The cerebral cortex of mammals is largely responsible for their complex behavioural repertoire, and is a comparatively new structure in phylogenetic terms. The late expansion of the neocortex has resulted in an organ that is highly structured in two orthogonal planes. Parallel to the pial surface are six layers, each of which contains neurons with similar morphology and projection patterns. The formation of this pattern is now well understood: post-mitotic neurons migrate away from a proliferating peri-ventricular zone and form distinct layers (laminae) in the developing cortical plate.

The cortical layers are generated in an inside-out pattern; neurons of the deep layers 6 and 5 arrive first in the cortical plate, and are followed by cells of layers 4, 3 and 2. Progenitor cells undergo cyclical changes in their capacity to migrate, and the laminar fate of transplanted neurons correlates with their position in the cell cycle prior to transplantation; the later in the cycle they are transplanted, the deeper the layer in which they end up. It is probably correct to regard layers 1 and 6 as representing primitive structures found in the amphibia and in reptiles, and to consider them to be phylogenetically older than the cortical plate. The presence of these two zones suggests that the mammalian neo-cortex has a dual origin and nature. The cortical plate is a new and distinctly mammalian structure that has grown by the addition of new laminae under the primitive plexiform layer 1. The ‘inside-out’ neuronal migration mentioned above is characteristic of the mammalian cortex: late-produced cells migrate past older cells and end up in more superficial positions. In the reptilian cortex, the opposite situation obtains; the first cells to be produced migrate furthest, and later-born cells end up in progressively deeper positions. Furthermore, not all of the mammalian cortex is formed in the same way: the dentate gyrus develops in an outside-in sequence like that of reptiles (see reference 1).

The definitive six layers are found everywhere in the cortex and the connections with the thalamus of layers 4 (afferent) and layer 6 (efferent) appear to define boundaries between cortical areas. Co-cultures of pieces of cortex and thalamus form axonal connections that obey these laminar-specific arrangements, and interaction between in-growing axons from the thalamus and local cells are clearly necessary in their formation.

Perpendicular to the surface, the cortex is arranged in functional sets, with columns of neurons sharing afferent inputs and responses. Combinations of these columns form spatially distinct areas with specialist functions. This division of the cortex into 40 or so functionally distinct areas without clearly defined morphological margins might have come about by a number of mechanisms. It is possible that the cells in each area have been determined at their origin in the germinal zone near the ventricular surface, and that this origin thus has a ‘map’ of future destinations. This seems unlikely, despite attempts to draw analogies with the homeobox effects seen in the hindbrain, since transplant experiments suggest that local and functional interactions specify the identity of the cortex. Cells originating from quite diverse sites may come together to constitute a particular area. Hardy and Friedrich have shown that oligodendrocyte precursors, for example, arise in multiple foci in the neurectoderm, but differentiate into non-mitotic myelin-bearing cells only in specific areas in a tract-specific manner, supporting the notion of local regulation of progenitor differentiation. Cell markers appear to be associated with broad areas of the telencephalon, and do not change with maturation changes. Activity clearly plays a role in determining cytoarchitecture, a fact demonstrated most clearly in the visual pathways.

In the developing cortex, a system of radial glial fibres acts as axonal guides. On exiting the cell cycle, the neuroblast associates with a radial glial cell and migrates along it. Two-way signalling, involving receptors and ligands such as neuregulin...
and ErbB4, occurs between neuroblasts and glia, and is critical to the control of neuronal migration, which is slowed down or blocked altogether by inhibition of the signalling systems. The neural antigen astrotactin (an integrin), important in the formation of interstitial junctions between migrating neurons and their support, increases the rate at which neurons move, but antibodies to this integrin slow migration dramatically and disrupt the cytoskeleton of the migrating neurons.

The study of the Reeler mouse (an autosomal recessive mutant discovered over 50 years ago) provided the first insights into the molecular basis of laminar organization. The mouse has a mutation in the Reelin gene, which encodes a large extracellular matrix protein. Cells in the cortical marginal zone and granular cells in the cerebellum secrete reelin, which resembles tenascin in acting as a matrix protein to stabilize early patterns in many parts of the CNS. Anti-reelin antibodies disturb the process of developing normal architecture, and neuronal migration defects are the central abnormality. In these mice, neurons are developed in normal numbers and at the normal time, and initial neuronal migration occurs normally, but results in an inversion of the normal arrangement of cortical layers. The reelin mutation prevents migrating neurons separating from the radial glia, and so cells keep migrating until they reach the barrier of the subpial layer. Thus the first to migrate travel furthest, and later migrants find their paths blocked and stop short. A practically identical phenotype is produced by a defect where the abnormality is one that affects the cell membrane receptor for reelin in the matrix. Protein-receptor binding provides the stop signal for neuronal migration, and mice that lack all β-1 class integrins in neurons and glia die prematurely with severe brain malformations. In the lissencephalic brain, the normal six-layered cortical architecture fails to form. In classical (type I) lissencephaly, there is typically a four-layered cortex. Type II lissencephaly (‘cobbledstone cortex’) is believed to be due to neuronal overmigration, and is most commonly seen in patients with Walker-Warburg syndrome. In this condition, there are defects in the pial-glial limiting membrane, and neuroblasts migrate into the leptomeninges.

A recent study on polygyria in Man has provided more data about the formation of the cortex and its convolutions. There are several forms of this condition: bilateral frontal polymicrogyria (BF), bilateral frontoparietal polymicrogyria (BFPP), bilateral parieto-occipital polymicrogyria (BOPOP) and bilateral perisylvian polymicrogyria (BPSP). In each instance, mutations in the GPR56 gene family (this encodes a G-protein-coupled receptor—eight separate mutations have been identified) have been identified in homozygotes. It appears that mutations in specific genes affect cell proliferation only in particular regions of the peri-ventricular zone. The implications of this are profound; it suggests that there is a map in the proliferative zone rather than a mass of equipotent cells. Could mutations have resulted in sudden expansion of specific cortical areas? (think about speech and see ‘What’s the difference?’ in this series). It is also important to note that although the affected cortex has a larger than normal surface area, it is thinned. This is what has happened in the evolutionary development of the brain: as the cortex has expanded the number of radial units has gone up but the cortex has not thickened.

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References