness in children and adolescents is plotted as a function of age, the majority of PFC (including the lateral orbitofrontal, lateral prefrontal, medial and lateral frontal pole) follows a cubic trajectory or U-shape (Shaw et al., 2008). The development of the PFC is characterized by growth in early childhood, decrease in adolescence, and then a slight increase and stabilization in adulthood. This pattern is thought to be linked to the maturation of cortical circuits that underlie frontal lobe functioning, including language, decision-making, attention control, and working memory (Casey et al., 2005; Caviness et al., 1996; Giedd et al., 1996). Gray matter volume, also as measured by cortical thickness, reaches maximum volume in most of the frontal lobe between the ages of 11 and 12 (Giedd et al., 1999b). This contrasts with the cortex as a whole, where gray matter increases primarily from early childhood until the age of 6–9 (Courchesne et al., 2000). The dorsolateral PFC attains adult levels of cortical thickness particularly late, in early adolescence (Lenroot and Giedd, 2006).

From the ages of 5 to 11, regions in the PFC that correspond to Broca's area exhibit an increase in gray matter thickness relative to some neighboring regions (Sowell et al., 2004b), an occurrence that is thought to be related to the maturation of linguistic capacity. Developmentally normal and age-appropriate decreases in left dorsolateral PFC gray matter volume, likely reflecting

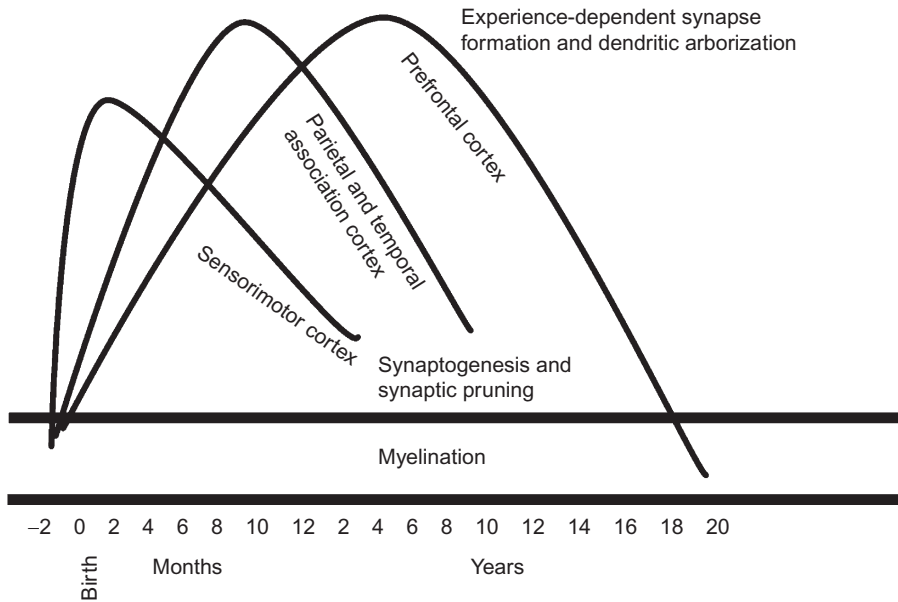


Fig. 2. A depiction of the time course of brain development in human prefrontal cortex, sensorimotor cortex, and parietal and temporal association cortex. Modified from [Thompson and Nelson \(2001\)](#).

neuronal pruning and increased myelination, were positively correlated with scores on vocabulary tests in one study ([Sowell et al., 2004a](#)). In the frontal lobe, this same phenomenon is positively correlated with scores on verbal memory tests ([Sowell et al., 2001](#)).

Unsurprisingly, the same U-shaped pattern reported by Shaw and colleagues is also described in the majority of neurodevelopmental studies examining gray matter in the PFC, regardless of what micro- or macrostructure is being examined; these gray matter components belong to the same neural circuits and have enduring reciprocal connections ([Fields and Stevens-Graham, 2002](#)). Gray and white matter both continue to experience macro- and microstructural changes throughout development, often even after adolescence, and these changes in structure parallel changes in functional organization that are in turn also reflected in behavior ([Diamond, 2001](#)).

As the brain increases in size throughout childhood and adolescence, many other microstructural

changes occur as well, including dendritic and axonal growth and synaptogenesis. These microstructural changes are also heterochronous; most of these events occur earliest in sensorimotor cortex and other primary cortex, and latest in PFC and other higher-order association cortex that integrate and process information from primary cortex ([Shankle et al., 1999](#)). Neurogenesis begins during the sixth gestational week, and, at birth, neuronal density in the frontal cortex is similar to that in many other regions, including the visual cortex. This soon changes, however; while neuronal density in the visual cortex has decreased to adult values by only 5 months of age, neuron density does not peak until much later in childhood in the frontal lobe. Throughout the cortex as a whole, neuronal number increases 60–70% between 24 and 72 months postnatally ([Shankle et al., 1999](#)). From 1939 to 1967, J. L. Conel published a comprehensive histological data set in which he measured a number of microscopic features (including neuron packing density, total cortical

and individual cortical layer thickness, myelinated large fiber density, large proximal dendrite density, and neuronal body size) in the developing human brain (Conel, 1939, 1941, 1947, 1951, 1955, 1959, 1963, 1967). His specimens ranged in age from birth to 5 years. In all PFC areas included in a meta-analysis of J. L. Conel's data set (BA 8–11 and 44–46), neuronal number measurements increase at every age point postnatally (0–72 months), save for between 3 and 6 months, where the neuron counts actually decrease. Neuron density is 55% higher in the frontal cortex of 2-year-olds than it is in adults, and 10% higher in 7-year-olds than in adults (Huttenlocher, 1990). Adult neuronal density in the frontal lobe is reached by 10 years of age (Huttenlocher, 1990).

Total gray matter volume is also greatest at the earlier stages of infancy, with sustained loss beginning around puberty. During infancy and childhood, gray matter volume in the frontal lobe is strongly and positively correlated with total brain volume, and a steep decline in gray matter proportional with volume occurs with age (Sowell et al., 2002). A longitudinal MRI study of gray matter development in juveniles from ages 4 to 21 discovered that the cortex matures in sequence from caudal to rostral (Gogtay et al., 2004) with an overall increase in gray matter from the ages of 4 to 12 and a decrease afterward (Pfefferbaum et al., 1994). An exception to this pattern is the frontal pole, where gray matter volume both peaks and begins to decrease earlier in childhood than it does in the rest of the PFC (Gogtay et al., 2004). However, cerebral energy metabolism studies have reported that lateral aspects of the PFC mature earlier in some ways than the most anterior regions, such as the frontal pole (Chugani and Phelps, 1991).

Within the frontal lobe, gray matter in the precentral gyrus develops the earliest, while more rostral regions, including the superior and inferior frontal gyri, mature later. The ventromedial areas of the PFC commonly reach maturity earlier than more lateral regions as well (Fuster, 2002). The dorsolateral PFC, a region involved in executive

functioning, begins to lose gray matter only at the end of adolescence. Reduction in gray matter volume continues in the frontal lobe until adulthood and is most pronounced in adolescence and early adulthood (Sowell et al., 1999b). Although this decrease in gray matter volume in childhood is correlated with age, one study found that gray matter thinning in the frontal lobe is significantly and positively related to verbal memory abilities, independent of the age of the child (Sowell et al., 2002).

At the same time, as gray matter volume decreases throughout childhood and adolescence, white matter experiences a related enlargement in volume as fiber tracts grow and myelinate. Myelination begins in the 29th gestational week with the brain stem, and the development of white matter also typically follows a caudal to rostral progression (Flechsigs, 1901, 1920). Humans (Giedd et al., 1999a; Gogtay et al., 2004; Klingberg et al., 1999; Levitt, 2003; Paus et al., 1999; Pfefferbaum et al., 1994; Watson et al., 2006) as well as our close relatives the chimpanzees (Watson et al., 2006) exhibit a nearly linear white matter volume increase and continued myelination until adolescence or early adulthood. Throughout the cortex as a whole, white matter volume increases 74% from infancy to mid-adolescence (Courchesne et al., 2000). The frontal lobe myelinates last, and in its most rostral regions myelination can continue well into the third decade of life (Sowell et al., 1999a). From ages 7 to 16, the frontal lobe experiences an increase in white matter volume that goes above and beyond what is expected from overall brain growth during these ages (Sowell et al., 2002). By 6 months of age, dendritic length is 5–10 times greater than it is at birth, yet dendritic length in the middle frontal gyrus is still only half of adult values at 2 years of age (Schade and Van Groenou, 1961). In contrast, adult dendritic length is reached in the visual cortex by the age of 1 year (Becker et al., 1984). The anteriomedial aspect of the frontal lobe, an area involved in attention and self-referential tasks (Zysset et al., 2003), is one of the last regions,

along with the temporal lobe, to myelinate postnatally (Barkovich, 2005). Interestingly, in one study, white matter development in the dorsolateral regions of the frontal cortex appears to vary far more according to age than it does in ventral or subcortical regions (Sowell et al., 1999a).

As with the U-shaped pattern of gray matter maturation, the steady and nearly linear increase in white matter that is observed through early adulthood has been tied to age-appropriate changes in cognition and behavior. Unsurprisingly, strong effects have been shown for cognitive abilities in which the PFC is known to be involved, including working memory, inhibitory control, and language. Working memory capacity is positively correlated with the development of connectivity between superior frontal and parietal lobes (Nagy et al., 2004; Olesen et al., 2003). Maturing connections between the PFC and striatum are credited with the development of inhibitory control, as measured by a performance on a go-nogo task in children (Durstun et al., 2002). “Inhibitory control” tasks rely on the more mature cognitive ability to suppress less relevant information and actions in favor of those more pertinent to the task at hand. Due to the immaturity of the PFC in the very young, children appear to differentially recruit these regions in inhibitory control tasks when compared to adults (Bunge et al., 2002; Durstun et al., 2002).

Synaptogenesis begins *in utero* at around the 20th gestational week. Like many other neurodevelopmental processes, the formation and organization of synapses in the PFC increases after birth, reaches a peak, and is followed by pruning and decline. Also as with the other processes described in this chapter, synaptogenesis occurs later in the PFC than it does in other areas. The middle frontal gyrus of the PFC reaches peak synaptic density late in infancy at 3.5 years, while auditory and visual cortex attains peak density at 3 months (Huttenlocher and Dabholkar, 1997; Huttenlocher and De Courten, 1987). At the age of 3 months, synaptic density in the PFC is less than half of what it will eventually reach, and

synapse elimination persists throughout adolescence. One early study suggested that synaptogenesis occurs at relatively the same time and rate in all parts of the neocortex in monkeys (Rakic et al., 1994).

The later maturation of more rostral regions of the cortex, particularly association cortex in the frontal lobe, is by now a well-established fact. Cerebral energy metabolism, a measure of regional activity, increases earlier in parietal, temporal, and occipital lobes (3 months) than it does in the PFC (8 months; Chugani and Phelps, 1986). Cytoarchitectonic asymmetries in PFC regions may also develop after they do in primary cortex (Amunts et al., 2003). Temporal association areas and regions with fronto-temporal connection also mature later. Diffusion tensor MRI (DTI) studies, which allow for the visualization of white matter tracts, have shown that a number of frontal connections mature more slowly than other white matter fibers. The uncinate fasciculus, which connects limbic system structures with the orbitofrontal cortex, a region involved with processing emotions and reward, and the head of the caudate nucleus, which possesses extensive interconnections with the PFC, do not fully mature until the third decade of life (Lebel et al., 2010). In infants, pyramidal neurons in regions that mature later, including the frontal lobe, have less complex dendritic trees than areas that mature early, such as primary sensorimotor cortices (Travis et al., 2005). Later in development, however, this trend is reversed; in adults, frontal association areas have the most complex dendritic trees (Jacobs et al., 1997, 2001).

During normal, healthy aging, gray matter volume and gray matter to white matter ratios decrease throughout the cortex. Whole brain volume decreases as well; in one study, individuals aged 71–80 years possess brain volumes that were close to those of healthy 2- and 3-year-old children, having decreased by about 26% (Courchesne et al., 2000). White matter volume in the cortex as a whole reaches a plateau around

age 30 and decreases slightly but steadily in later years during normal aging.

Although, as described above, much of the cortex experiences age-related change, the PFC has long been reported to suffer the highest degree of change associated with aging (Jernigan et al., 2001; Salat et al., 1999a,b). Gray matter volume in PFC is disproportionately affected in healthy aging (Raz et al., 1997), particularly in comparison to sensorimotor cortex (Coffey, 1994; Cowell et al., 2007) but also in comparison to the temporal lobe (De Carli et al., 1994; Kemper, 1994; Raz, 1996). Many of the cognitive functions that are known to decline in senescence are those subserved by the PFC: working memory, behavioral inhibition, decision-making, and meta-memory (Salat et al., 1999a). The dorsolateral and orbitofrontal regions experienced a loss of gray matter volume at the rate of 4.9% per decade in one sample that comprised individuals ranging from 48 to 77 years (Raz et al., 1997). However, a later study by some of the same researchers reported a significant loss of volume from middle age in orbitofrontal gray matter and frontal white matter, but not in lateral frontal gray matter (Raz et al., 2010).

Another study examined total PFC volume, gray matter volume in PFC, and white matter volume in PFC in “young elderly” (mean age = 70 years) and “old elderly” (mean age = 90 years). These researchers found that from 70 to 90, there appeared to be a decrease in the gray matter to white matter ratio, and that in the very old, the decrease in white matter volume is greater than the loss in gray matter volume (Salat et al., 1999a). There were also significant negative correlations between age and total PFC volume and between age and white matter volume.

However, not all aspects of the PFC undergo change in healthy aging or change in the same way. PFC subregions appear to exhibit differential patterns of aging. One study partitioned PFC volume into many comparisons, including orbital versus dorsal regions, lateral versus medial regions, and right hemisphere versus left (Cowell

et al., 2007). Age-related decreases in volume were significantly more prominent in medial than lateral PFC, particularly in male subjects. There was also significant age-related decline in dorsal medial PFC volume by age 70. In contrast to many reports on total gray and white matter volumes, synaptic density in layers III and V of the superior middle frontal gyrus (BA 9) remains largely constant from the years of 20 to 89 (Scheff et al., 2001). On the other hand, another study reported that synaptic density in the frontal lobe as a whole decreases with age (Masliah et al., 1993).

There is reduced activation in the aging PFC compared to younger subjects during visuospatial tasks (Solbakk et al., 2008) and working memory and attention tasks (Milham et al., 2002; Reuter-Lorenz, 2002). In the same vein, there also appear to be significant age-related declines in blood flow to the PFC (Waldemar, 1995). In contrast, some tasks, such as perceptual and episodic memory tasks, elicit greater response from the PFC of older individuals, which may denote a compensatory increase in recruitment of these regions (Cabeza et al., 2002; Grady, 2000).

## Evolution

### *Gross anatomical cross-species comparisons: Frontal lobe*

In many mammalian species, including primates, 9 out of 11 major brain regions (cerebellum, mesencephalon, diencephalon, olfactory cortex, parahippocampal cortex, hippocampus, neocortex, septum, and striatum) exhibit a robust covariance in size (Finlay et al., 2001). Deviations from allometry (Rilling, 2001) are of great interest to comparative neuroanatomists, as is the endeavor of accounting for structures whose growth does not scale with the rest of the brain. Yet, it has also been noted that an overemphasis on allometric relationships of large brain regions may obscure potentially important niche-specific adaptations



of certain species (Holloway, 2001). In response to this, mosaic evolution argues that selection can act on specific brain regions, resulting in the enlargement or diminution of particular functional subsystems in response to environmental demands (Barton, 2001; Barton and Harvey, 2000). The fact that brain regions that are connected functionally or anatomically tend to evolve together, independent of other structures, supports the importance of mosaic evolution as a factor (Barton and Harvey, 2000). Individual brain regions are likely linked, but not tightly so, to the size of other brain regions; brain evolution is both limited by the rules of neural development and is possibly the site of species-specific adaptations (Striedter, 2005).

In absolute terms, the human frontal lobe is three times larger than that of our closest living relatives, the great apes, but the significance of this fact has been debated (Passingham, 2002) and is still being considered. Moreover, does thinking of a complex and heterogeneous neural system like the frontal lobe as a discrete entity obscure important differences? In the past two decades, an increasing number of studies have examined the human frontal lobe and PFC in comparison to other primates, utilizing a wide variety of methodologies including stereology, MRI, minicolumn analysis, and DTI. The comparative analysis of specific regions within the frontal cortex has the ability to inform debates on the evolution of the human frontal lobe. In this section, we discuss comparative structural and microstructural work on the human PFC, concentrating on the question of whether, and if so, in what ways, the human PFC or any of its subdivisions differ from other primates, in particular, the apes.

Due to the current impossibility of accurately identifying the PFC while relying solely on gross anatomical landmarks like sulci and gyri (Semendeferi et al., 2002), most imaging studies have examined the frontal lobe as a whole. Based on older studies, such as the classical work by Brodmann (1912) that employed samples of

nonhuman primates that rarely included any great apes, or studies that only included one specimen per nonhuman species, it was long thought by many that human brain evolution was characterized by a disproportionate increase in the relative volume of the frontal lobes (Blinkov and Glezer, 1968; MacBride et al., 1999; Uylings and Van Eden, 1990). Although this finding was not without controversy at the time (Holloway, 1968; Passingham, 1973), a more recent comparison of the frontal cortex and its subdivisions in living specimens of humans and their closest living relatives using MRI revealed that this is not the case (Semendeferi and Damasio, 2000; Semendeferi et al., 1997, 2002). In the most recent of these studies (Semendeferi et al., 2002), the frontal cortex was parceled into two subdivisions that are accurately identifiable using gross anatomical markers: the cortex of the precentral gyrus and the remaining rostral frontal cortex on the dorsolateral, medial, and orbital surfaces of the frontal lobe. To date, this is the largest and most comprehensive attempt to examine the human frontal cortex in concert with that of the other living hominoids. The nonhuman sample comprises 6 chimpanzees, 3 bonobos, 2 gorillas, 4 orangutans, 4 gibbons, and 5 macaques; this group of 20 individual specimens was compared with 10 human specimens. Although the human frontal cortex is clearly bigger than that of the great apes in absolute terms, as a whole, it is not larger than expected for an ape brain of human size, based on both logarithmic and linear regressions (Semendeferi et al., 2002). Similarly, the proportion of the cortex occupied by the frontal cortex is not greater in humans than it is in great apes. The two partitions of the frontal cortex, the precentral gyrus and the rostral frontal cortex, were likewise no larger than expected in humans. These findings support previous work on the issue of absolute and relative frontal cortex size (Semendeferi and Damasio, 2000; Semendeferi et al., 1997).

When the relative volume of the dorsolateral, mesial, and orbital subdivisions of the frontal lobe is calculated in humans and great apes, also

utilizing MRI scans, human values again do not differ from that expected for a human brain of great ape size (Semendeferi et al., 1997). Volumes were estimated using sulci that are homologous across great apes and humans. In all species, the orbital subdivision of the frontal lobe is the smallest, followed by the mesial and dorsolateral sectors. The relative volumes of all three subdivisions are very similar across all species, including humans. Cortical surface measurements, which were also performed for the entire frontal lobe and for the three subdivisions, likewise did not reveal any relative differences between humans and the other primates. Interestingly, an examination of the scaling of frontal cortex in mammalian species, including 25 primates, revealed that the order Primates is characterized by a hyperscaled frontal cortex that increases in size relative to both the isocortex and the whole brain with strongly positive allometry (Bush and Allman, 2004). The PFC is furthermore unique in primates in that it includes a small-celled granular layer absent in other mammals, although nonprimate mammals do possess analogues to the PFC (Uylings et al., 2003).

Although studying the frontal lobe as a whole is an important stage in our endeavor to determine the anatomical substrates underlying the uniquely human in human cognition, it is also merely a first step. The frontal lobe comprises numerous anatomical components and diverse functional areas, and, therefore, consideration of it as a discrete unit can only tell us so much. A number of recent studies have examined the relative size of gray and white matter in the frontal lobe or PFC, while others have examined the volume, neuron density, and columnar organization of functional subregions within the PFC.

When white matter is considered separately from gray matter, the human frontal lobe also remains undistinguished from apes in terms of overall relative volume (Schenker et al., 2005). White matter in the frontal lobes was divided into two sectors: the white matter immediately underlying the cortex, which was termed “gyral white matter,” and the rest of white matter, or “core.”

The relative volume of gray matter and the two sectors of white matter in the frontal lobe was measured using MRIs of living humans and apes. The dorsolateral, mesial, and orbital subdivisions of the frontal lobe were outlined, and the relationship between cortex and gyral white matter within each subdivision was analyzed. In all three subdivisions of the frontal lobe, human values for core white matter volume were as large as expected. However, gyral white matter, which comprises white matter directly underneath the gyrus, was larger than anticipated in both the frontal and temporal lobes. Gyral white matter myelinates later in development than core white matter (Yakovlev and LeCours, 1967) and may connect neighboring cortical regions which lie on opposite sides of the gyrus (Van Essen, 1997). Thus, enlarged gyral white matter may indicate increased interconnectivity within and between adjacent cortical regions.

The question of whether the PFC, or its gray or white matter subdivisions, is differentially enlarged in humans is a matter that has received some attention as of late. As mentioned, it is nearly impossible to accurately identify the PFC, especially across a wide cross-section of species, based solely on gross anatomical features. One study measured gray matter, white matter, and total volumes for the PFC in humans, bonobos, chimpanzees, gorillas, orangutans, gibbons, and several monkey species (Schoenemann et al., 2005). In this study, the PFC was demarcated in MRIs, using the region of the frontal cortex anterior to the genu of the corpus callosum as a proxy definition for PFC. The authors concluded that PFC white matter is significantly larger in humans than in nonhuman primates, but that there is no difference between humans and other primates regarding PFC gray matter. However, there is some concern that, as cytoarchitectonic criteria of great apes were not used, that the volume of the PFC as defined in relation to the genu of the corpus callosum is underestimated in these species (Sherwood et al., 2005). Additionally, when the human data from this study are regressed to

a best-fit line that is based only on the great ape data, rather than all of the nonhuman primate data, white matter in the PFC is at best, only slightly larger in humans than expected. Also of note is a recent study examining nonhuman anthropoids, including great apes, which reported that the hyperscaling of both the frontal lobe and the whole neocortex to the rest of the brain is primarily due to frontal white matter volumes (Smaers et al., 2010, 2011).

***Comparative work on PFC subdivisions:  
Volumetric, DTI, and micolumn studies***

Although the frontal lobe as a whole does not seem to have been differentially enlarged throughout human evolution, there is evidence for its reorganization, as some regions with known functional correlates are either bigger or smaller in the human brain than expected when

compared with the same region in great apes. Several of these functional subdivisions of the PFC that are homologous across humans and great apes have been examined histologically in a comparative context (Fig. 3).

Limbic frontal cortex, BA 13, occupies a portion of the orbitofrontal cortex and is part of the neural substrate underlying emotional reactions to social stimuli (Damasio and Van Hoesen, 1983). It is found in the posterior orbitofrontal cortex and shares strong reciprocal connections with the insular, temporal polar, and parahippocampal cortices, as well as with basal forebrain structures like the ventral striatum, nucleus basalis of Meynert, and amygdala (Nauta, 1962; Van Hoesen, 1981). BA 13 has been identified across humans, chimpanzees, bonobos, gorillas, orangutans, and gibbons, and its volume was estimated in all species using stereological analyses (Semendeferi et al., 1998). BA 13 is conserved in its structure, and features such as size

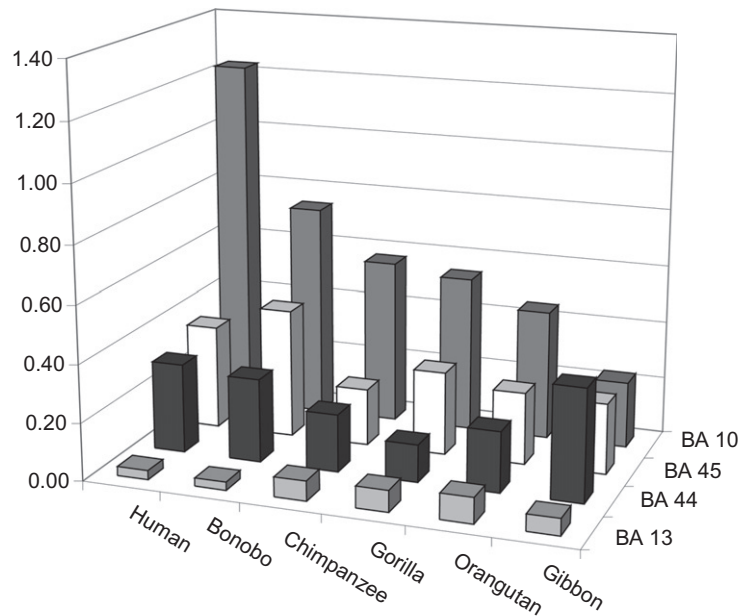


Fig. 3. Relative volumes (as a percentage of whole brain size) of four regions of the prefrontal cortex in humans and great apes. Data from Schenker (2007) and Semendeferi et al. (1998, 2001).

of cortical layers, density of neurons, and space available for connections are similar across hominoids, with only subtle differences present. However, in contrast to the homogeneity found in its organization, variation is present in the relative size of this cortical area, when it is considered as a percentage of total brain volume. Area 13 occupies a smaller percentage of the human and bonobo brains than it does in other hominoid species; the absolute size of BA 13 is quite similar among humans and all of the great apes, save the bonobos (Semendeferi et al., 1998). Its volume is not correlated with the volume of the brain as a whole. It is parsimonious to suggest that BA 13 was part of the Plio-Pleistocene hominoid and hominid brain; BA 13 may have hypothetically occupied a restricted area in the most posterior parts of the medial orbital gyrus and the posterior orbital gyrus, with structural features similar to those present in extant species.

BA 10, which lies at the most anterior aspect of the PFC, is a region of association cortex known to be involved in higher cognitive functions, such as planning future actions and decision-making (Fuster, 2008). BA 10, also called the frontal pole in hominoids, has been identified across humans and most of the apes (Semendeferi et al., 2001). Area 10 has similar cytoarchitectonic features among hominoids, and it forms the entirety of the frontal pole in humans, bonobos, chimpanzees, orangutans, and gibbons, but its presence is not yet established in gorillas. It has two components in the macaque brain: one on the dorsolateral aspect and one on the orbital. In gibbons, area 10 occupies only the orbital sector of the frontal pole, while in chimpanzees, orangutans, and humans, it occupies both sectors. Aspects of the frontal pole's organization vary slightly across hominoid species, including the relative width of its cortical layers and the space available for connections. BA 10 is larger in humans than in apes both in absolute terms and relative to the rest of the brain. Based on least squares regression, the expected volume for BA 10 in an ape brain of

human size is little more than half of the observed volume. Supragranular layers II and III also have more space between neurons in the human brain, possibly for connections with other higher-order association areas, a hypothesis lent further support by recent findings regarding minicolumn size in the human PFC, which are discussed in more detail later in this chapter (Semendeferi et al., 2011). This suggests that the neural substrates supporting cognitive functions associated with this part of the cortex enlarged and became specialized during hominid evolution. In the great apes, BA 10 expanded from its restricted orbital location and came to occupy the entire frontal pole in hominoids.

Broca's area, or BAs 44 and 45, comprises part of the inferior frontal gyrus in the human brain. These regions are involved in language production, particularly linguistic motor control, sequencing, planning, syntax, and phonological processing (Broca, 1861; Damasio et al., 2004; Price, 2000). Given their association with language production, the question of their presence and homology in nonhuman primates is of obvious interest. Based on cytoarchitectonic criteria, both regions have been identified in the inferior frontal gyrus of chimpanzees, bonobos, gorillas, and orangutans (Schenker et al., 2008) and display similar cytoarchitectonic characteristics in all hominoid species examined, including humans. There are no relative volumetric differences in Broca's area between humans and the apes (Schenker, 2007). In humans, there is a distinct trend for both BA 44 and 45 to be larger in the left hemisphere than the right; this trend reaches significance in BA 44 for males and in BA 45 for females (Uylings et al., 2006). This asymmetry is not present in chimpanzees (Schenker et al., 2010), suggesting that Broca's area in the left hemisphere expanded in relative size during human evolution, possibly as an adaptation for our species' language abilities. The arcuate fasciculus, a white matter fiber tract that connects regions in the dorsolateral frontal cortex to language regions in the temporal cortex, is more

complex in humans than in chimpanzees (Rilling et al., 2008a) and also exhibits a population-level leftward asymmetry in humans, though not in chimpanzees (Glasser and Rilling, 2008).

Thus, although the PFC as a whole is not differentially enlarged over the course of human brain evolution (Smaers et al., 2011), it seems that there is strong evidence for reorganization within the PFC. In addition to volumetric and asymmetry differences among subdivisions, spacing distance between neurons in layer III also sets the human PFC apart. The human frontal pole and Broca's area, BA 44/45, both exhibit differences in columnar organization when compared with the same regions in great apes (Fig. 4). Spacing distance between neurons (HSD, or horizontal spacing distance) and gray level ratio (GLR that measures the area fraction occupied by cell bodies) have been measured in both of these regions, across a histological sample of humans and apes. The combination of increased HSD and decreased GLR values can be used to identify the presence of wider minicolumns in the cortex, signifying enlarged intracolumnar and intercolumnar

neuropil space in layer III (Buxhoeveden et al., 1996, 2001; see Semendeferi et al., 2011 for an in-depth discussion of the methods).

HSD is significantly larger in humans than in the great apes in both regions of Broca's area, while GLR is lower in humans than in all of the great apes (Schenker et al., 2008), indicating wider minicolumns. However, relative to brain size, humans have narrower minicolumns than great apes in both regions. Wider minicolumns have likewise been found in the human frontal pole, or BA 10, when it is compared with apes (Semendeferi et al., 2011), based on HSD and GLR measurements. Spacing distance, as measured by HSD, in the human frontal pole, in particular, stood out by being 30% larger than in the frontal pole of the other species. However, as in BA 44/45, when these measurements are placed within the context of overall brain size, humans have relatively narrower minicolumns in BA 10 than do apes.

Within the human brain, the frontal pole also has wider minicolumns than BA 3 (primary somatosensory cortex) or BA 17 (primary visual

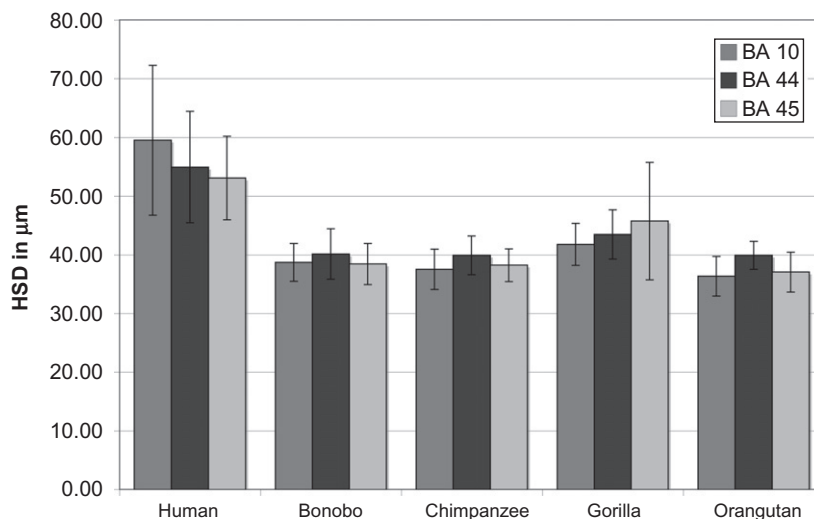


Fig. 4. Horizontal spacing distance ( $\mu\text{m}$ ) in three regions of the prefrontal cortex (BA 10, 44, and 45) in all species examined. Data from Schenker et al. (2008) and Semendeferi et al. (2011).

cortex), although this pattern does not appear in any apes (Semendeferi et al., 2011). In apes, BA 4 (primary motor cortex) possesses wider minicolumns than BA 10, although HSD was not significantly different between BA 10 and BA 4 in humans. Minicolumns were found to be wider in dorsolateral, medial, and orbital regions of the PFC than in BA 17 in normal human adult brains (Buxhoeveden et al., 2006), which supports the hypothesis that minicolumns are wider throughout the PFC in humans. Another comparison (Casanova et al., 2006) also reports a very similar pattern to those previously described; in that study's control humans, interneuronal distance is reported to be highest in PFC region BA 9, followed closely by BA 4, then BA 3 and BA 17.

This recent research suggests that neurons in layer III are significantly more widely spaced throughout the PFC in humans than they are in great apes, while spacing in sensorimotor and visual cortex is similar in humans and apes. One interpretation of the functional significance of absolutely wider minicolumns, such as those noted in this and the previously mentioned studies, is that they are associated with being more generalized processors (Gustafsson, 1997, 2004). Minicolumns largely comprise pyramidal neurons in layer III, along with their myelinated axons and apical dendrites (DeFelipe, 2005; Peters and Sethares, 1996). The human PFC is also known to exhibit more complex dendritic branching than visual cortex (Elston et al., 2006). Interspecific differences in dendritic structure have also been noted; pyramidal cells in the human PFC are more branched and spinous than those in the temporal and occipital lobes and are also more branched and spinous than those in the PFC of macaques and marmosets (Elston et al., 2001). In the human PFC, layer III projections possess more branched and spinous dendritic arbors than in temporal, occipital, or parietal cortex (Elston et al., 2001; Jacobs et al., 2001; Petanjek et al., 2008). The long-range cortico-cortical projections of layer IIIc neurons (Lewis et al., 2002), in

particular, are thought to be critical to working memory and other higher-order cognitive processes in primates (Elston et al., 2006; Fuster, 2000b), suggesting that the reported differences in dendritic tree structure are related to cognitive differences (Zeba et al., 2008). These findings may be indicative of some degree of reorganization characteristic of the human PFC in general, and possibly the frontal lobe as a whole. Human minicolumns are reported to be wider in the lateral superior temporal cortex (BA 22) than in chimpanzees (Buxhoeveden et al., 2001), which suggests that wider minicolumns may be a human trait throughout association cortex beyond the PFC.

A novel class of neurons, Von Economo neurons (VENs), has been identified in the anterior cingulate cortex and frontal insula in humans (Allman et al., 2002; Fajardo et al., 2008) and great apes (Allman et al., 2010; Nimchinsky et al., 1999), though not in other nonhuman primates (Nimchinsky et al., 1999). Frontoinsular cortex and the anterior cingulate project to the frontal pole, the other parts of frontal and insular cortex, the septum, and the amygdala. These specialized large projection neurons are also present in several other species of large-brained social mammals, including elephants (Hakeem et al., 2009) and cetaceans (Butti et al., 2009), leading to the proposal that they are the result of convergent evolution in large-brained mammals that require rapid computation of social information (Allman et al., 2010). Also of note is the fact that VENs appear most numerous on the crowns of gyri, which when combined with the finding that gyral white matter is expanded in humans (Schenker et al., 2005) suggests that gyral areas of the PFC may have undergone specific changes during human evolution.

In the realm of neurotransmitters, differences in innervation have been found in the PFC of humans and chimpanzees, both when they are compared to the PFC of macaques, and when compared to primary motor cortex in all three species. In humans and chimpanzees, both BA 9

and 32, which are involved in working memory and theory of mind, respectively, possessed a higher number of dopaminergic afferents in layers III, V, and VI (Raghanti et al., 2008a) and greater density of serotonin transporter-immunoreactive axons in layers V and VI (Raghanti et al., 2008b); for a lengthier discussion of this line of work, see Chapter 11.

Thus, the past 15 years of research into comparative neuroanatomy support the idea (Allen, 2009; Semendeferi et al., 2002) that human brain evolution is characterized by distinct changes in the local circuitry and interconnectivity of the PFC. In particular, modifications throughout the human PFC include increased gyral white matter, a relatively smaller BA 13, a relatively larger BA 10, and greater spacing between layer III neurons in BA 10, 44, and 45. Microstructural changes shared among humans and our closest relatives, the African apes, include VENS.

## Pathology

The PFC is affected in a number of conditions and disorders. Here we discuss the impact of autism and schizophrenia on the PFC and frontal lobe in terms of histological and microscopic studies. The late maturation of the PFC, as detailed in the section “Development,” makes it particularly vulnerable to developmental disorders (Bradshaw and Sheppard, 2000; Dumontheil et al., 2008; Ghika, 2008). The dorsolateral PFC and anterior cingulate cortex are two regions of the PFC that are affected in both autism and schizophrenia. Collectively, along with lateral orbital PFC, interconnected regions of the basal ganglia, and the supplementary motor area, these regions are called the frontostriatal system, and they work together to subserve many of the cognitive capacities that characterize the human species (Goldman-Rakic, 1988).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social cognition, theory of mind,

language, communication, and by stereotypical patterns of behavior (Geschwind, 2009). ASD has a complex and often inconsistent neuropathological profile (Salmond et al., 2007; Schmitz and Rezaie, 2008), likely due to the “spectrum” aspect of the disorder; the phenotype of ASD is heterogeneous, and it is probable that there are significant interindividual differences in the samples examined.

Children with ASD typically display larger brains than average throughout their infancy and toddler years, but by school age these global differences disappear, and brain volumes are normal or even slightly smaller than normal (Courchesne et al., 2011; Redcay and Courchesne, 2005). This trajectory is strongly suggestive of prenatal or quite early postnatal factors playing the determining role in the development of this neuropathology. Head circumference measurements, which are highly correlated with whole brain volumes early in development, are notably larger in infants and very young children who are diagnosed (sometimes later, due to their age) with ASD (Courchesne et al., 2004; Dementieva et al., 2005). This is suspected to be the result of abnormal white and gray matter developmental processes; while head circumference is normal or even below normal in early infancy, it then reliably increases to the 84th percentile between 6 and 14 months. Between the second and third years of life, 90% of autistic children examined in one study had head circumferences larger than average (Courchesne et al., 2001).

These global differences are so robust that young autistic and nonautistic brains can be distinguished solely on cerebral and cerebellar volumes, with 95% accuracy (Akshoomoff et al., 2004). Overgrowth is most marked in frontal and temporal lobes, and far less so in occipital (Carper et al., 2002). However, this differential enlargement in the ASD brain stops after early childhood (Dawson et al., 2007), and autopsies of adult individuals with ASD report average brain weight in the vast majority of cases

(Courchesne et al., 1999), while one even reported a reduced frontal lobe volume in adults (Schmitz et al., 2007). A recent analysis of over 500 MRIs of autistic individuals from age 1 to 50 years confirms the pattern seen in autopsies (Courchesne et al., 2011).

Several structural MRI studies from the past decade corroborate the existence of abnormalities in the frontal regions. Carper and Courchesne (2005) divided the frontal lobe into dorsolateral, medial frontal, precentral gyrus, and orbitofrontal regions in children with ASD and measured their respective volumes. The dorsolateral and medial frontal cortices were significantly enlarged in individuals aged 2–5 years when compared with controls. Frontal sulci are shifted anteriorly in older autistic children, a finding consistent with early overgrowth in this region (Levitt et al., 2003). Development of the dorsolateral PFC seems particularly disrupted in autism; there is an increase in size of 48% from ages 2 to 9 in normal controls, but only a 10% increase in age-matched autistic children. Thus, overgrowth occurs quite early in autistic children, and there is subsequently a striking lack of the age-related increase in volume seen in normal developmental processes, as detailed in the section “Development.” Accordingly, the frontal cortex of autistic adults contains abnormally high levels of proapoptotic molecules and decreased amounts of antiapoptotic ones (Araghi-Niknam and Fatemi, 2003).

When gray and white matter volumes within the frontal lobe are considered separately, gray matter is significantly larger in individuals with ASD regardless of the age of the sample; autistic individuals in these studies ranged from 7–15 years of age in Palmen et al. (2005) to 13–29 years of age in Hazlett et al. (2006). Structural MRI studies have also noted decreases of gray matter in the left inferior frontal gyrus in young adults (Abell et al., 1999). However, some argue that it is white matter volume, not gray matter volume, that is unique in autistic children; white matter tracts in the PFC of autistic children from 5 to

11 are reported to be 36% larger than those in normal controls (Herbert et al., 2004) and myelination occurs prematurely throughout the frontal cortex (Ben Bashat et al., 2007). DTI has noted white matter abnormalities in both dorsolateral and medial PFC (Barnea-Goraly et al., 2004).

Regardless of whether gray matter, white matter, or both experience abnormal development in autistic children, the initial overgrowth has been presumed to lead to abnormal connectivity patterns forming early in development. These abnormalities in neural networks in turn result in the behaviors that characterize ASD. This supposition has been borne out by more recent MRI studies of autistic individuals, which note that executive function deficits observed in autistic children are not correlated to gross measures such as dorsolateral PFC volume (Griebeling et al., 2010). Further evidence for abnormalities in neurogenesis and neuronal migration comes from the recent discovery that there are poorly defined boundaries between gray and white matter in the frontal lobe (Avino and Hutsler, 2010) and that the dorsolateral PFC, in particular, has less clear lamination (Mukaetova-Ladinska et al., 2004).

Although histological studies of young children with autism are rare (Bauman and Kemper, 2005), those that exist confirm abnormalities in both gray and white matter volumes during development. While these volumetric abnormalities occur throughout much of the brain, the frontal lobes, in particular, exhibit a noteworthy enlargement of both gray and white matter in toddlers (Carper et al., 2002). There are more spindle cells, specialized pyramidal cells involved in social information processing, in the frontal lobes of autistic children (Santos et al., 2010), although this difference may not exist in adult brains (Kennedy et al., 2007). Postmortem histological studies have likewise not produced a consensus on what the neuropathology of autism looks like in adults. An early histological study found few abnormalities in the neocortex; there were



smaller and more closely packed neurons and less distinct laminar architecture in anterior cingulate in eight of the nine brains (Kemper and Bauman, 1998).

By far, the most common type of histological study on autistic brains is minicolumnar analysis, which was described in more detail earlier in this article. An examination of columnar organization has revealed intriguing regional differences within the PFC in both autistic children and adults. The columnar organization of dorsolateral PFC (BA 9) is disrupted in adults with ASD; minicolumns are unusually narrow compared to controls (Buxhoeveden et al., 2006; Casanova et al., 2002, 2006). There is also increased neuronal density in BA 9, suggesting that there are more neurons than expected in that region. Although neuropil space was reduced in dorsolateral PFC (BA 9) in autistic brains, this difference was not significant. There is significantly greater neuropil space in autistic brains in the frontal pole (BA 10) and anterior cingulate (BA 24) than in normal, age-matched controls (Casanova et al., 2006). There were no differences seen in orbitofrontal cortex (BA 11) or the part of Broca's area examined in the same study (BA 44). However, when the frontal cortex is parceled into dorsolateral, mesial, and orbital regions, narrower minicolumns can be seen throughout the entire frontal cortex, especially the dorsolateral and orbitofrontal sectors (Buxhoeveden et al., 2006). Neither of the aforementioned studies noticed any differences between autistic and normal brains in visual or sensorimotor cortex. Minicolumnar pathology has been suggested as an important characteristic of a number of developmental and psychological disorders, including ASD and schizophrenia (Casanova and Tillquist, 2008).

There have been many attempts over the years to discern reliable biomarkers for early detection of autism (Pierce et al., 2009), but most candidates are not present in all or even most autistic individuals examined. However, VENs, specialized projection neurons discussed above

in this article, appear to be involved in autism; in one study, autistic brains fell into two groups, where VENs were either present in significantly higher numbers or significantly lower numbers than in controls (Simms et al., 2009). Additionally, there are hints that immune dysfunction is common in autism. Microglia, glial cells crucial to immune response, have been found to exhibit abnormalities in autistic individuals; microglia were active in the dorsolateral PFC in 70% of 13 cases, and also displayed increased density and somal enlargement (Morgan et al., 2010).

There is not a strong consensus among the data regarding what abnormalities are present in the brains of schizophrenics, nor where these abnormalities are located. Autopsies of schizophrenics have reported decreases in total brain weight (Brown et al., 1986; Bruton et al., 1990; Pakkenberg, 1987) and a number have reported reduced head circumference in infants, indicative of diminished total brain volume (McNeil et al., 1993). However, only 22% of 50 structural MRI studies found differences between the whole brain, primarily with brain size decreased (Shenton et al., 2001). One possible explanation for this degree of incongruity is that any volumetric variation in the whole cortex may simply be too small to be detected via MRI; one meta-analysis of total brain volumes in 58 studies found that mean cerebral volume is 2% smaller in schizophrenics (Wright et al., 2000). The majority of studies report ventricular enlargement as well as decreased hippocampal volume (Arnold, 1999; Harrison, 1999; Honea et al., 2005).

This divergence of opinion extends to the frontal lobe and the PFC. In a meta-analysis of structural MRI literature, 60% of 50 studies found some difference between the frontal lobes of schizophrenic and normal control brains (Shenton et al., 2001). Once again, volumetric differences in a region as large as the frontal lobe may be undetectable by MRI studies (Shenton et al., 2001); one histological study reported reduction in PFC

cortical thickness of 8%, which is noteworthy but not statistically significant (Selemon et al., 1998). There are few structural MRI studies of schizophrenic individuals that address frontal subdivisions, but those that do describe volumetric abnormalities in a host of brain regions, including the inferior frontal gyrus and the medial frontal gyrus in the PFC; over half of the studies examined in a meta-analysis report volume deficits in the left hemisphere for both of these regions (Honea et al., 2005). Hundred percent of 12 studies that looked specifically at superior temporal gyrus gray matter report dissimilarities (Shenton et al., 2001), while the majority of studies (10 out of 15) that looked at both gray matter and white matter in the same region also reported differences between schizophrenic brains and controls.

Cytoarchitectonic findings are similarly divided. In a meta-analysis (Selemon, 2001), four studies report increased neuronal density in BA 9 in schizophrenic brains (Rajkowska et al., 1998; Rajkowska-Markow et al., 1999; Selemon et al., 1995, 2003), while one reported increased neuronal density in BA 46 (Selemon et al., 1998). Three studies reported no differences in neuronal density in BA 24 (Benes, 1991; Cotter et al., 2000; Kalus et al., 1997), while later studies have found a reduction of neuronal density specifically in calbindin-binding neurons in BA 24 (Cotter et al., 2002). Another study that examined BA 10 found decreased small neuron density but increased pyramid density (Benes et al., 1991). The anterior cingulate cortex in schizophrenics is characterized by some as having smaller and more widely spaced neurons in layer II (Benes and Bird, 1987; Benes et al., 1987). Decreased neuronal density has also been reported in the anterior cingulate (Benes et al., 1986; Benes et al., 1991) and dorsolateral PFCs (Benes et al., 1986). However, other studies report that there is in fact an increase in the density of smaller neurons in dorsolateral PFC, along with a decrease in the neuropil space (Rajkowska et al., 1998; Selemon et al., 1998). Decreased neuronal

size has also been observed in both the anterior cingulate (Benes et al., 1986) and in the dorsolateral PFC (Rajkowska et al., 1998).

There is decreased neuronal density throughout several regions of the PFC, while some regions exhibit increased cellular density. The regions with decreased density include primary motor cortex (BA 4), the frontal pole (BA 10), and the anterior cingulate, BA 24 (Benes et al., 1986), although another study reported no differences in neuronal density in motor cortex (Arnold et al., 1995). Smaller and more dispersed neurons have also been reported for BA 24 (Benes and Bird, 1987). Throughout dorsolateral PFC (BA 9 and 46), neuronal density is increased (Goldman-Rakic and Selemon, 1997) by 17% in BA 9 (Selemon et al., 1995) and 21% in 46 (Selemon et al., 1998). Minicolumnar analysis of dorsolateral PFC also reports increased cell density in schizophrenic BA 9 (Casanova et al., 2008). Other studies examining the density of neurons in dorsolateral PFC (BA 9) found no differences in the brains of schizophrenic individuals (Akbarian et al., 1995), while others report decreased neuronal density in the same region (Selemon et al., 1995). Pyramidal neurons in layer III of frontal cortex display significantly decreased density of dendritic spines (Garey et al., 1998), which may explain the loss of cortical volume reported in some regions of the frontal lobe in schizophrenics without a concomitant loss in neuron number. This hypothesis is further supported by reduced synaptophysin protein in dorsolateral PFC, a finding which implies reduced presence of synapses (Glantz and Lewis, 1997; Perrone-Bizzozero et al., 1996).

The microstructural abnormalities that characterize the frontal pole, dorsolateral PFC, and anterior cingulate cortex in schizophrenia do not seem to extend to all regions of the PFC; an examination of BA 9 and 44, while confirming a 12% increase in neuronal density in BA 9, did not find any differences regarding neuronal density, glial density, cortical thickness, or somal size in BA 44 (Selemon et al., 2003).

## Conclusion

The human brain is the largest primate brain, but accumulating evidence suggests that absolute size may not be the only variable that sets humans apart from other primates. Specific reorganizational events in neural circuitry took place, either as a result of adjusting to increases in total brain size or as adaptive responses to specific selection pressures (Krubitzer and Kaas, 2005; Krubitzer and Kahn, 2003). While the human frontal lobe is not enlarged in humans relative to apes, there are indeed significant volumetric and microstructural differences within the PFC. Minicolumns, the vertical arrangement of neurons that is a vestige of the radial migration of neurons during development, are wider in humans than in great apes in all PFC regions where they have been examined (BA 10, 44, and 45), but not in sensorimotor cortex or visual cortex. Additionally, minicolumns in these late-developing PFC regions are the most widely spaced in the human cortex, while motor cortex possesses the most widely spaced minicolumns in all of the apes. It is only after the split from the last common ancestor with the chimpanzees that PFC neuronal spacing became the largest, compared to sensorimotor and visual cortex in the human brain and compared to PFC in the other apes.

There are other important volumetric differences in the human PFC that suggest reorganization during human evolution. Gyrus white matter is enlarged in the human frontal lobe compared to the great apes, although human frontal lobe gray matter volume is not. Limbic frontal area 13 is relatively smaller in humans than it is in great apes, while frontal pole (BA 10) is relatively larger. There are no relative volumetric differences in Broca's area, BA 44 and 45, but chimpanzees do not exhibit the leftward asymmetry that characterizes human Broca's area. Thus, it appears that frontal pole and left Broca's area expanded in humans after the split with the African apes, while area 13 diminished.

Living in complex environments has been recognized as a considerable factor in the evolution

of primate cognition (Byrne, 2007; Rilling et al., 2008b; Whiten, 2010). As discussed in the Introduction, the PFC is crucial for normal executive and social-emotional functioning, a suite of cognitive abilities that humans needed for navigating both complex social groups and changeable, hazardous environments throughout their evolution. Normal frontal lobe development and function are also compromised in several neurological and psychiatric disorders, including autism. We believe that a phylogenetically recent reorganization of frontal cortical circuitry took place (involving an increase in size of some regions, the decrease of others, and increased neuronal spacing distance) that may be critical to the emergence of human-specific executive and social-emotional functions. Relatedly, a developmental pathology in these same systems underlies many neurological disorders, including autism, which involves disturbances in both executive and socio-emotional functioning. Anatomically, autism is characterized by early overgrowth, and then diminution, throughout the PFC.

The PFC exhibits a notably lengthened development, and is one of the last regions of the brain to complete maturation, as based on anatomical indices including cortical thickness, gray matter volume, white matter volume, neurogenesis, synaptic density, and degree of dendritic development. The majority of these developmental processes follow a U-shaped trajectory, with an initial peak and then decline. In general, development proceeds in a caudal to rostral fashion, with the most anterior regions maturing the latest. However, a few exceptions exist; the most rostral area of the PFC, the frontal pole, matures earlier than lateral PFC, as do the ventromedial regions. Just as the unusually prolonged development of the human PFC translates into increased vulnerability to disorders such as autism, it may also enable some of the microstructural species differences described in this chapter.

In conclusion, the field of comparative neuroanatomy holds great promise in its potential to aid in the elucidation of the cognitive difference between humans and other primates, as well as

when these differences may have arisen on an evolutionary timescale. Conventional wisdom holds that there is a grade shift in cognitive abilities between humans and extant great apes (Tomasello, 1998; Tomasello and Rakoczy, 2003), suggesting that many traits are the sole province of human intelligence, and evolved sometime after chimpanzee and hominin lineages diverged from a common ancestor. At this time, it seems that evolution in human ancestors was accompanied by discrete modifications in local circuitry and interconnectivity of selected parts of the brain. These modifications may have also predisposed humans to a number of neurological and psychological disorders, including autism and schizophrenia.

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