

# 2

## BUILDING A BRAIN

*This chapter describes several aspects of the pre- and postnatal development of the brain, with specific reference to humans where data permit. In the first section, some of the stages of prenatal brain development are outlined, including the proliferation, migration, and differentiation of cells such that they give rise to particular brain structures. Next, a basic overview of primate brain anatomy is provided with specific emphasis on the neocortex. A distinction is made between two dimensions of the cortex: its areal or regional structure, and its laminar (layered) structure. The following section on postnatal development reports that while human brain volume quadruples between birth and adulthood, this is mainly due to increases in nerve fiber bundles, and myelination, but not additional neurons. Further, some measures of structural and neurophysiological brain development, such as the density of synaptic contacts, show a characteristic “rise and fall” during postnatal development. The following section addresses the question of the extent to which the differentiation of the neocortex into areas or regions is prespecified. The “protomap” hypothesis states that the areal differentiation of the cortex is determined by intrinsic molecular markers or prespecification of the proliferative zone. In contrast, the “protocortex” hypothesis suggests that an initially undifferentiated protocortex is divided up largely as a result of input through projections from the thalamus and is activity-dependent. A review of currently available evidence supports a middle-ground view in which large-scale regions are prespecified, while small-scale functional areas require activity-dependent processes. This implies that cortical networks impose architectural constraints on the representations that emerge within them, but there are no innate representations. Further evidence in support of this conclusion comes from a variety of studies on cortical plasticity in newborn rodents. In some of these studies sensory inputs to cortical areas are diverted to other regions, or pieces of cortex are transplanted from one region to another. In both of these cases cortical tissue acquires representations according to the nature of the input, rather than its developmental origins. In some cases these representations can even be used to guide the behavior of the animal. With some caveats, I suggest that similar conclusions*



can be drawn about primate cortical development and plasticity. The next section focuses on a clear area of difference between human cortical development and that of other primates: the very extended period of postnatal development. This greatly extended period reveals two differential aspects of cortical development not as clearly evident in other primates: an inside-out pattern of development of layers, and differences in the timing of development across regions. These differential aspects of human cortical development will provide the basis for associations between brain and cognitive development described in later chapters. The chapter concludes with discussion of the postnatal development of some subcortical structures, and with a brief review of our knowledge of the development of neurotransmitters and modulators. The developmental levels of several neurotransmitters mirror aspects of the differential structural development of cortex.

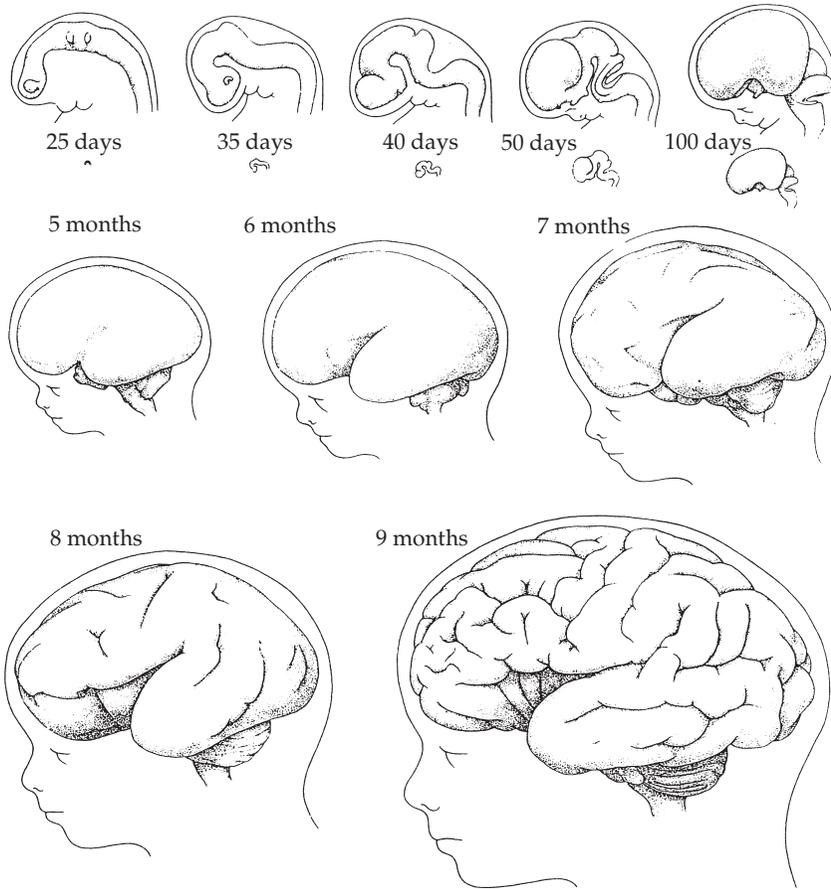


## 2.1 PRENATAL BRAIN DEVELOPMENT

The sequence of events during the prenatal development of the human brain closely resembles that of many other vertebrates. Shortly after conception a fertilized cell undergoes a rapid process of cell division, resulting in a cluster of proliferating cells (called the blastocyst) that somewhat resembles a bunch of grapes. Within a few days, the blastocyst differentiates into a three-layered structure (the embryonic disk). Each of these layers will further differentiate into a major organic system. The endoderm (inner layer) turns into the set of internal organs (digestive, respiratory, etc.), the mesoderm (middle layer) turns into the skeletal and muscular structures, and the ectoderm (outer layer) gives rise to the skin surface and the nervous system (including the perceptual organs).

The nervous system itself begins with a process known as *neurulation*. A portion of the ectoderm begins to fold in on itself to form a hollow cylinder called the *neural tube*. The neural tube differentiates along three dimensions: length, circumference, and radius. The length dimension gives rise to the major subdivisions of the central nervous system, with the forebrain and midbrain arising at one end and the spinal cord at the other. The end which will become the spinal cord differentiates into a series of repeated units or segments, while the front end of the neural tube organizes differently with a series of bulges and convolutions forming (see figure 2.1). By around 5 weeks after conception these bulges can be identified as protoforms for major components of the mammalian brain. Proceeding from front to back: the first bulge gives rise to the cortex (telencephalon), the second gives rise to the thalamus and hypothalamus (diencephalon), the third turns into the midbrain (mesencephalon), and others to the cerebellum (metencephalon), and to the medulla (myelencephalon).

The circumferential dimension (tangential to the surface) in the neural tube is critical, because the distinction between sensory and motor systems develops along this dimension: dorsal (top-side) corresponds roughly to sensory cortex,



**Figure 2.1** A sequence of drawings of the embryonic and fetal development of the human brain. The drawings of brains beneath 25–100 days are the same images but drawn to the same scale as those in the row below. The forebrain, midbrain, and hindbrain originate as swellings at the head end of the neural tube. In primates, the convoluted cortex grows to cover the midbrain, hindbrain, and parts of the cerebellum. Prior to birth, neurons are generated in the developing brain at a rate of more than 250,000 per minute.

ventral (bottom-side) corresponds to motor cortex, with the various association cortices and “higher” sensory and motor cortices aligned somewhere in between. Within the brain stem and the spinal cord, the corresponding alar (dorsal) and basal (ventral) plates play a major role in the organization of nerve pathways into the rest of the body.

Differentiation along the radial dimension gives rise to the complex layering patterns and cell types found in the adult brain. Across the radial dimension of the neural tube the bulges grow larger and become further differentiated. Within these bulges cells *proliferate* (are born), *migrate* (travel), and *differentiate into*



*particular types*. The vast majority of the cells that will compose the brain are born in the so-called *proliferative zones*. These zones are close to the hollow portion of the neural tube (which subsequently become the ventricles of the brain). The first of these proliferation sites, the *ventricular zone*, may be phylogenetically older (Nowakowski, 1987). The second, the *subventricular zone*, only contributes significantly to phylogenetically recent brain structures such as the neocortex (i.e. “new” cortex). These two zones yield separate glial (support and supply cells) and neuron cell lines and give rise to different forms of migration. But first we will consider how young neurons are formed within these zones.

FURTHER READING: TAKAHASHI, NOWAKOWSKI, & CAVINESS, 2001, NOWAKOWSKI & HAYES, 2002

Neurons and glial cells are produced by division of proliferating cells within the proliferative zones to produce clones (a clone is a group of cells which are produced by division of a single precursor cell – such a precursor cell is said to give rise to a lineage). *Neuroblasts* produce neurons, and *glioblasts* produce glial cells. Each of the neuroblasts gives rise to a definite and limited number of neurons, a point to which I will return later. In at least some cases particular neuroblasts also give rise to particular types of cell. For example, less than a dozen proliferating cells produce all the Purkinje cells of the cerebellar cortex, with each producing about 10,000 cells (Nowakowski, 1987).

After young neurons are born, they have to travel or *migrate* from the proliferative zones to the particular region where they will be employed in the mature brain. There are two forms of migration observed during brain development. The first, and more common, is *passive cell displacement*. This occurs when cells that have been generated are simply pushed further away from the proliferative zones by more recently born cells. This form of migration gives rise to an outside-in pattern. That is, the oldest cells are pushed toward the surface of the brain, while the most recently produced cells are pulled toward the inside. Passive migration gives rise to brain structures such as the thalamus, the dentate gyrus of the hippocampus, and many regions of the brain stem. The second form of migration is more active and involves the young cell moving past previously generated cells to create an “inside-out” pattern. This pattern is found in the cerebral cortex and in some subcortical areas that have a laminar structure (divided into parallel layers).

It is important to emphasize that prenatal brain development is not a passive process involving the unfolding of genetic instructions. Rather, from an early stage interactions between cells are critical, including the transmission of electrical signals between neurons. In one example, patterns of spontaneous firing of cells in the eyes (before they have opened in development) transmit signals that appear to specify the layered structure of the lateral geniculate nucleus (see O’Leary & Nakagawa, 2002; Shatz 2002). Thus, waves of firing intrinsic to the

developing organism may play an important role in specifying aspects of brain structure before sensory inputs from the external world have any effect.

*FURTHER READING: SHATZ, 2002*

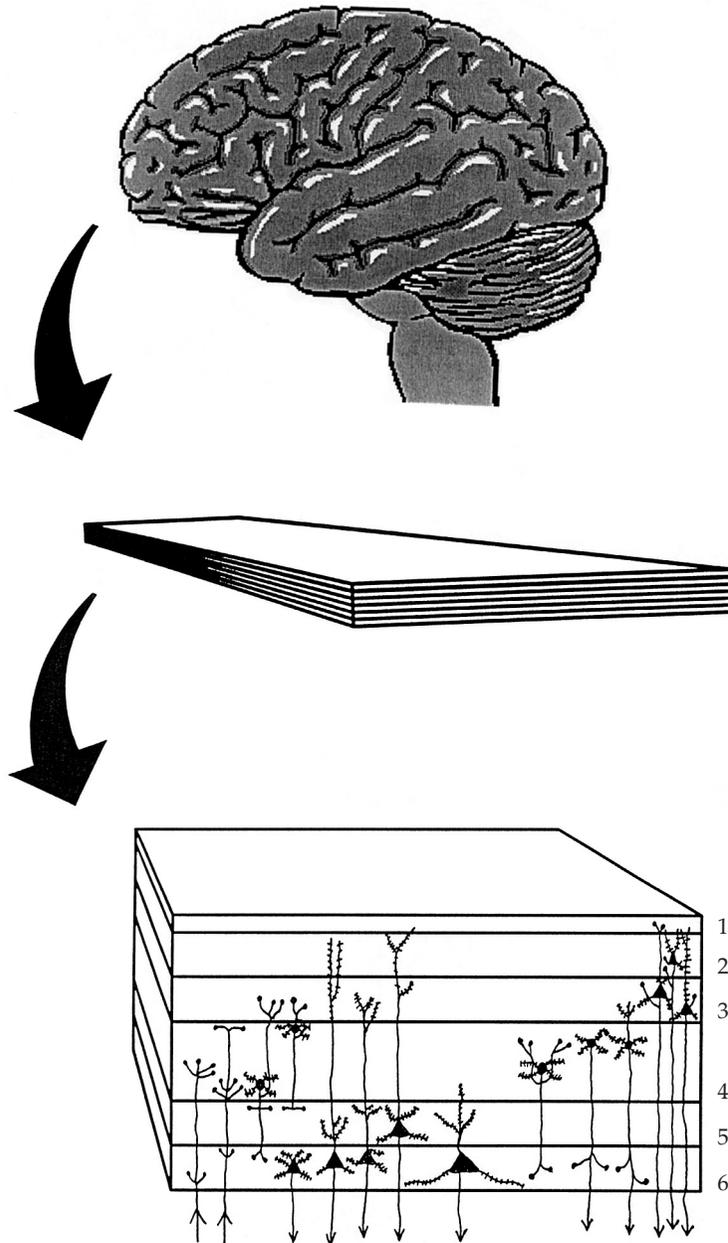


## 2.2 AN OVERVIEW OF PRIMATE BRAIN ANATOMY

The mammalian brain follows a basic vertebrate brain plan found in lower species such as salamanders, frogs, and birds. The major differences between these species and higher primates is in the dramatic expansion of the cerebral cortex together with associated structures such as the basal ganglia. Human brain development follows closely the sequence of events observed in other primates, albeit on a slower schedule. A model of the evolution of the brain that successfully predicts the timing of different neural development events in various mammalian species (Finlay & Darlington, 1995) has recently been extended to human prenatal development (Clancy, Darlington, & Finlay, 2000). The model predicts that the more delayed the general time course of brain development in a species, the larger the relative volume of the later developing structures (such as the cerebral cortex, and particularly the frontal cortex) will be. In accordance with this general prediction, the slowed rate of development in humans is associated with a relatively larger volume of cortex, and an especially large frontal cortex. But, as we will see later, the relatively delayed time course of human brain development has another important benefit. It allows a prolonged postnatal period during which interaction with the environment can contribute to the tuning and shaping of circuitry.

The rapid expansion of the area of cortex has resulted in it becoming increasingly convoluted. For example, the area of the cortex in the cat is about 100 cm<sup>2</sup>, whereas that of the human is about 2,400 cm<sup>2</sup>. This suggests that the extra cortex possessed by primates, and especially humans, is related to the higher cognitive functions they possess. However, the basic relations between principal structures of the brain remain similar from mouse to human. The neocortex of mammals is basically a thin (about 3–4 mm) flat sheet. Although complex, its general layered structure is relatively constant throughout its extent (see figure 2.2).

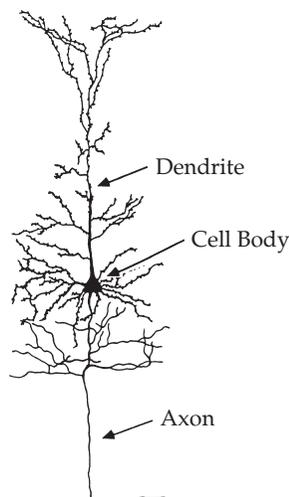
Most of the sensory inputs to the cortex pass through a structure known as the thalamus. Each type of sensory input has its own particular nuclei within this region. For example, the lateral geniculate nucleus (LGN) carries visual input to the cortex, while the medial geniculate nucleus (MGN) carries information from the auditory modality. Because of the crucial role of the thalamus in mediating inputs to the cortex, some have hypothesized that it also plays a crucial role in cortical development – an idea that will be discussed at greater length later. The flow of information between thalamus and cortex is not unidirectional, however,



**Figure 2.2** A simplified schematic diagram which illustrates that, despite its convoluted surface appearance (top), the cerebral cortex is a thin sheet (middle) composed of six layers (bottom). The convolutions in the cortex arise from a combination of growth patterns and the restricted space inside the skull. In general, differences between mammals involve the total area of the cortical sheet, and not its layered structure. Each of the layers possesses certain neuron types and characteristic input and projection patterns (see text).

since most of the projections from lower regions into the cortex are matched by projections from the cortex back down. Some output projections from the cortex pass to regions that are believed to be involved in motor control, such as the basal ganglia and the cerebellum. However, most of the projections from the cortex to other brain regions terminate in roughly the same regions from which projections arrived (such as the thalamus). In other words, the flow of information to and from the cortex is largely bidirectional. For this reason, it is important not to confuse the terms “input” and “output” with “sensory” and “motor”. All sensory and motor systems make extensive use of both input and output fibers, with information passing rapidly in both directions along collateral pathways.

The brain has two general types of cells, neurons and glial cells. Glial cells are more common than neurons, but are generally assumed to play no direct role in computation. However, as we shall see later they play a very important role in the development of the cortex. The computational unit of the brain has long been thought to be the neuron (Shepherd, 1972). Neurons come in many shapes, sizes, and types, each of which presumably reflects their particular computational function. There appear to be approximately 25 different neuronal types within the cortex, although several of these types are relatively rare, and some are restricted to particular layers. About 80 percent of neurons found in the cortex are *pyramidal cells*, so-called because of the distinctive pyramid shape of the soma (cell body) produced by the very large apical dendrite (input process), which is always tangential to the surface of the cortex (figure 2.3). These are the neurons whose long axons (output processes) are so often found in the fibers feeding into other cortical and subcortical regions. While pyramidal cells are found in many of the layers of the cortex (generally they are larger in the lower layers and smaller in



**Figure 2.3** A typical cortical pyramidal cell. The apical dendrite is the long process that extends to the upper layers, and may allow the cell to be influenced by other neurons. An axon projects to subcortical regions.



the upper layers), their apical dendrites often reach into its most superficial layer, layer 1 (see below). This long apical dendrite allows the cell to be influenced by large numbers of cells from other (more superficial) layers and regions. This may be computationally important if the pyramidal cell is a very stable and inflexible class of cell whose output is modulated by groups of plastic and flexible inhibitory regulatory neurons. Figure 2.2 also shows a schematic section through an area of primate cortex cut at right angles to the surface of the cortex, revealing the layered structure. I will refer to this as the *laminar* structure of the cortex. As just noted, each of the laminae has particular cell types within it, and each layer has typical patterns of inputs and outputs.

Most areas of the neocortex (in all mammals) are made up of six layers. The basic characteristics that define each layer appear to hold in most regions of the cortical sheet. Layer 1 has few cell bodies. It is made up primarily of long white fibers running along the horizontal surface, linking one area of cortex to others some distance away. Layers 2 and 3 also contain horizontal connections, often projecting forward from small pyramidal cells to neighboring areas of cortex. Layer 4 is the layer where most of the input fibers terminate and it contains a high proportion of spiny stellate (star-shaped) cells on which these projections terminate. Layers 5 and 6 have the major outputs to subcortical regions of the brain. These layers contain a particularly high proportion of large pyramidal cells, with long descending axons. There are also many neurons involved in intrinsic cortical circuits.

Although this basic laminar structure holds throughout most of the neocortex, there are some regional variations. For example, the input layer (layer 4) is particularly thick and well developed in sensory cortex. Indeed, in the visual system, it is possible to distinguish at least four “sublayers” within layer 4. Conversely, layer 5 (one of the output layers) is particularly well developed in motor cortex, presumably due to its importance in sending output signals from the cortex. It is also clear that different parts of the cortex have different projection patterns to other parts of the cortex. While there may only be a small number of these characteristic projection patterns from one region of cortex to another, there is no single pattern that can be said to be characteristic of all cortical regions. Hence this is another dimension of variation that can contribute to regional specialization within the cortex. Further dimensions could include the presence of particular neurotransmitters, and the relative contribution of excitatory vs inhibitory neurotransmitters. Finally, as we will see later, regions may vary in the timing of key developmental events, such as the postnatal reduction in the number of synapses (Huttenlocher, 1990).



## 2.3 POSTNATAL BRAIN DEVELOPMENT

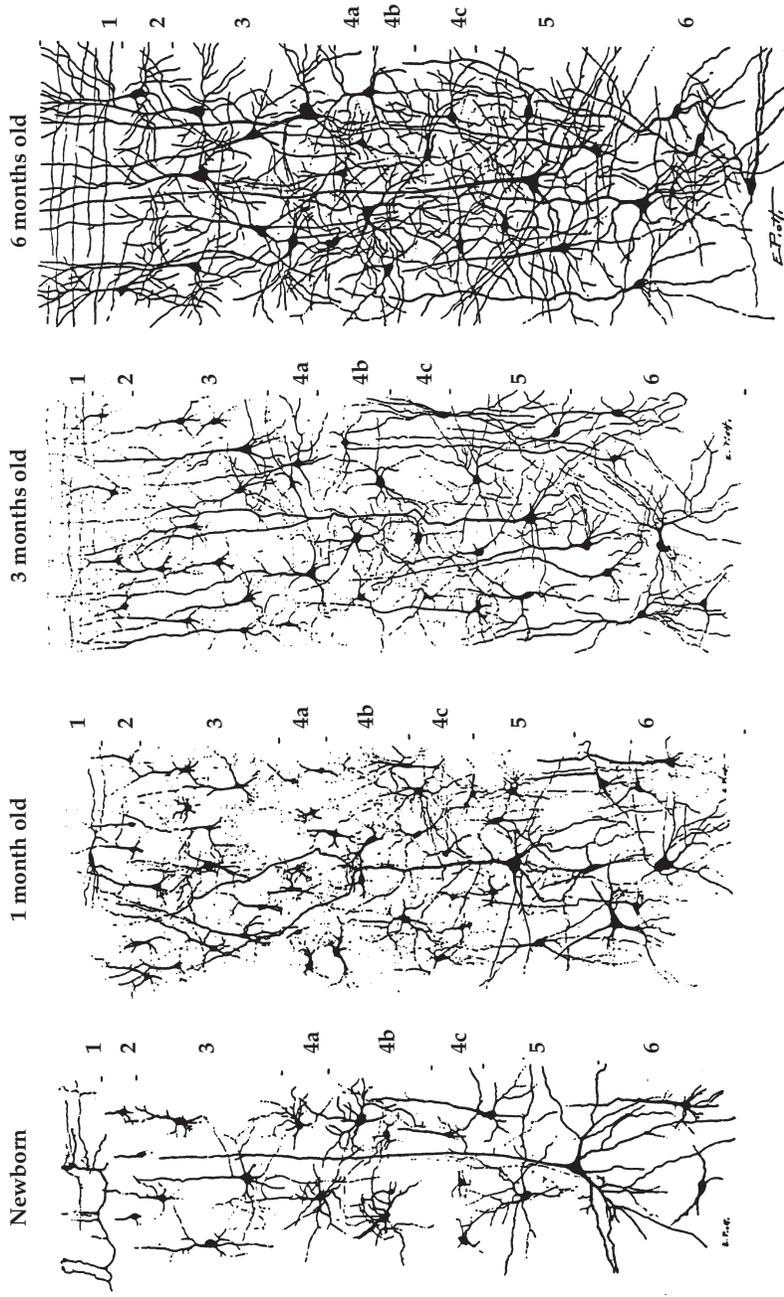
There are a number of ways to study the postnatal development of neuronal structure in the brain. Traditionally, investigators have used neuroanatomical

analysis of postmortem tissue. Such analysis tends to be based on relatively small numbers of children due to the extensive work involved and the difficulties associated in gaining such tissue. Furthermore, those children who come to autopsy have often suffered from trauma or diseases that complicate generalizations to normal brain development. *In vivo* studies of adults using magnetic resonance imaging (MRI) (Courchesne, Hesselink, Jernigan, & Yeung-Courchesne, 1987; Jernigan, Press, & Hesselink, 1990) and PET scanning of infants and adults (Petersen, Fox, Posner, Mintun, & Raichle, 1988; Chugani, Phelps, & Mazziotta, 2002) can inform us about the structural development of the brain. But these techniques are expensive, and are usually restricted to children with clinical symptoms that justify neural imaging. Hence generalizations to normal brain development must be made with caution in these cases as well. Despite these difficulties, a number of progressive and regressive neuroanatomical and neurophysiological changes have been observed during postnatal development in children. Specifically, a number of measures of brain anatomy and function show a characteristic “rise and fall” developmental pattern during this period. While the progressive and regressive processes should not be viewed as distinct stages, for the purposes of exposition I will discuss them in sequence.

A number of lines of evidence indicate that substantive additive changes occur during postnatal development of the brain. At the most gross level of analysis, brain volume quadruples between birth and adulthood. This increase comes from a number of sources, but, in general, not from additional neurons. The formation of neurons and their migration to appropriate brain regions takes place almost entirely within the period of prenatal development in the human. Although there may be some addition of neurons in the hippocampus and elsewhere (see later), the vast majority are present by around the seventh month of gestation (Rakic, 1995). In contrast to the lack of new nerve cell bodies, there is dramatic postnatal growth of synapses, dendrites, and fiber bundles. Further, nerve fibers become covered in a fatty myelin sheath that adds further to the mass of the brain.

Perhaps the most obvious manifestation of postnatal neural development as viewed through the confocal microscope is the increase in size and complexity of the dendritic tree of most neurons. An example of the dramatic increase in dendritic tree extent during human postnatal development is shown in figure 2.4. While the extent and reach of a cell’s dendritic arbor may increase dramatically, it also often becomes more specific and specialized. Less apparent through standard microscopes, but more evident with electron microscopy, is a corresponding increase in measures of the density of synaptic contacts between cells.

Huttenlocher and colleagues have reported a steady increase in synaptic density in several regions of the human cerebral cortex (Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Huttenlocher, 1990, 1994). While an increase in synaptogenesis begins around the time of birth for all cortical areas studied to date, the most rapid bursts of increase, and the final peak density, occur at different ages in different areas. In the visual cortex there is a rapid burst at 3 to 4 months, and the maximum density of around 150 per cent of adult level is



**Figure 2.4** A drawing of the cellular structure of the human visual cortex based on Golgi stain preparations from Conel (1939–67).

reached between 4 and 12 months. A similar time course is observed in the primary auditory cortex (Heschl's gyrus). In contrast, while synaptogenesis starts at the same time in a region of the prefrontal cortex, density increases much more slowly and does not reach its peak until after the first year. (It should be noted at this point that there are a variety of possible measures of synaptic density – per cell, per unit dendrite, per unit brain tissue, etc. Careful selection of measures is required so that factors such as increases in dendritic length do not unduly influence the results. Huttenlocher, 1990, discusses some of these issues of appropriate measurement.)

*FURTHER READING: BOURGEOIS, 2001, HUTTENLOCHER, 2002*

Another additive process is myelination. Myelination refers to an increase in the fatty sheath that surrounds neuronal pathways, a process that increases the efficiency of information transmission. In the central nervous system, sensory areas tend to myelinate earlier than motor areas. Cortical association areas are known to myelinate last, and continue the process into the second decade of life (see later). Because myelination continues for many years after birth, there has been a great deal of speculation about its role in behavioral development (Yakovlev & Lecours, 1967; Parmelee & Sigman, 1983; Volpe, 1987). However, interest in the causal role of myelination has begun to wane in the last few years since it became clear that under-myelinated connections in the young human brain are still capable of transmitting signals.

*FURTHER READING: SAMPAIO & TRUWIT, 2001*

A positron emission tomography study of human infants (Chugani et al., 2002) reported a sharp rise in overall resting brain metabolism (glucose uptake) after the first year of life, with a peak approximately 150 per cent above adult levels achieved somewhere around 4–5 years of age for some cortical areas. While this peak occurred somewhat later than that in synaptic density, an adult-like *distribution* of resting activity within and across brain regions was observed by the end of the first year.

*FURTHER READING: CHUGANI ET AL., 2002*

I now turn to regressive events during human postnatal brain development. Such events are commonly observed by those studying the development of nerve



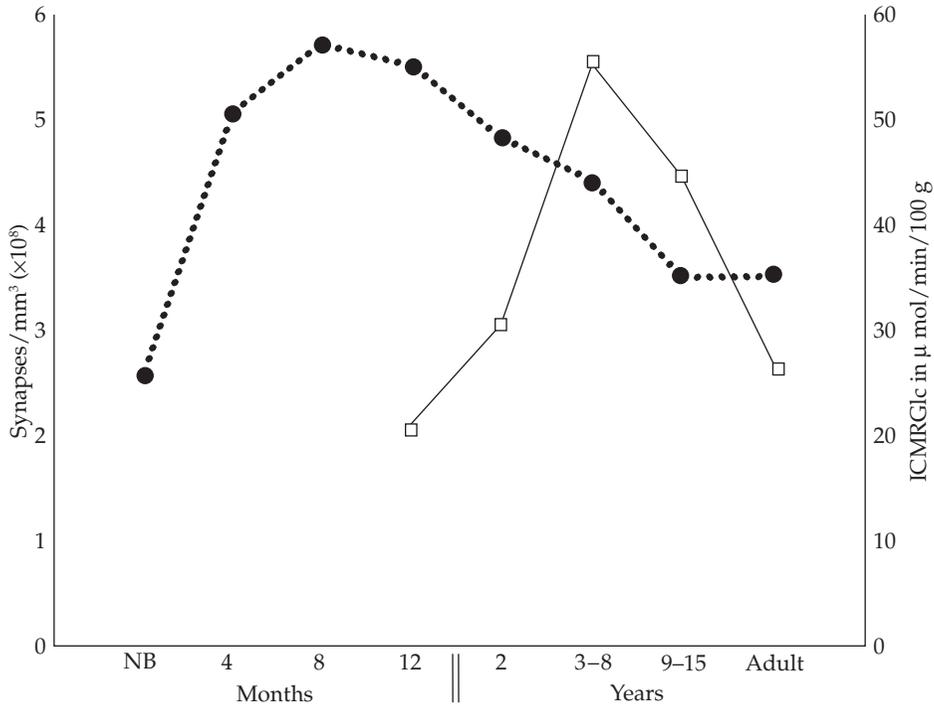
cells and their connections in the vertebrate brain (for reviews see: Cowan, Fawcett, O'Leary, & Stanfield, 1984; Hopkins & Brown, 1984; Clarke, 1985; Purves & Lichtman, 1985; Janowsky & Findlay, 1986). That processes of selective loss have a significant influence on postnatal primate brain development is evident from a number of quantitative measures. For example, in the PET study just mentioned the authors found that the absolute rates of glucose metabolism rise postnatally until they exceed adult levels, before reducing to adult levels after about 9 years of age for most cortical regions.

Consistent with these PET findings, Huttenlocher (1990, 1994) reports quantitative neuroanatomical evidence from several regions of the human cortex that following the increase in density of synapses described above there is then a period of synaptic loss. Like the timing of bursts of synaptogenesis, and the subsequent peaks of density, the timing of the reduction in synaptic density varies between cortical regions. For example, synaptic density in the visual cortex returns to adult levels between 2 and 4 years, while the same point is not reached until between 10 and 20 years of age for regions of the prefrontal cortex. Huttenlocher (1990, 1994) suggests that this initial overproduction of synapses may have an important role in the apparent plasticity of the young brain, a matter that will be discussed in more detail later. There is no strong evidence for this pattern of rise and fall either for the density of dendrites or for the number of neurons themselves in humans or other primates. However, in rodents and other vertebrates cell loss may be more significant.

*FURTHER READING: GREENOUGH ET AL., 2002*

One explanation for the decrease in glucose uptake observed in the PET studies is that it reflects the decrease in synaptic contacts. This hypothesis was investigated in a developmental study conducted with cats (Chugani, Hovda, Villablanca, Phelps, & Xu, 1991). In this study, the peak of glucose uptake in cat visual cortex was found to coincide with the peak in overproduction of synapses in this region. However, when similar data from human visual cortex are plotted together (see figure 2.5), it is apparent that the peak of glucose uptake lags behind synaptic density. An alternative to the hypothesis that reduction of metabolic activity is the result of the elimination of neurons, axons, and synaptic branches is that the same activity may require less “mental effort” once a certain level of skill has been attained.

Most of the developments in the brain discussed so far concern aspects of the structure of the brain. However, there are also developmental changes in what has been known as the “soft soak” aspects of neural function, molecules involved in the transmission and modulation of neural signals. While these will be discussed in more detail in a later section, it is interesting to note at this point that a number of neurotransmitters in rodents and humans also show the rise and fall



**Figure 2.5** Graph showing the development of density of synapses in human primary visual cortex (dotted line: data taken from Huttenlocher, 1990), and resting glucose uptake in the occipital cortex as measured by PET (solid line: data taken from Chugani et al., 1987). ICMRGlc is a measure of the local cerebral metabolic rates for glucose.

developmental pattern (see Benes, 1994, for review). Specifically, the excitatory intrinsic transmitter glutamate, the intrinsic inhibitory transmitter GABA (Gamma-aminobutyric acid), and the extrinsic transmitter serotonin all show this same developmental trend.

*FURTHER READING: BENES, 2001; CAMERON, 2001; BERENBAUM, MOFFAT, WISNIESKI, & RESNICK, 2003*

Thus, the distinctive “rise and fall” developmental sequence is seen in a number of measures of structural and neurophysiological development in the human cortex. The number of measures and different laboratories in which this somewhat counter-intuitive developmental sequence has been observed leads to a degree of confidence in its validity. However, it should be stressed that (i) not all measures show this pattern (e.g. myelination); (ii) measures such as synaptic density are



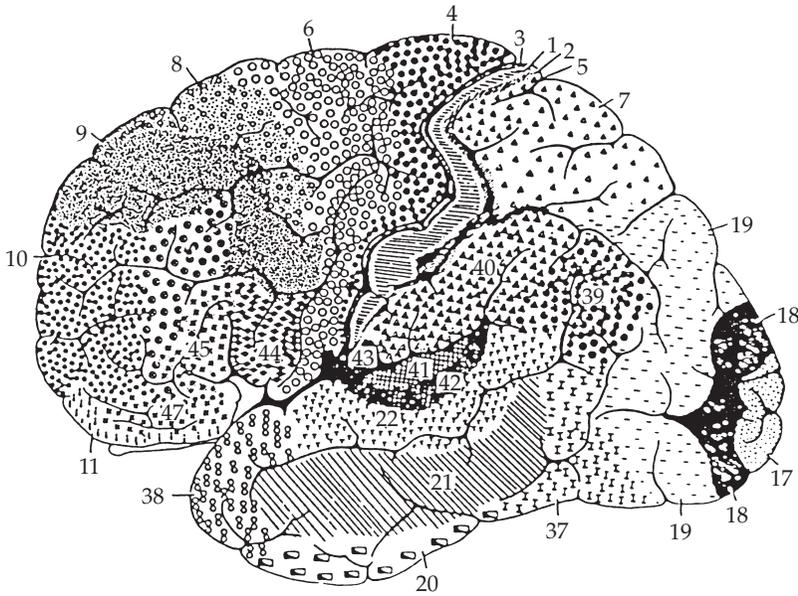
static snapshots of a dynamic process in which both additive and regressive processes are continually in progress: in other words, there are probably not distinct and separate progressive and regressive phases; and (iii) models which are exclusively dependent on regressive processes are unlikely to be adequate.

In addition to these caveats, all of the additive and subtractive events just described for normal human brain development must be weighed against a growing literature on individual differences within the normal range. As more sophisticated brain imaging techniques are developed, it becomes increasingly evident that there is considerable variation in structure and function in normal adult subjects. For example, Tramo and his colleagues (Tramo et al., 1994) reconstructed the cortical areas of two identical twins from MRI scans. Even in the case of genetically identical individuals, the variation in cortical areas was striking, with the occipital lobe occupying 13–17 percent of cortical area in one individual, and 20 percent in the other. These differences between individuals in brain structure may also extend to brain functioning. For example, using functional MRI, Schneider and colleagues studied the areas of activation following upper or lower visual field stimulation. While it had classically been assumed that the upper and lower visual field mapped on to the regions above and below the sulcus, there is in fact a lot of variation, with some normal subjects showing an upper/lower visual field cut that straddles this structure (Schneider, Noll, & Cohen, 1993). This new evidence for variability complements an older literature on individual differences in handedness and hemispheric organization for language (e.g. Kinsbourne & Hiscock, 1983; Hellige, 1993). In view of this variability in normal adults, efforts to construct a timetable for “normal” postnatal brain development in humans must be interpreted with caution.



## 2.4 THE DEVELOPMENT OF CORTICAL AREAS: PROTOMAP OR PROTOCOLCORTX?

An ongoing debate among those who study the developmental neurobiology of the cortex concerns the extent to which its structure and function are prespecified, in the sense that they are the result of genetic, molecular, and cellular level interactions and not determined by the pattern of firing of neurons. Orthogonal to the laminar dimension of cortical structure is its differentiation into regions or areas. Figure 2.6 illustrates one of the best-known schemes for dividing the cerebral cortex into areas. In the adult primate most of these cortical areas can be determined by very detailed differences in the laminar structure, such as the precise thickness of certain layers. Often, however, the borderlines between areas are indistinct and controversial. It is commonly assumed that these anatomically defined areas are also functionally distinct. While this has proved to be the case for early sensory and motor areas, there are many cases of functional regions or borders that do not neatly correspond to known neuroanatomical divisions. It



**Figure 2.6** Cytoarchitectural map of the cerebral cortex. Some of the most important specific areas are as follows. Motor cortex: motor strip, area 4; pre-motor area, area 6; frontal eye fields, area 8. Somatosensory cortex: areas 3, 1, 2. Visual cortex: areas 17, 18, 19. Auditory cortex: areas 41 and 42. Wernicke's speech area: approximately area 22. Broca's speech area: approximately area 44 (in the left hemisphere) (from Brodmann, in Brodal, 1981).

should be stressed that the division of the cortex into areas with differing functional specializations is not an exact science in that the detailed features of neuroanatomy relevant for supporting different functions are unknown.

Despite these caveats, a century of neuropsychology has taught us that the majority of normal adults tend to have similar functions within approximately the same areas of cortex. This observation has led to a common assumption that the division of the cerebral cortex into structural and functional areas is genetically prespecified. However, as we will see, this assumption is, at best, only partially correct.

The framework outlined in chapter 1 can be used to ask whether aspects of cortical structure are specified prior to postnatal experience. This question can be asked of both the laminar and the areal structure of cortex. Of course the two dimensions of cortical structure are not entirely independent, since structural areal divisions are partly specified by detailed differences in laminar structure. However, the framework in chapter 1 allowed for the possibility that while the basic architecture of a network is innate (basic circuitry, learning rules, type and number of cells, etc.), the detailed patterns of (dendritic and synaptic) connectivity are



dependent upon experience. In such a case we may say that while the *network imposes architectural constraints on the representations that emerge within it, there are no innate representations.*

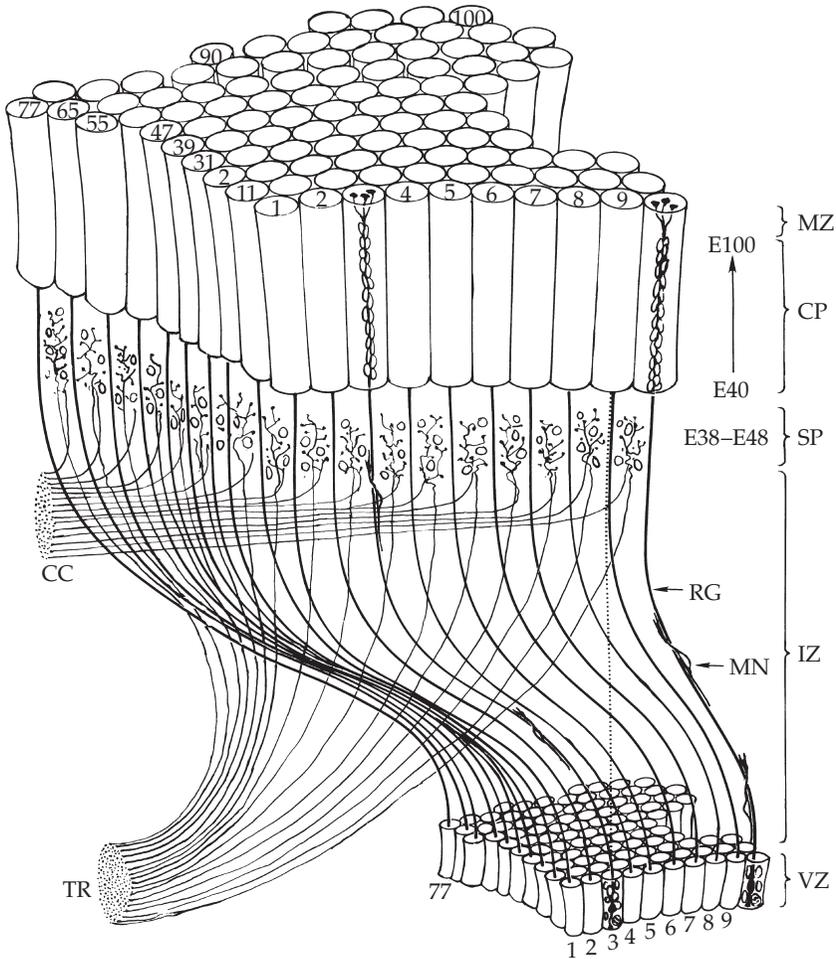
In the review that follows I will suggest that several aspects of the structure of the cerebral cortex, including the general laminar structure and large-scale regions, do not require neural activity to be established. Crucially, however, much of the fine-scale division into functional areas involves activity-dependent processes. I begin by returning to the prenatal development of cortex, and arguably the most complete theory of the development of cortical structure: the radial unit model proposed by Pasko Rakic (1988).

As mentioned earlier, most cortical neurons in humans are generated outside the cortex itself in a region just underneath what becomes the cortex, the “proliferative zones.” This means that these cells must migrate to take up their locations within the cortex. How is this migration accomplished? Rakic has proposed a “radial unit model” of neocortical differentiation that gives an account of how *both* the areal and the layered structure of the mammalian cerebral cortex arise (Rakic, 1988). According to the model, the laminar organization of the cerebral cortex is determined by the fact that each proliferative unit (in the subventricular zone) gives rise to about one hundred neurons. The progeny from each proliferative unit all migrate up the same radial glial fibre, with the latest to be born travelling past their older relatives. A radial glial fibre is a long process that stretches from top to bottom of the cortex and originates from a glial cell. Thus, radial glial fibres act like a climbing rope to ensure that cells produced by one proliferative unit all contribute to one radial column within the cortex. Rakic’s proposed method of migration is illustrated in figure 2.7.

FURTHER READING: RAKIC, 2002

There are some consequences of the radial unit model for the role of genetic regulation in species differences. For example, Rakic (1988) has pointed out that a single round of additional symmetric cell division at the proliferative unit formation stage would double the number of ontogenetic columns, and hence the area of cortex. In contrast, an additional single round of division at a later stage, from the proliferative zones, would only increase the size of a column by one cell (about 1 per cent). There is very little variation between mammalian species in the layered structure of the cortex, while the total surface area of the cortex can vary by a factor of 100 or more between different species of mammal. It seems likely, therefore, that species differences originate (at least in part) in the timing of cell development (i.e. the number of “rounds” of cell division that are allowed to take place within and across regions of the proliferative zones).

A related view on the evolution of mammalian brain has been put forward by Finlay and Darlington (1995). These authors compared data on the size of brain



**Figure 2.7** The radial unit model of Rakic (1987). Radial glial fibers span from the ventricular zone (VZ) to the cortical plate (CP) via a number of regions: the intermediate zone (IZ) and the subplate zone (SP). RG indicates a radial glial fiber, and MN a migrating neuron. Each MN traverses the IZ and SP zones that contain waiting terminals from the thalamic radiation (TR) and corticocortico afferents (CC). As described in the text, after entering the cortical plate, the neurons migrate past their predecessors to the marginal zone (MZ).

structures from 131 mammalian species, and concluded that the order of neurogenesis is conserved across a wide range of species and correlates with the relative enlargement of structures as overall brain size increases. Specifically, disproportionately large growth occurs in the late-generated structures such as the neocortex. By this analysis, the structure most likely to differ in size in the relatively slowed neurogenesis of primates is the neocortex.



Rakic's model explains how cortical cells arrange themselves into the thickness of the cortex, but how does the differentiation into specific layers emerge? While we are far from being able to answer this question definitively at this point, one view is that differentiation into particular cell types occurs *before* a neuron reaches its final location. That is, a cell "knows" what type of neuron it will become (pyramidal, spiny stellate, etc.) before it reaches its adult location within the cortex. Some evidence suggests that cells do indeed begin to differentiate before they reach their final vertical location. For example, in genetic mutant "reeler" mice, cells that acquire inappropriate laminar positions within the cortex still differentiate into neuronal types according to their time of origin, rather than the types normally found at their new location. This implies that the information required for differentiation is present at the cell's birth in the proliferative zones; it is not dependent upon their distance from the proliferative zones, or on the characteristics of the neighborhood in which that cell ends up. That is, in the proliferative zones for the neocortex, some cell types may be determined at the stage of division.

Although in many cases a cell's identity may be determined before it leaves the proliferative zones, some of the properties that distinguish among cell types may form later. For example, Marin-Padilla (1990) has proposed that the distinctive apical dendrite of pyramidal cells, which often reaches into layer 1, is a result of the increasing distance between this layer and other layers resulting from the inside-out pattern of growth. Specifically, the increasing separation between layer 1 and the subplate zone which results from young neurons moving into what will become layers 2 to 6 means that cells which have their processes attached to layer 1 will become increasingly "stretched" – that is, their leading dendrite will become stretched tangential to the surface of the cortex, resulting in the elongated apical dendrite so typical of cortical pyramidal cells. As mentioned earlier, this long apical dendrite allows the cell to be influenced by large numbers of cells from other (more superficial) layers.

Another aspect of the laminar structure of cortex that appears to be regulated by intrinsic cellular and molecular interactions concerns the major connections between cells, in particular the inputs from the thalamus. As mentioned earlier, the main input layer in the cortex is layer 4. A series of experiments by Blakemore and colleagues established that the termination of projections from the thalamus in layer 4 is governed by molecular markers. Slices of brain tissue are able to survive and grow in a Petri dish for several days under the appropriate conditions. Indeed, pieces of thalamus of the appropriate age will actually innervate other pieces of brain placed nearby. Molnar and Blakemore (1991) investigated if and how a piece of visual thalamus (LGN) would innervate various types of cortical and non-cortical brain tissue.

In initial experiments they established that when a piece of thalamus (LGN) and a piece of visual cortex were placed close together in the dish, afferents from the LGN not only invaded a piece of visual cortex of the appropriate age, but also terminated in the appropriate layer 4. Thus, layer 4 appears to contain some molecular stop signal that tells the afferents to stop growing and form connections

at that location. Next, they conducted a series of choice experiments in which the visual thalamus had a piece of visual cortex and some other piece of brain placed nearby. The thalamic afferents turned out to dislike cerebellum, rarely penetrating it, but the afferents did grow into hippocampus. However, the growth into hippocampus (a piece of brain that is closely related to neocortex – see section 2.8) was not spatially confined in the way it had been for visual cortex, suggesting that it was just a “growth-permitting substrate.”

The evidence discussed so far indicates that the laminar structure of cortex probably arises from local cellular and molecular interactions, rather than it being shaped as a result of thalamic and sensory input. That is, the identity and location of neurons are determined before birth. Similarly, incoming fibers “know” in which layer to stop and make synaptic contacts. I now turn to the question of whether the areal structure of the cortex is determined in a similar way.

There are two possibilities that have been put forward to account for the division of cortex into areas:

- 1 The areal differentiation of cortex is due to a *protomap* (Rakic, 1988). By this view, differentiation into cortical regions occurs early in the formation of the cortex, and is due to intrinsic (to the cortex or its proliferative zones) factors. The activity of neurons is not required. The cortex is viewed as a mosaic from the start such that each cortical area has individually specified features particularly suitable for the input it will receive or the functions it will perform.
- 2 The different areas of cortex arise out of an undifferentiated *protocortex*. By this view, differentiation occurs later in the development of cortex, and it depends on extrinsic factors like input from other parts of the brain or sensory systems. The activity of neurons is required (O’Leary, 2002; Killackey, 1990). The division of cortex into areas in the adult brain is influenced by information relayed from the thalamus, and from interactions with other areas of cortex via inter-regional connectivity.

FURTHER READING: O’LEARY, 2002; RAKIC, 2002

There is a large, complicated, and sometimes apparently conflicting literature on the areal differentiation of neocortex (for recent reviews see: Kingsbury & Finlay, 2001; Pallas, 2001; Ragsdale & Grove, 2001). Some recent experiments appear, at first sight, to be compelling evidence for the protomap view. For example, the newborns of a strain of “knockout” rodent (see chapter 1) that genetically lack connections between the thalamus and the cortex still have normal, well-defined regional gene-expression boundaries within their cortex (Miyashita-Lin, Hevner, Wassarman, Martinez, & Rubinstein, 1999) and some other characteristics of wild-type mice. In another example, *in vitro* studies in which cortical tissue is maintained in culture, and thus isolated from potential



extrinsic patterning cues, still show patterns of gene expression consistent with the development of the hippocampus (Tole, Goodreau, Assimakopoulos, & Grove, 2000). Despite these and other studies supporting the idea of genetically specified regionalization of cortex, there are some important caveats, and also a surprising amount of evidence in support of the opposing protocortex view.

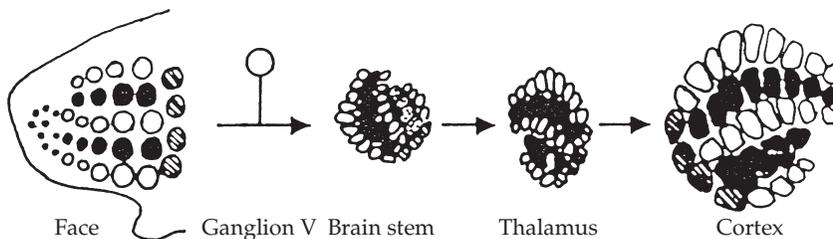
- 1 Most of the patterns of gene expression thought to contribute to the differentiation of cortex do not show clearly defined boundaries, but rather show graded expression across large extents of cortex. This suggests that regionalization of cortex could emerge from a combination of different gradients of gene expression. Kingsbury and Finlay (2001) refer to this as a “hyperdimensional plaid” and contrast this with a “mosaic quilt” (protomap) view.
- 2 At present, there are few examples of clear regionalization that map on to functional areas, and there are good reasons to believe that these cases are exceptions to the general rule. For example, comparisons across a large number of species have led several experts to argue that primary sensory areas that receive direct input from the primary sensory thalamic nuclei are less susceptible to change between species than most of the rest of the cortex (e.g. Krubitzer, 1998). In particular, the primary visual cortex in primates has unique characteristics that have led some to propose that it is the most recently evolved part of cortex. In the primary visual cortex, inputs from the visual thalamus may regulate the extent of cell proliferation in the ventricular zone (see Kennedy & Dehay, 1993), ensuring that this area of cortex has a rate of neuron production nearly twice that in neighboring areas. The entorhinal cortex, the region of cortex most closely associated with the hippocampus, shows some differentiation from surrounding cortex as early as 13 weeks after gestation (Kostovic, Petanjek, & Judas, 1993). However, for the majority of cortex in the mouse, and the vast majority in humans, there is currently no evidence for cortical divisions arising through the expression of a single gene.
- 3 Despite primary sensory regions being the best candidates for genetic pre-specification, we will see in the next section of this chapter that even these regions can have their properties significantly changed through experience. Thus, input may be vital for the maintenance of cortical divisions.
- 4 Evidence for cortical differentiation prior to birth does not allow us to conclude that neuronal activity is not important since spontaneous neural activity within the brain is known to be important for differentiation (Shatz 2002).

*FURTHER READING: SHATZ, 2002*

To summarize so far, the basic laminar structure of the cerebral cortex in mammals appears to be very general. Cellular and molecular level interactions determine many aspects of the layered structure of cortex and its patterns of

connectivity. Cortical neurons are often differentiated into specific computational types before they reach their destination (although some of the characteristic features of cell types are shaped by their journey to that site, e.g. the long apical dendrite that typifies pyramidal cells reflects a literal “stretching” of processes during the migration process). However, this does not mean that cells in a particular area are prespecified for processing certain kinds of information. The division of cortex into distinct regions and areas takes place along the areal dimension. Recent reviews of the evidence converge on a view mid-way between the protomap and protocortex hypotheses (Kingsbury & Finlay, 2001; Pallas, 2001; Ragsdale & Grove, 2001). This view is that graded patterns of gene expression potentially create large-scale regions with combinations of properties that may better suit certain computations (protomap). It is within these large-scale regions that smaller scale functional areas arise through mechanisms associated with the protocortex view. A hypothetical example is that one region may receive particular thalamic input, overlaid with a certain pattern of neurotransmitter expression, and the presence of certain neuromodulators. This combination of circumstances, combined with neural activity, may then induce further unique features such as particular patterns of short-range or long-range connectivity. Differentiation into smaller areas within the larger regions may occur through the selective pruning of connections (see chapter 10).

A good example of how a region of cortex can become differentiated comes from work on the so-called “barrel fields” that develop in the somatosensory cortex of rodents. Each barrel field is an anatomically definable functional grouping of cells that responds to a particular whisker on the animal’s snout (see figure 2.8). Barrel-fields are an aspect of the areal structure of cortex that emerges postnatally, and are sensitive to whisker-related experience over the first days of life. For example, if a whisker is removed, then the barrel field that normally corresponds to that whisker does not emerge, and neighboring ones may occupy some of the cortical space normally occupied by it (for review see Schlaggar & O’Leary, 1993). Figure 2.8 illustrates how the areal divisions of the cortex arise as



**Figure 2.8** Patterning of areal units in somatosensory cortex. The pattern of “barrels” in the somatosensory cortex of rodents is an isomorphic representation of the geometric arrangement of vibrissae found on the animal’s face. Similar patterns are present in the brain stem and thalamic nuclei that relay inputs from the face to the barrel cortex.



a result of similar divisions in structures closer to the sensory surface. In this case, it is almost as if the sensory surface *imposes* itself on to the brain stem, thence to the thalamus, and finally on to the cortex itself. The barrel field compartments emerge in sequence in these areas of the brain, with those closest to the sensory surface forming first, and the cortex patterns emerging last. While there is little evidence that barrel fields are prespecified in the cortex (but see Cooper & Steindler, 1986), a map of sensory space comes to occupy the somatosensory cortex in a reliable and replicable way.

In this section I have reviewed some of the literature on laminar and areal specification of cortex during normal development, concluding that there is evidence for both the protomap and protocortex views. This apparently conflicting evidence can be reconciled by the notion that large-scale regions of cortex have particular combinations of graded gene expression that are then refined into smaller areas through activity-dependent processes.

## 2.5 CORTICAL PLASTICITY

While some differentiation of cortex may occur early in development through intrinsic molecular and genetic factors, the nature of the information entering a region of cortex may be important in ensuring the maintenance and further progression of this differentiation. Further, neural activity driven by inputs may be able to change the function and detailed neuroanatomy of a region. Indeed, a number of experiments have shown that regions of the mammalian cerebral cortex can support a variety of different representations early in development. The evidence for this includes the following:

- 1 Reducing of the extent of thalamic input to a region of cortex early in life influences the subsequent size of that region (Rakic, 1988; Dehay, Horsburgh, Berland, Killackey, & Kennedy, 1989; O'Leary, 2002). Conversely, changing the quantity of cortex available for thalamic innervation changes the overall pattern of cortical differentiation and not just the affected region.
- 2 When thalamic inputs are "re-wired" such that they project to a different region of cortex from normal, the new recipient region develops some of the properties of the normal target tissue (e.g. auditory cortex takes on visual representations – Sur, Garraghty, & Roe, 1988; Sur, Pallas, & Roe, 1990).
- 3 When a piece of cortex is transplanted to a new location, it develops projections characteristic of its new location rather than its developmental origin (e.g. transplanted visual cortex takes on the representations that are appropriate for somatosensory input – O'Leary & Stanfield, 1989).

I will now consider each of these in more detail.

(1) The effect on the cortex of manipulating the extent of sensory input (via the thalamus) to an area has been investigated in experiments where the thalamic input to an area of cortex is surgically reduced (Dehay, Kennedy, & Bullier, 1988). Surgical intervention in newborn macaque monkeys can reduce the thalamic projections to the primary visual cortex (area 17) by 50 percent. This reduction results in a corresponding reduction in the extent of area 17 in relation to area 18. That is, the border between areas 17 and 18 shifts such that area 17 becomes much smaller. Despite this drastic reduction in the radial size of area 17, it is important to note that its laminar structure remains normal. Further, the area which is still area 17 looks identical to its normal structure, and the region which becomes area 18 has characteristics normally associated with that area, and none of those unique to area 17 (Rakic, 1988). Thus, there is (surprisingly) little effect of reducing the extent of sensory projections to area 17 on the subsequent laminar structure of areas 17 and 18. The specific effect of this manipulation is to reduce the *area* of 17 relative to 18, despite the evidence of some prespecification of neuron numbers in this particular region discussed earlier. This indicates that even those cortical areas for which there is some evidence for prespecification can be subsequently modified.

Even the outputs characteristic of areas 17 and 18 follow the shift in border between them. For example, while area 18 normally has many callosal projections to the other hemisphere, area 17 does not. The region which is normally area 17, but becomes area 18 in the surgically operated animals, has the callosal projection pattern characteristic of normal area 18. A reasonable conclusion reached on the basis of these observations is that the region of cortex that would normally mature into area 17 develops properties that are characteristics of the adjacent area 18 as a result of reducing its thalamic input. Thus, at least some of the area-specific characteristics of cortex appear to be regulated by extrinsic factors, even for regions that show the greatest degree of prespecification.

In the converse experiment to those just discussed, when the cortical sheet is surgically reduced (in the opossum embryo), it produces a complete, although smaller and distorted, area map (Huffman et al., 1999). Relatedly, in genetically altered strains of mice that lack certain regulatory genes (*Emx2* or *Pax6*), the resulting area map is distorted (Bishop et al., 2000; Mallamaci, Muzio, Chan, Parnavelas, & Boncinelli, 2000). Specifically, regions where these genes are normally expressed at high levels become “compressed” while other regions expand. These experiments illustrate that gradients of gene expression set up scaffolding which then interacts with thalamic input to result in functional areas. However, in atypical situations resulting from surgical or genetic manipulation, thalamic inputs can also shape regions that are not their normal targets.

(2) Cross-modal plasticity of cortical areas has now been demonstrated at the neurophysiological level in several mammalian species (for review see Pallas, 2001). For example, in the ferret, projections from the retina can be induced to project to auditory thalamic areas, and thence to auditory cortex. Following a

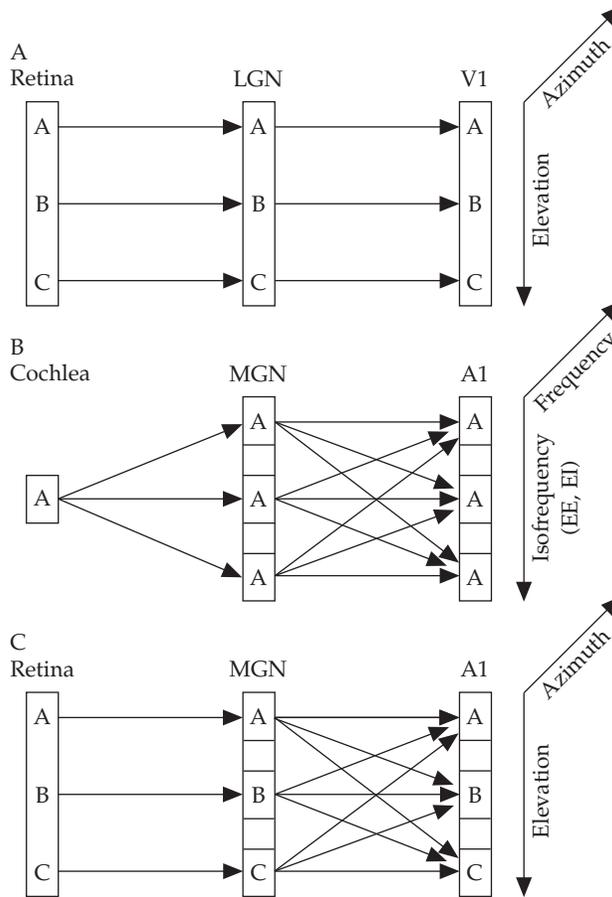


technique initially developed by Frost (1990), this is done by placing lesions in the normal visual cortex and in the lateral geniculate (the thalamic target of retinal projections). Lesions are also placed such that auditory inputs do not innervate their normal thalamic target, the medial geniculate. Under these pathological conditions, retinal projections will re-route to innervate the medial geniculate nucleus (MGN). Projections from the MGN then project to the auditory cortex as normal. The experimental question concerns whether the normally auditory cortex becomes visually responsive (i.e. in accord with its input), or whether it retains features characteristic of auditory cortex. The answer turns out to be that auditory cortex does become visually responsive. Furthermore, cells in what would have been auditory cortex also become orientation- and direction-selective, and some become binocular.

While these observations are provocative, they do not provide evidence that the auditory cortex as a whole becomes functionally similar to the visual cortex. It is possible, for example, that the visually driven cells in the auditory cortex would fire in isolation from the activity of their colleagues. That is, there may be no organization above the level of the individual neuron. In order to address this issue, evidence that there is a spatial map of the visual world formed across this area of cortex is needed. In order to study this issue, Sur and colleagues recorded from single neurons in a systematic way across the re-wired cortex (Sur et al., 1988; Roe, Pallas, Hahm, & Sur, 1990). These experiments revealed that the previously auditory cortex had developed a two-dimensional retinal map. In normal ferrets, the primary auditory cortex contains a one-dimensional representation of the cochlea. Along one axis of the cortical tissue electrode penetrations revealed a gradual shift from responses to low frequencies to responses to high frequencies (see figure 2.9). Along the orthogonal dimension of cortex, frequency remained constant (the isofrequency axis). In contrast, the visual representation developed in the re-wired animals occupied both dimensions (elevation and azimuth). The authors conclude: "Our results demonstrate that the form of the map is not an intrinsic property of the cortex and that a cortical area can come to support different types of maps" (Roe et al., 1990)

Although these neuroanatomical and neurophysiological data support the idea that the auditory cortex can support visual representations, it remains to be established whether these representations can be used to guide the behavior of the animal in the normal way. To investigate this question, Sur and colleagues trained adult ferrets, re-wired in one hemisphere at birth, to discriminate between visual and auditory stimuli presented to the normal hemisphere. After this they probed the functioning of the re-wired hemisphere by presenting visual stimuli that activated only the re-wired pathway. The ferrets reliably interpreted the visual stimulus as visual rather than auditory (von Melchner, Pallas, & Sur, 2000). These results indicate that visual inputs can direct the construction of the appropriate processing circuitry.

(3) Additional evidence for cortical plasticity comes from studies on rodents in which pieces of cortex are transplanted from one region to another early in



**Figure 2.9** Schematic representation and summary of projections from the sensory receptor surface through the thalamus to the cortex in (A) the normal visual system, (B) the normal auditory system, and (C) lesioned ferrets with retinal projections induced into the auditory pathway.

development. These experiments allow neurobiologists to address the question of whether transplanted areas take on representations appropriate for their *developmental origins*, or the function of the *new location* in which they find themselves.

Pieces of fetal cortex have been successfully transplanted into other regions of newborn rodent cortex. For example, visual cortex neurons can be transplanted into the sensorimotor region and vice versa. Experiments such as these, conducted by O'Leary and Stanfield (1985, 1989), among others, have revealed that the projections and structure of such transplants develop according to their new spatial location rather than their developmental origins. For example, visual cortical neurons transplanted to the sensorimotor region develop projections to the spinal



cord, a projection pattern characteristic of the sensorimotor cortex, but not the visual cortex. Similarly, sensorimotor cortical neurons transplanted to the visual cortical region develop projections to the superior colliculus, a subcortical target of the visual cortex, but not characteristic of the sensorimotor region. Thus, the inputs and outputs of a transplanted region take on the characteristics of their new location.

A further question concerns the internal structure of the transplanted region. As discussed earlier, the somatosensory cortex of the rat (and other rodents) possesses characteristic internal structures known as “barrel fields.” Barrel fields are an aspect of the areal structure of the cortex, and are clearly visible under the microscope. Each of the barrels corresponds to one whisker on the rat’s face. Barrels develop during postnatal growth, and can be prevented from appearing in the normal cortex by cutting the sensory inputs to the region from the face. Furthermore, barrel structure is sensitive to the effects of early experience such as repeated whisker stimulation, or whisker removal (see Schlaggar & O’Leary, 1993, for review). The question then arises whether transplanted slabs of visual cortex take on the barrel field structures that are typical of somatosensory cortex in the rat.

Schlaggar and O’Leary (1991) conducted a study in which pieces of visual cortex were transplanted into the part of the somatosensory cortex that normally forms barrel fields in the rodent. They found that when innervated by thalamic afferents, the transplanted cortex developed barrel fields very similar to those normally observed. Thus, not only can a transplanted piece of cortex develop inputs and outputs appropriate for its new location, but the inputs to that location can organize the internal structure of the cortical region.

At this stage, mention should be made of two caveats to the conclusion that the majority of cortical tissue is largely equipotent early in life. First, most of the transplant and re-wiring studies have involved primary sensory cortices. Some authors have argued that primary sensory cortices may share certain common developmental origins that other types of cortex do not (Galaburda & Pandya, 1983; Pandya & Yeterian, 1990; Krubitzer, 1998). It is possible that certain lineages of cortex which differ in detailed ways from other areas of cortex may be more suited for dealing with certain types of information processing. With regard to the transplant experiments discussed earlier, it may be that cortex is only equipotential within a lineage (e.g. primary-to-primary or secondary-to-secondary).

The second caveat to the conclusion that cortex is equipotential is that while transplanted or re-wired cortex may look very similar to the original tissue in terms of function and structure, it is rarely absolutely indistinguishable from the original. For example, in the re-wired ferret cortex studied by Sur and colleagues the mapping of the azimuth (angle right or left) is at a higher resolution (more detailed) than the mapping of the elevation (angle up or down) (Roe et al., 1990). In contrast, in the normal ferret cortex azimuth and elevation are mapped in equal detail.



## 2.6 DIFFERENTIAL DEVELOPMENT OF HUMAN CORTEX

The main phylogenetic changes in cortical development in primates appear to be in the extent of cortical tissue and the more prolonged period of development in primates and humans. Even between *Homo sapiens* and other primates there is a wide difference in timing, with human postnatal cortical development being extended (roughly by a factor of four) longer than other primates. As discussed earlier, this prolonged postnatal development in humans stretches out differential laminar and regional cortical developments that are more compressed in time in other species. In the case of laminar development, although most cortical neurons are in their appropriate locations by the time of birth in the primate, the “inside-out” pattern of growth observed in prenatal cortical development extends into postnatal life. Extensive descriptive neuroanatomical studies of cortical development in the human infant by Conel over a thirty-year period lead him to the conclusion that the postnatal growth of cortex proceeds in an “inside-out” pattern with regard to the extent of dendrites, dendritic trees, and myelination (Conel, 1939–67). Conel’s general conclusions have been validated with more modern neuroanatomical methods (e.g. Purpura, 1975; Rabinowicz, 1979; Becker, Armstrong, Chan, & Wood, 1984), and a modern re-analysis of Conel’s original data has deemed it to be highly consistent and reliable (Shankle, Kimball, Landing, & Hara, 1998). In particular, the maturation of layer 5 (deeper) in advance of layers 2 and 3 (superficial) seems to be a very reliably observed sequence for many cortical regions in the human infant (Rabinowicz, 1979; Becker et al., 1984). For example, the dendritic trees of cells in layer 5 of primary visual cortex are already at about 60 per cent of their maximum extent at birth. In contrast, the mean total length for dendrites in layer 3 is only at about 30 per cent of their maximum at birth. Furthermore, higher orders of branching in dendritic trees are observed in layer 5 than in layer 3 at birth (Becker et al., 1984; Huttenlocher 1990). Interestingly, this inside-out pattern of growth is not evident in the later occurring rise and fall in synaptic density. For this measure, there are no clear differences between cerebral cortical layers.

Differential development in human postnatal cortical growth is also evident in the areal dimension. Huttenlocher (1990, 1994; Huttenlocher & Dabholkar, 1997) reports clear evidence of a difference in the timing of postnatal neuroanatomical events between the primary visual cortex, the primary auditory cortex, and the frontal cortex in human infants, with the latter reaching the same developmental landmarks considerably later in postnatal life than the first two. It is worth noting that this differential development within the cerebral cortex has not been reported in other primate species (Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986; Bourgeois, 2001). Rakic et al. report that all areas of cortex appear to reach their peak in synaptic density about the same time – around 2–4 months in the rhesus monkey, roughly corresponding to from 7 to 12 months in the human child. Contrary to Huttenlocher’s findings, this suggests that there may be a

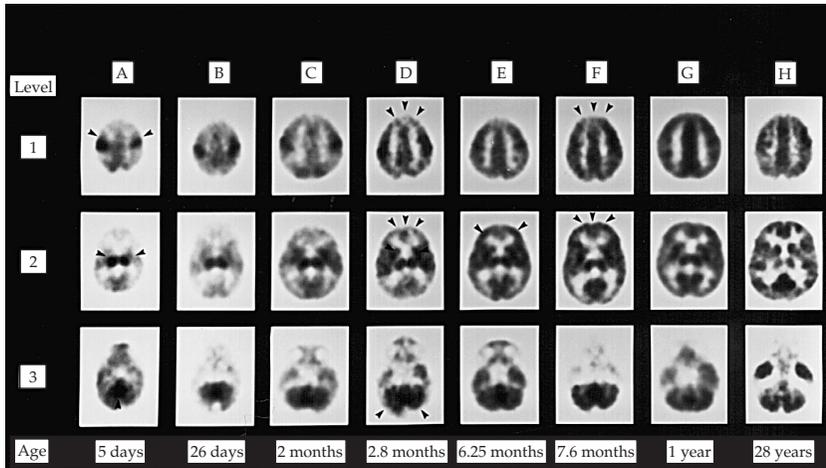


common genetic signal to increase connectivity across all brain regions, simultaneously, regardless of their current maturational state. A sudden event of this kind stands in marked contrast to known region-by-region differences in the time course of cell formation, migration, myelination, and metabolism in the human cortex (Conel, 1939–1967; Yakovlev & Lecours, 1967). The most likely difference between the human results and those from the macaques is that the protracted postnatal development of humans means that regional differences are more evident. In the macaque, however, possible regional differences are compressed into a much shorter time, making them harder to detect (Huttenlocher, 1994). However, Goldman-Rakic (1994) suggests that the differences between the macaque and human results may be due to the neuroanatomical techniques used. Further, the decline in synaptic density in the human brain may not differ between regions, but occur simultaneously at puberty (Bourgeois, 2001).

*FURTHER READING: BOURGEOIS, 2001; HUTTENLOCHER, 2002*

Consistent with the reports from human postmortem tissue, a study in which the functional development of the human brain was investigated by PET has also found differential development between regions of cortex (Chugani & Phelps, 1986; Chugani et al., 2002). In infants under 5 weeks of age glucose uptake was highest in sensorimotor cortex, thalamus, brain stem, and the cerebellar vermis. By 3 months of age there were considerable rises in the parietal, temporal, and occipital cortices, basal ganglia, and cerebellar cortex. Maturational rises were not found in the frontal and dorsolateral occipital cortex until approximately 6 to 8 months. These developments are shown in figure 2.10.

In addition to the formation of dendritic trees and their associated synapses, most fibers become myelinated during postnatal development. As described earlier, myelin is a membrane wrapping around axons that improves conduction. Owing to the increased lipid content of the brain caused by myelination of fibers, structural MRI images can reveal a clear gray–white matter contrast, and this allows quantitative volume measurements to be made during development (see Sampaio & Truwit, 2001). While some controversy remains about the interpretation of images from infants under 6 months (due to a higher than adult water content in both gray and white matter at this age), there is consensus that the appearance of brain structures is similar to that of adults by 2 years of age, and that all major fiber tracts can be observed by 3 years of age (Huttenlocher & Dabholkar, 1997; Bourgeois, 2001). Some reports suggest that after a rapid increase in gray matter volume up to about 4 years of age, there is then a prolonged period of slight decline that extends into adult years (Chugani et al., 2002; but see Huttenlocher & Dabholkar, 1997). Whether this decline in gray matter is due to dendritic and synaptic pruning remains unknown, although in some studies the time course of the rise and fall coincides (Huttenlocher & Dabholkar, 1997).



**Figure 2.10** PET images illustrating developmental changes in local cerebral metabolic rates for glucose (ICMRGlc) in the normal human infant with increasing age. Level 1 is a superior section, at the level of the cingulate gyrus. Level 2 is more inferior, at the level of caudate, putamen, and thalamus. Level 3 is an inferior section of the brain, at the level of cerebellum and inferior position of the temporal lobes. Gray scale is proportional to ICMRGlc with black being highest. Images from all subjects are not shown on the same absolute gray scale of ICMRGlc; instead, images of each subject are shown with the full gray scale to maximize gray scale display of ICMRGlc at each age. (A) In the 5-day-old, ICMRGlc is highest in sensorimotor cortex, thalamus, cerebellar vermis (arrows), and brain stem (not shown). (B, C, D) ICMRGlc gradually increases in parietal, temporal, and calcarine cortices; basal ganglia; and cerebellar cortex (arrows), particularly during the second and third months. (E) In the frontal cortex, ICMRGlc increases first in the lateral prefrontal regions by approximately 6 months. (F) By approximately 8 months, ICMRGlc also increases in the medial aspects of the frontal cortex (arrows), as well as the dorsolateral occipital cortex. (G) By 1 year, the ICMRGlc pattern resembles that of adults (H).

Changes in the extent of white matter are of interest since they presumably reflect inter-regional communication in the developing brain. While increases in white matter extend through adolescence into adulthood, particularly in frontal brain regions (Huttenlocher et al., 1982), the most rapid changes occur during the first 2 years. Myelination appears to begin at birth in the pons and cerebellar peduncles, and by 3 months has extended to the optic radiation and splenium of the corpus callosum. Around 8–12 months the white matter associated with the frontal, parietal, and occipital lobes becomes apparent.

*FURTHER READING: SAMPAIO & TRUWIT 2001*



The differential laminar and regional development observed in the human, as described in this section, provides the basis for many of the associations between brain growth and cognitive change to be described in the following chapters. But first we need to review some other aspects of postnatal brain development.



## 2.7 POSTNATAL BRAIN DEVELOPMENT: THE HIPPOCAMPUS AND SUBCORTICAL STRUCTURES

This chapter has focused primarily on the cerebral neocortex since this is the part of the brain that shows most protracted postnatal development. However, other brain structures such as the hippocampus and cerebellum also show some postnatal development and, as we will see, have been associated with cognitive changes in infancy and childhood. The postnatal development of some subcortical structures (such as the hippocampus, cerebellum, and thalamus) poses something of a paradox: on the one hand, there is much behavioral and neural evidence to indicate that these structures are functioning at birth, while, on the other, they all show some evidence of postnatal development and/or functional re-organization. One explanation for this is that as the neocortex develops postnatally, its interactions with subcortical regions undergo certain changes. Thus, while some subcortical structures are capable of functioning relatively independently of the cortex early in life, the increasing development of the cortex requires some structural and functional adjustment.

The limbic system is normally taken to include the amygdala, the hippocampus, and the limbic regions of cortex (cingulate gyrus and parahippocampal gyrus [entorhinal cortex]). While these latter cortical regions follow the same developmental timetable as other regions of the cortex, they are differentiated from the rest of cortex at an early stage, and are therefore unlikely to show the same degree of plasticity. As discussed earlier, gyral development (folding) does not necessarily indicate architectural specificity. Nevertheless, the gyral folding associated with the cingulate region is discernible as early as 16–19 weeks of gestational age in humans and the parahippocampal gyrus within the temporal lobe at 20–3 weeks gestational age (Gilles, Shankle, & Dooling, 1983). In contrast, other prominent gyri in the cortex do not emerge until 24–31 weeks. The major nuclear components of the limbic system, such as the hippocampus, start to differentiate from the developing temporal lobe around the third and fourth months of fetal development. After this, further differentiation of the hippocampus takes place, resulting in it becoming a rolled structure tucked inside the temporal lobe and surrounded by tissue known as the dentate gyrus (see Seress, 2001, for review). It has been known for some time that in rodents neurogenesis continues into postnatal life in the dentate gyrus region (Wallace, Kaplan, & Werboff, 1977). Recently, it has been confirmed in humans that granule neurones continue to be produced throughout adulthood (for review see Tanapat, Hastings, & Gould, 2001).

This new production of neurons is influenced by hormones (see next section), and, at least in rats, some types of learning enhance the number of new neurons produced. The computational importance of adult neurogenesis in this region remains to be determined.

*FURTHER READING: SERESS, 2001; TANAPAT ET AL., 2001*

The cerebellum is a brain structure thought to be involved in motor control, but which probably also plays a role in some aspects of “higher” cognitive functioning. Within 2 months after conception the cerebellum has formed its three primary layers, the ventricular (V), intermediate (I), and marginal (M) layers. However, its development is prolonged and neurogenesis in this region continues postnatally with only about 17 percent of the final number of granule cells present at birth, and neurogenesis possibly continuing until 18 months (Spren et al., 1995). Despite being one of the few regions of the human brain to show postnatal neurogenesis, cerebellar functional development as measured by resting PET shows high glucose metabolic activity as early as 5 days old (postnatal), the same schedule as other sensorimotor regions such as the thalamus, brain stem, and sensorimotor cortex (Chugani, 1994).



## 2.8 NEUROTRANSMITTERS AND NEUROMODULATORS

The aspects of brain development discussed so far have mainly concerned its neurons and “wiring.” However, there are also developmental changes in what has been referred to as “soft soak” aspects of neural function. Soft soak refers specifically to the chemicals involved in the transmission and modulation of neural signals. Neurons and their dendrites can be thought of as lying in a bath composed of various chemicals that modulate their functioning. In addition, other chemicals play a vital role in the transmission of signals from one cell to another. Neurotransmitters in the cerebral cortex may be classified into those that arise within the cortex (intrinsic), and those that arise from outside the cortex (extrinsic) (see Benes, 1994). The intrinsic transmitters can be further divided according to whether they have an excitatory effect or inhibitory effect on postsynaptic sites.

The intrinsic excitatory transmitter glutamate is thought to play an important role in the axons of pyramidal cells that project to intrinsic cortical microcircuits, other cortical regions, and subcortical regions (Streit, 1984). In rats, the developmental time course of different glutamatergic pathways varies considerably. In general, however, it is the receptors for the transmitter, rather than the quantity of the transmitter, that increase with postnatal age. This development seems to



follow the rise and fall pattern seen in other aspects of neural development. Specifically, in the rat between postnatal days 10 and 15 the amount of glutamate binding in cortical regions increases rapidly and reaches a peak around ten times the levels observed in adults (Schliebs, Kullman, & Bigl, 1986). By day 25 these levels have reduced drastically.

GABA (Gamma-aminobutyric acid) is probably the most important intrinsic inhibitory transmitter in the mammalian brain. While there are a variety of ways to measure GABA activity which sometimes give differing results (see Benes, 1994), in the human the same overall pattern of rise and fall seen for glutamate is also observed for GABA. Specifically, the density of GABA receptors increases rapidly in the perinatal period and doubles over the first few weeks before later declining (Brooksbank, Atkinson, & Balasz, 1981). The extent to which the rise and fall in these intrinsic neurotransmitters mirrors that observed in the structural measures discussed earlier such as glucose uptake and synaptic density is currently unclear and requires further research. It is clear, however, that the levels of GABA can be influenced by the extent of sensory experience (Fosse, Heggelund, & Fonnum, 1989).

Extrinsic neurotransmitters arise from a number of different subcortical locations. One of these transmitters, acetylcholine, originates mainly from the basal forebrain (Johnston, McKinney, & Coyle, 1979). Interestingly, the innervation of cortex by cholinergic fibers follows the "inside-out" pattern of growth described earlier, with the deeper cortical layers being innervated before the more superficial ones. In humans, this cholinergic innervation begins prenatally, though adult levels are not reached until about 10 years old (Diebler, Farkas-Bergeton, & Wehrle, 1979). However, the binding sites within the cortex for this transmitter decrease from birth onwards, possibly due to synaptic pruning (Ravikumar & Sasatry, 1985).

Another neurotransmitter with origins outside the cortex is norepinephrine (or noradrenaline), which originates in a cluster of nuclei called the locus coeruleus. As well as its role as a neurotransmitter, norepinephrine has been associated with cortical plasticity (Kasamatsu & Pettigrew, 1976). In several mammals there is an extensive network of noradrenergic fibers in the cortex at birth which may be more dense than that seen in adults (Coyle & Molliver, 1977). Currently, little developmental information is available on this transmitter in primates (Benes, 1994).

Serotonin originates in the brainstem raphe nuclei, and in both rats and primates the level increases rapidly over the first few weeks of life (Johnston, 1988). In rhesus monkeys the adult pattern of projection of serotonin fibers is reached by the sixth week postnatal, though levels of serotonin continue to rise after this (Goldman-Rakic & Brown, 1982). There is some evidence (from specific binding sites) of a later decrease in serotonin in human cortex and hippocampus (Marcusson, Morgan, Winblad, & Finch, 1984). Like acetylcholine, serotonin is found mainly in the deeper cortical layers at birth, consistent with the structural inside-out gradient of development discussed earlier.

The fourth main extrinsic cortical transmitter, dopamine (which originates in the substantia nigra), likewise shows an inside-out pattern around the time of birth, at least in rats (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988). Dopaminergic fibers show the adult pattern of projection into the frontal and cingulate cortex through extended postnatal development in rats (Bruinink, Lichtensteinger, & Schlumpf, 1983).

In summary, it appears that:

- Most intrinsic and extrinsic transmitters are present in the cortex at birth, at least in rats and probably also in humans, but show changes in distribution and overall levels for some time after birth.
- Several transmitters of both intrinsic and extrinsic origins show the characteristic rise and fall evident in some measures of structural neuroanatomical development. Owing to a paucity of human data, it is currently not possible to say to what extent these developmental patterns overlap.
- Several transmitters of extrinsic origin show the same inside-out gradient of cortical development observed in structural measures.
- Neurotransmitters may play multiple roles during development. For example, noradrenaline may also regulate cortical plasticity.
- Some transmitters show a differential distribution throughout the cortex. This differential distribution may play some role in the subsequent specialisation of regions of cortex for certain functions.

*FURTHER READING: BENES, 2001; CAMERON, 2001; BERENBAUM ET AL., 2003; RICHARDS, 2003*



## 2.9 GENERAL SUMMARY AND CONCLUSIONS

This chapter has reviewed the pre- and postnatal development of the human brain. While many of the landmarks of development are similar between humans and other mammals, the timing of human brain development is characterized by being slower and more protracted. According to some theories, this slowed development allows the building of relatively more cortex, and particularly frontal cortex. One major feature of human postnatal development is that brain volume quadruples between birth and adulthood, mainly due to increases in nerve fiber bundles, dendrites, and myelination. Another major feature is that several measures of structure and neurophysiology, such as the density of synaptic contacts, show a characteristic “rise and fall” during postnatal development.

The issue was raised as to whether the differentiation of the neocortex into anatomical and functional areas is prespecified. The “protomap” hypothesis states that the differentiation of the cortex into areas is determined by intrinsic molecular



markers or prespecification of the proliferative zones. The “protocortex” hypothesis states that an initially undifferentiated protocortex is divided up largely as a result of input through projections from the thalamus and is activity-dependent. A review of currently available evidence supports a middle-ground view in which large-scale regions are prespecified, while the establishment of small-scale functional areas require activity-dependent processes.

The very extended period of postnatal development seen in the human brain reveals two differential aspects of cortical development not as clearly evident in other primates: an inside-out pattern of development of layers, and differences in the timing of development across regions. These differential aspects of human cortical development will provide the basis for associations between brain and cognitive development described in later chapters.