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Reviews

Getting there and being there in the cerebral cortex

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Received 4 November 1994; accepted 11 November 1994

Abstract. The mammalian neocortex is composed of functional areas that are specified to process particular aspects of information. How is this specification achieved during development? Since cells migrate to their final positions in the developing nervous system, a central issue is the relation between cellular migration and positional information. This review combines evidence for early positional specification in the developing cortex with evidence for cellular dispersion during migration. A model is suggested whereby stable cues provide positional information and minorities of 'displaced' cells are respecified accordingly. Comparison with other parts of the CNS reveals that cellular dispersal is ubiquitous and has to be included in any mechanism relaying positional specification. Ontogenetic and phylogenetic considerations suggest that radial glial cells might provide the positional information in the developing nervous system.
Key words. Migration; patterning; cell fate; cortical areas; radial glia; hindbrain; neural crest.

Neurons are located at specific positions and perform specific functions. This reflects the distinct phenotypes expressed by neurons at different positions: they project to different targets and receive specific inputs, they express various neurotransmitters, receptors and ion channels and develop a characteristic morphology. Therefore a fundamental question is how the correlation between position and phenotypic specialization is acquired during development. Since neurons migrate to their final position, this question is wrapped around migration (fig. 1). Are cells specified *before* or *after* migration?

A particularly striking regional organization is present in the mammalian neocortex. Different cortical areas analyse particular aspects of sensory or motor information, but they share common organizational principles. How and when is this positional specification acquired during cortical development (see fig. 2)? Answers to this question polarize into two suggestions. Regional differences in the cortex could be predetermined at early developmental stages, assuming a protomap in the proliferative zone preceding the functional map present in adult cortex[119]. Alternatively, cortical precursor cells might be equipotential and neurons would acquire their positional specification rather late during development (fig. 2)[109]. As mentioned above, these models are related to the migration of neurons. How do the cells choose their final position and how are cell fate decisions related to this choice? This is asking whether neurons are specified *before* migration and therefore select their correct position and cell fate, or whether neurons acquire their phenotypic specializations *after* they have arrived randomly at their respective positions (figs 1 and 2). One way to address this issue is to examine whether migration is confined or random. Restricted migration is often regarded as evidence for premigratory specification and random migration seems to argue for postmigratory specification of neurons. This conclusion, however, can be misleading. The migrational pattern itself does not reveal the mechanism by which it is achieved. The migrational pattern, however, has to be known to examine how and when positional and fate specifications are made during development.

This review will discuss the relation of migrational patterns and regional specification during cortical development. Before doing so, it seems instructive to consider the answers to these questions that have been found in other parts of the CNS.

Positional specification and migration in the CNS

Two examples are set out below in which the relation of migration, positional specification and cell fate has been better examined than in the developing cortex, where these questions are just beginning to be asked. Moreover, these two precedents serve to illustrate two major issues discussed later for the developing cortex. First, they represent the two potential timings of positional specification. With approximation and simplification the neural crest derivatives may be said to be specified at later, postmigratory, stages whereas in the developing hindbrain early positional information seems to instruct cells prior to migration. Second, these examples will serve to underline that the timing of specification can-

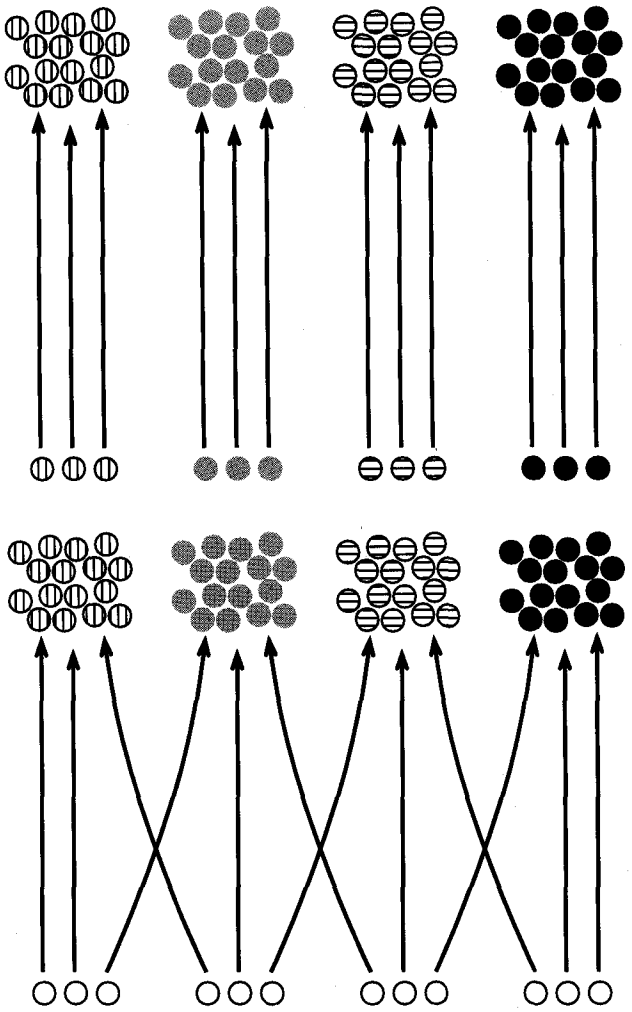

Figure 1 illustrates the central question of this review: how is it that specific types of neurons differentiate at particular locations? Since neurons have to migrate to their final positions, this question polarizes into the two possibilities illustrated here: is positional specification present *prior* to migration (upper panel) or is it instructed *after* neurons have acquired their final locations (lower panel)? In each case, the migrational pattern can be either ordered or dispersed. Thus, cellular migration and positional specification are related, but neither allows conclusions about the other.

not be inferred from the migrational pathway itself, but emerges from a variety of experimental approaches aiming at cellular specification in vivo and in vitro.

Neural crest cells originate from the neural tube along the rostrocaudal axis. They leave the neural tube just after its closure and disperse ventrolaterally along well-defined routes, accumulating at specific locations (for an overview see e.g. refs 2, 77, 89). At these respective positions cells differentiate into a variety of cell types, as illustrated in figure 3 (adapted from ref. 89). For example, at location 1 neural crest derivatives become melanocytes, at a different location 2 they become neuronal and glial cells, and at the most ventral position 5 they develop into adrenomedullary cells. Cells located at these different positions exhibit a wide range of different phenotypes that are all derived from an individual neural crest cell labeled prior to migration (fig. 3)[18,19,37]. However, not all the different cell types are generated by a single early neural crest cell. Thus, migration even of clonally related cells cannot answer when and how specification is acquired. Are there different types of neural crest cells specified at least to some extent prior to migration, or is the acquisition of different phenotypes influenced by the final position where cells arrive stochastically? The picture emerging from decades of research seems to be that neural crest cells have a broader potential at the onset of migration and then become progressively restricted in their potential towards the end of migration (for a more detailed discussion see ref. 2). This has been demonstrated by isolation in vitro that examines the specification of cells[3,11,31,136], and by transplantation in vivo to examine the potential of cells[77,78,81,132]. After isolation or transplantation of premigratory neural crest cells a greater variety of descendents is observed[11,132,136] than after isolation or transplantation of postmigratory neural crest cells taken from their final positions[3,31,77,78,81].

Neural crest cells generate a variety of cell types that differs, however, along the rostrocaudal axis (for an overview see ref. 2). For example, enteric ganglia are generated only by neural crest cells at the vagal and sacral level and exclusively cranial neural crest generate cartilage, bone and dentine[81,106,107]. There are fundamental differences between trunk and cranial neural crest that seem to relate to how these regions are patterned. Trunk neural crest cells are multipotential in their rostrocaudal specification: when they are transplanted along this axis they generate the respective appropriate cell types according to their new position[77]. This is different for the cranial neural crest that apparently carry a rostrocaudal specification and after transplantation generate and induce specific tissues and organs at the 'wrong' locations[106–108]. Thus, premigratory crest cells in the head carry positional information in one dimension, the rostrocaudal axis, but not for the dorsolateral extension (for differences between these axes in the spinal cord see ref. 80) where they generate a variety of different cell types at different locations as described above. This is critical to bear in mind for any discussion of positional specification.

The prominent differences between trunk and cranial neural crest correspond to profound differences in the mechanisms of patterning between the caudal and rostral neural tube. In the hindbrain, both CNS neurons and neural crest cells are in register with a transient segmental organization, visible as repetitive units that are called rhombomeres[90,91]. In contrast, similar units found in the spinal cord (the neuromeres) have no underlying segmented organization[86]. The rhombomere organization seems to be set up by early patterned

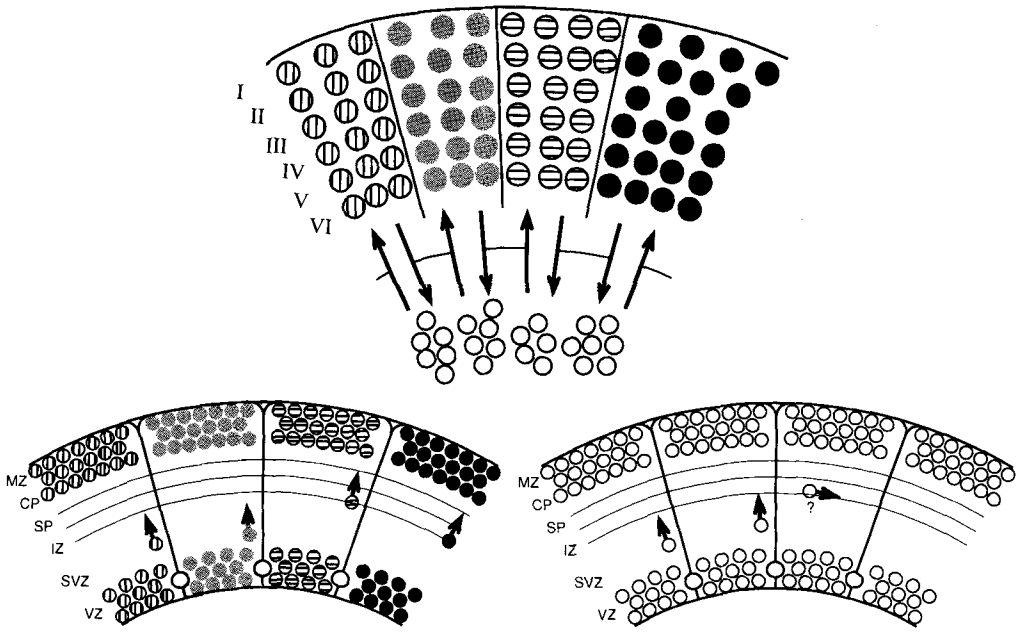

Figure 2 is a schematic illustration of the functional area specification in the adult mammalian neocortex (upper panel) and the two models of how this specification is achieved during development (lower panels). The horizontal layers are indicated on the left.
During development, cortical neurons migrate along radial glial cells that span the distance between the ventricular and pial surface. They then settle in the cortical plate, the predecessor of the cortical layers 2–6. Abbreviations of the layers in the developing cortex: MZ = marginal zone, CP = cortical plate, SP = subplate zone (for the sake of simplicity cells located at this position are omitted to better illustrate the horizontal fiber paths), IZ = intermediate zone, SVZ = subventricular zone, VZ = ventricular zone. Tangential migration of cortical neurons seems to occur predominantly along the subplate, intermediate and subventricular zone (indicated by the cell and question mark in the lower panel to the left).
Positional information could be present in the ventricular zone ('protomap'), where cortical neurons are generated (lower left panel). Primarily radial migration (along radial glial cells) would provide positional continuity from the ventricular zone (the 'protomap') to the cortical plate that forms most of the adult cortical layers (the 'map').
The alternative model (lower right panel) suggests that specification occurs only at later developmental stages after interaction with afferent fibers (arrows in the upper panel; the horizontal lines in the lower panels indicate the presence of these fibers that, however, do not yet make contact with their final target cells). Accordingly, cells in the developing cortex are homogenous and equipotential ('protocortex').

expression of transcription factors that are also involved in segmentation in other species (for reviews see refs 45, 75). This is most strongly supported by manipulating their expression patterns: this then alters rhombomere organization and the cell fates in the affected rhombomeres[22,23,75,88]. Once the pattern is set up, it is autonomous and resistent to transplantation[54]. The patterned positional information then organizes various cellular aspects, like proliferation, axonal projection and migration[16,25,36,91].

After rhombomeres are established, migration is confined within a given rhombomere[36], however, only to a quantitative extent, since a small but consistent proportion of cells migrate from one into the other rhombomere[16]. This is illustrated in figure 4. In principle, such a migrational pattern could be achieved by two mechanisms: either cells are prespecified and are restricted in their mixing supposedly by the expression of specific adhesion molecules[53], or they are all the same, but isolated in different compartments by the prominent rhombomere boundaries that express specific cellular, molecular and mechanical properties[58] (fig. 4). The experimental evidence rather supports the first scenario, but the exact mechanisms and the sequence of events still remains to be determined. For our discussion we learn from this example that a restricted pattern of migration itself does not reveal the specification of the migrating cells. Thus, cellular dispersion does not prove that the migrating cells are multipotential (as described for the neural crest) and restricted migration does not show restricted cellular potentials. Moreover, confinements are quantitative phenomena and models about positional specification have to account for a minority of displaced cells (see below). With this in mind, we will now address the relation of regional specification and migration in the mammalian neocortex.

Positional specification in the cortex

The cortical organization is particular in its pronounced dichotomy of a homogeneous organization throughout the cortex and a heterogeneous specification of distinct areas. This dichotomy is reflected in the debate about

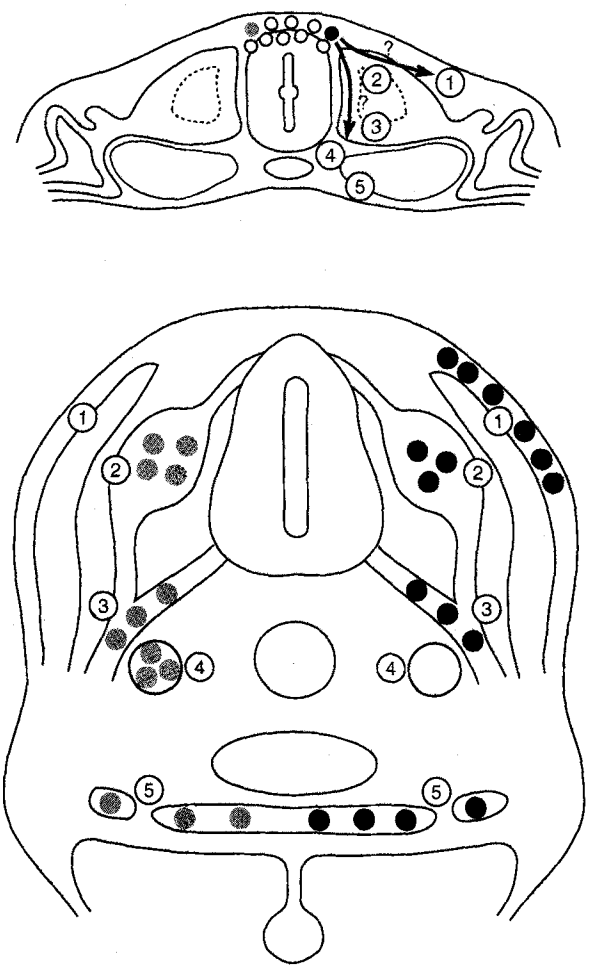

Figure 3 summarizes the migration, final positions and cell fate decisions of clonally related neural crest cells (adapted from ref. 89). Bronner-Fraser and colleagues used single cell dye injections to label precursor cells prior to migration (upper panel) and then analyzed their descendents after migration (lower panel)[18,19]. Neural crest cells migrate along specific paths (arrows) and populate various parts of the dorsolateral axis, where they acquire distinct phenotpyes: at position 1 melanocytes, at positions 2 and 3 neurons and glia, at position 4 sympathetic neurons and at position 5 adrenomedullary cells. Whereas clonally related cells can acquire a range of different positions and phenotypes, there are also differences: descendents of the grey precursor cell (left side) do not populate the most dorsal position 1 and form melanocytes, whereas the descendents from the black precursor cell (right side) do not contribute to the sympathetic nervous system.

development. The view of the cortex as a homogeneous information-processing device stresses the similarity between cortical areas and attributes a major role to the sensory input. Accordingly, the developmental hypothesis, the 'protocortex', suggests late specification of equipotential cortical cells[109]. From the other perspective, the importance of the positional specifications suggests that they are laid down early as a 'protomap' that influences various aspects of cellular phenotypes.

Focused on this dichotomy of homo- and heterogeneity, the adult cortical organization will be briefly described to provide the basis for the developmental issues. The functional heterogeneity across the surface of the cortex is undisputed and has already been observed several thousand years ago by Egyptian physicians[21]: localized cortical lesions were found to correlate with specific impairments in function. This functional parcellation of the cortex has been studied through the centuries and has led to the mapping of the cortical surface (e.g. refs 112, 150). Now, we know that cortical neurons that deal with particular aspects of stimuli are arranged in radial columns[65,105]. This is best illustrated in the visual cortex. For example, neurons analyzing colour or a specific orientation of visual stimuli are stacked on top of each other to form a radial column of a few hundred micrometers thickness[65]. Adjacent columns analyze related aspects (like all the different orientations) and the entity of columns processing all the different aspects of a sensory stimulus originating from one point in the sensory surroundings are called 'hypercolumns' or 'modules'. Several modules are devoted to analyzing particular submodalities, for example motion. The whole entity of radial arrays dealing with the same modality then constitute the visual cortex, the somatosensory or the acustic cortex. Most broadly, areas dealing with motor tasks are assembled rostrally, and sensory areas in the occipital and parietal cortex.

The histological correlates to these functional specifications are less obvious and are still being discovered. Clearly, neurons located in different areas differ in their connectivity. Efferent projections from the motor cortex are to contact other target neurons than efferent projections from sensory coretx and, conversely, they have to receive their appropriate afferent innervation conveying the respective sensory stimuli (fig. 2). Further aspects of neuronal phenotypes also vary, to a quantitative extent, between cortical areas: there are differential expression patterns of transmitters, neuropeptides and various receptor molecules[20,57,66,67,150,151]. Finally, histological staining techniques reveal patterns that correspond to functional areas[12,56,62,87]. For example, cytochrome oxidase or acetylcholinesterase intense regions ('blobs' and stripes in primate cortex) correspond precisely to areas processing specific aspects of visual information.

However, all these differences are variations of a common theme. The organization of the cortex is strikingly similar throughout the functional areas (e.g. refs 40, 109, 124). As mentioned above, there are quantitative differences in the expression of neuropeptides etc., but the overall cellular composition is fairly homogeneous. The majority of cortical neurons are projection neurons that exhibit a characteristic pyramidal-like morphology and use excitatory amino acids as transmitters, and the remaining interneuronal population exhibit a different morphology and use the inhibitory transmitter GABA[15,63,111,113,137]. The relative composition of these major cell types seems to be rather constant between a

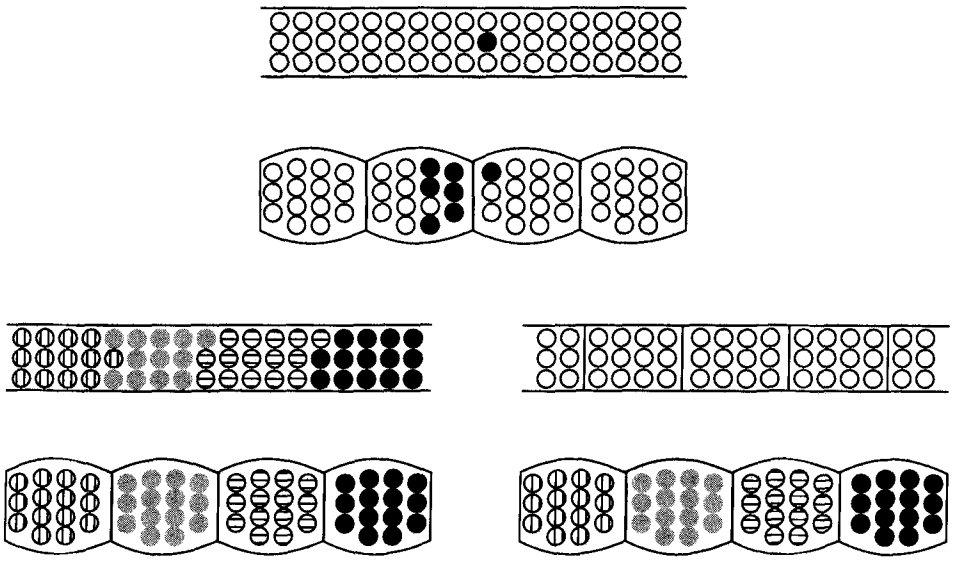

Figure 4 illustrates the migrational pattern (upper panel) and potential ways of regional specification (lower panel) for the developing hindbrain. The hindbrain is set up via a transient segmented organization that restricts cell migration to a great extent within the segment boundaries. A minority of cells, however, can also cross between the segments (upper panel; data from Fraser and colleagues[16,36]).
Similarly to the models proposed for the developing cortex (see fig. 2), positional specification can be achieved by two potential mechanisms (lower panels). Either cells carry positional information *prior* to migration and isolation in the segments (left lower panel), or their specification occurs *after* they are isolated in different compartments and exposed to distinct environmental influences (right lower panel). So far, the experimental evidence rather argues in favor of the first model.

variety of different areas[15,57]. Moreover, the neuronal diversity in the cortex is arranged in horizontal layers in which neurons throughout different areas share their projection targets or other morphological and neurochemical traits (see e.g. refs 40, 100, 113).

Thus, there are two organizational principles in the cortex, a horizontal one and a radial one, and in both neurons have specific properties in common. To each of these there is a developmental correlate. Neurons arranged at the same layer position are generated at similar times during development[4,13,97,118]. From their generation side, the ventricular zone, cortical neurons migrate – radially – towards the pial surface where they form cortical layers in an inside-first outside-later fashion. This migration from the ventricular zone to the pial side is guided by radial glial fibers that extend across the entire cortical width[55,117]. Thus the birthdate of cortical neurons is the developmental correlate for the horizontal, layered organization and the radial migration is comparable to the radial organization of the adult cortex (fig. 2). The pivotal question is whether these developmental correlates are significant. For example, does the birthdate of neurons determine their layer and the radial migration their tangential position? In other words, do neurons know their position prior to migration, or do they just migrate anywhere and later become specified at their eventual position? In general, these questions are yet to be answered. As for the lamina position, transplantation studies have provided evidence that it is specified before the onset of migration[101]. When cortical cells are transplanted during S-phase to a host cortex that currently forms a different layer, they adapt to their new environment and migrate to the layer position that is generated in the host. However, when transplanted only a few hours later, just after completion of the S-phase in their final division, the transplanted cells maintain their fate and migrate to the layer position appropriate for their own birthdate. Thus at least the lamina position seems to be specified prior to migration. It remains to be determined whether this specification includes further fate decisions, like the projection or morphology that is characteristic for cells at particular layer positions. Moreover, there is a considerable amount of cellular dispersal between different cortical layers (especially in rodent cortex), i.e. cells of the same birthdate are scattered at different laminar positions. Are these cells not specified or will they become respecified? As will be discussed in detail below, models concerned with the acquisition of position-specific cell fates have to consider cellular dispersal.

Whether radial position is specified similarly to the lamina position to some extent prior to migration is less clear and the experimental evidence for or against it will be discussed. The anatomy of radial glial cells along which cortical neurons migrate[38,55,117,120] and the radial arrangement of cells in developing cortex has prompted the suggestion of the radial unit hypothesis[119]. This hypothesis predicts that migration along the radial glial fibers maintains a radial alignment between a neuron's place of birth (in the ventricular zone) and its final position in adult cortex. This has been taken further to suggest the existence of positional specification present in

the ventricular zone (the 'protomap') preceding as an anlage the adult positional specifications (the 'map'). Before we continue to discuss these issues, it is important to be clear that these are two distinct predictions: one about the migrational pattern, in 'radial units', and the other about positional information present in the ventricular zone[119,120]. As pointed out above, the first does not directly relate to the latter; restricted migration is one, but only one, way to transmit positional information from the ventricular zone to the adult cortical 'Grey Matter'. In the absence of radial migration, positional information could still be present. Hence, these questions will be discussed sequentially – first, the data about neuronal migration in the developing cortex will be reviewed, focussing on radial restriction or tangential dispersion (the molecular basis of neuronal migration that has been excellently reviewed will be mostly excluded: refs 24, 55, 120, 121), and then we will examine the available evidence for early positional specification in the cortex.

Migration in the cortex

Neuronal migration in the cortex is radial in that cells migrate from the ventricular zone towards the pial side (fig. 2). This process seems to be essential for neuronal differentiation: when postmitotic cells remain in the ventricular zone, their further development is strongly impaired. For example, in slice cultures from embryonic rat cortex, neuronal migration stops after some time in vitro and the cells that remain in the ventricular zone fail to differentiate[41]. In the same cultures, however, cells that do migrate differentiate normally (Götz and Bolz, unpubl. observ.). When migration is impaired in vivo, for example by irradiation or drug treatment, differentiating neurons form islands outside the ventricular zone[68,148]. Cell-cell interactions within the ventricular zone sustain mitotic activity (Temple and Davis, Neurosci. Abstr., 1992), thereby seemingly interfering with differentiation, and only when contact to other ventricular zone cells is lost does mitotic activity stop and cells differentiate. Thus, the radial movement of neurons out of the ventricular zone seems to be essential for normal differentiation.

There is also a prominent tangential component of migration in developing cortex. Indirect evidence for tangential movements was gained some time ago, but new labeling techniques have now enabled its direct observation[35,110]. First, anatomical studies have observed horizontally oriented cells during migration in the neocortex[30,59,130,135]. Second, cell cohorts migrating in tangential streams were visualized – though in still and black and white pictures – when cells had been labeled at their birthdate (by the use of DNA-base-analoga) and their movement was examined later in sequential times series[13,14,28]. Third, fluorescent dyes now allow the migration of living cells to be followed using time lapse video microscopy[35,60,110]. These experiments have shown directly that the majority of cells in cortical slice preparations migrate radially, some (22%), however, alter their radial migration to a tangential direction[110]. These directional changes were all observed in the intermediate zone (see fig. 2), but similar data were obtained when migration was studied in the ventricular zone: 66% of all labeled cells move no further than 200 μm tangentially during 8 hours, the period of observation[35]. Early during development, however, shorter tangential movements were found in the ventricular zone during an even longer 48 hours observation time (O'Leary and Borngasser, Neurosci. Abstr. 1992).

Labeling with genetic markers that are introduced in individual precursor cells allows one to assess the dispersion of labeled cells at much later developmental stages. Replication-incompetent retroviruses are used as vectors to introduce a stable genetic marker (usually LacZ encoding the enzyme β-galactosidase) into dividing cells[115,125,126]. Once this marker is inserted into the DNA, it is passed on to the progeny of the infected cell and the distribution of these descendants can then be studied in adulthood. Moreover, this technique can be used to assess cell lineage, since all the progeny derived from one infected precursor cell, i.e. a clone, is labeled (however, problems arise when migration *and* cell lineage are both unknown[74,144]). One of the major results of this approach is that the dispersion of cells differs considerably in different parts of the brain (fig. 5). Labeled cells in the retina and the midbrain are found in tightly packed radial clusters and most do not spread further than 50 μm[46,48,139]. In pronounced contrast, the clusters found in the cortex (and in the avian telencephalon[47]), are much more loosely arranged: the majority of labeled clusters cover between 200 μm in the hippocampus and 300 μm in the neocortex[7,51,144]. Moreover, about a third of all cells labeled in the neocortex disperse over much longer distances, some even over centimeters[7,144,145]. Interestingly, the proportion of wide-spread clones is comparable to the proportion of the tangentially migrating dye-labeled cells (see above). A further consensus of various studies is that most tangential dispersion occurs in the intermediate zone[7,13,28,110,145].

In summary, the following picture about migration in the cortex emerges: Migration of cortical cells is clearly more dispersed than in other parts of the brain where cells migrate in tight radial clusters. Thus, the prediction of cells migrating in 'radial units' is met in some parts of the CNS, but not in rodent cortex. However, in primate cortex, which has prompted the radial unit hypothesis, it remains still untested. The developing primate cortex exhibits prominent radial columns of cells (Dehay and Kennedy, pers. commun.) that are less apparent in rodent cortex. Columnar arrangements of cells can also be observed without any labeling in the developing retina

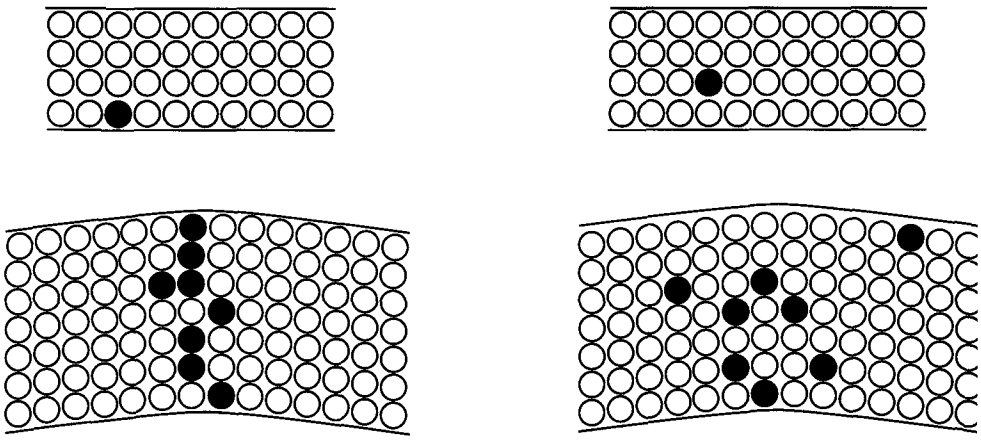

Figure 5 illustrates the radial dispersion of neuronal cells in different parts of the CNS. These data are derived from labeling with a stable genetic marker that is introduced in individual precursor cells (upper panels) by a retroviral vector[7,47,48,51,52,104,114,139]. Clonally related cells in the mammalian retina and avian midbrain are arranged in radial clusters (left panels) whereas more tangential dispersion is observed in the mammalian (and avian) telencephalon (right panels).

(e.g. ref. 123) where retroviral studies have revealed radial columns of migrating cells. Therefore it will be very interesting to examine migrational patterns in primate cortex (see also the final remarks below). However, even in the species and parts of the brain (rodent retina and avian tectum) where columnar migration has been demonstrated, its relation to the adult columnar organization still awaits experimental evidence.

How is the tangential dispersion in rodent cortex related to cortical areas? There are two classes of tangential cellular dispersion: a minority of cells spreading over large distances and a majority of cells remaining within a radius of a few hundred micrometer. The first, wide-spread population clearly cross functional boundaries; in fact they even enter different telencephalic domains[13,14,28,92]. This is particularly striking because different parts of the telencephalon exhibit a distinct organization and development. For example, cells originating in the six-layered neocortex migrate into and contribute to the three-layered limbic cortex[14], the hippocampus[28] or even the olfactory bulb[92]. The most pronounced difference in organization of the telencephalon is found between the nuclear basal ganglia and the laminated neocortex. Even there cells disperse and apparently contribute to the other compartment[13,145]. Fishell and colleagues[35], however, have found that transition between these compartments in the ventricular zone is hindered – the only migrational restriction so far reported in the telencephalon. Later during development, however, neocortically derived cells seem to be able to cross between these compartments and enter the basal ganglia[13]. These results are consistent with recent reaggregation experiments that found adhesive differences between cells taken from the basal ganglia and the neocortex at early stages that then disappear during later development (Götz et al., Neurosci. Abstr. 1994). Taken together, these observations suggest that regional specification is set up at early developmental stages and later cellular dispersal can be accommodated. This prompts the interesting question of how the migrating cells are incorporated into a completely differently organized telencephalic region.

The second major cell population does not migrate far enough to cross between telencephalic domains, but the cells seem to disperse freely across functional boundaries within the cortex. This can be seen in the rodent somatosensory cortex, where functional regions can be easily visualized[144] (Moore and Price, unpubl. observ.). Moreover, a quantitative analysis of clonal dispersion in the hippocampus revealed a free, stochastic dispersion of *neuronal* (for discussion see below) clones across area boundaries[51]. Thus, in contrast to the results obtained in the hindbrain[16,36], cortical fields do not reveal any migrational restriction or boundary. An essential similarity, however, is that some cells in each system intermingle between functional regions, although to a different extent. This is the case even in the best example for compartments, the segmental boundaries in insect nervous system, where a minority of cells also cross between the different segments[141]. In order to assess potential mechanisms of positional specification, one has to examine whether the majority of cells disperse, thereby blurring any positional identification, or whether the majority of cortical cells remains rather locally restricted and could thereby maintain positional information. Thus, rather than asking about the migration of individual cells or clones, this is asking where the bulk of cells generated at a given position in the cortex will finally be located.

The extent of tangential dispersion in the cortex

In order to quantify tangential dispersion in the cortex, it has to be considered which cell types disperse tangentially, how many of them, and how far they disperse. Exceptions confirm the rule. If only specific cell types migrate tangentially, the majority of cortical neurons would remain rather radially arranged. For example, even in the avian tectum, where tangential migration is so tightly restricted, specific cells break the rule and move along perpendicular axonal processes[48]. When migrating neurons encounter the first axons, only the later efferent projection neurons leave the radial glia and migrate horizontally along the tectobulbar axons. In the uppermost tectal layer, afferent axons from the retina are encountered, and in this case only astrocytes choose this substrate to set off in tangential directions. Similarly in the cortex: specific cell types like future olfactory interneurons migrate along a tangential route in the subventricular zone[92]. At earlier stages, a specific GABAergic population of primordial plate cells migrate along two opposite tangential routes, medially towards the callosum and laterally into the hippocampus[28]. The prevalence of horizontal axons in these layers seems to suggest that a primary substrate for tangential migration in the cortex might also be axonal processes comparable to the observation in the midbrain[48].

Apparently directed cellular movements can also be due to morphogenetic distortions that occur during development. For example, during later stages of cortical neurogenesis a prominent cellular stream directed laterally was observed in the intermediate zone[13,14]. These cells are heading to lateral cortical regions that are left without an underlying proliferative zone, as a consequence of distortions caused by the relative expansion of different telencephalic parts. During cortical development, the cortical plate, where the postmitotic neurons settle, constantly increases in contrast to the proliferative zone, the ventricular zone. Therefore the ventricular surface decreases relative to the enlarging pial surface. This relative distortion occurs primarily along the lateral extension[134] and can be visualized in the curvature of the radial glial cells[102,104]. On top of this distortion, the ventricular zone in the lateral cortex is displaced medially by the enlarging basal ganglia[13]. Hence, two factors cooperate on the progressive medial displacement of the ventricular zone relative to the laterally extending cortical plate. Consequently, upper layer neurons of the lateral cortex (that are generated at the end of neurogenesis) have to be derived from the ventricular zone at further medial positions. These cells then have to migrate along the intermediate zone (because there is no ventricular zone in the most lateral parts) to generate the upper layers in the lateral cortex. In fact, when the wide-spread tangential migration in the retroviral studies was analyzed, they were found to occur primarily along two directions one of which coincides in time and orientation with the lateral stream described in the ^{3}H-thymidine studies[13,14,104,144].

The examples described so far imply the neuronal nature of the migrating cells. However, glial cells are known to migrate laterally along the subventricular/intermediate zone[70,82,93,147] and hence should be included in the tangentially migrating cell populations observed in the retroviral or time-lapse studies[7,104,110,144,145]. In fact, both the time and proportion of tangentially dispersing cells in the cortex is consistent with the timescale of glial migration and the proportion of glial precursor cells. Tangential dispersion was found only during later stages of neurogenesis, i.e. at the onset of gliogenesis in the cortex, and the peak of tangential dispersion coincides exactly with the peak of gliogenesis in the cortex (mouse[7,134], rat[13,145]). As mentioned above, there is a consensus that tangentially migrating cells in the neocortex constitute about a third of the cells labeled with various techniques[35,110,144,145]. This proportion corresponds exactly to the proportion of glial precursor cells in the cortex[52,146]. Moreover, the tangential dispersion in the cortex occurs predominantly along the subventricular/intermediate zone, where migrating glial precursor cells move along as well[13,70,82]. Unfortunately, most of the migrational studies did not examine the cell types involved, but the sole phenomenology suggests a considerable contribution of glial cells to the tangential dispersion.

Taken together, the tangential cellular dispersion in the cortex[7,35,110,143–145] includes all these specific populations. This then leaves us with the notion that the majority of *neuronal* cells in the neocortex remains rather radially restricted within an area of a few hundred micrometers. Since cortical areas mostly comprise a larger area, most cortical neurons would be expected to remain within the same area.

In fact, the radial location of cellular majority can be visualized when the distribution of large numbers of cells rather than the one of individual cells is examined. Chimera are animals composed of (mostly two) populations of genetically different cells. This allows an examination of the extent to which different cells contribute to the formation of various tissues[8,27,44,138]. Such a study has recently provided striking visual evidence for radial columnar organization in developing cortex[138]. In this study, transgenic mice become chimeric due to the insertion of the genetic marker (LacZ) in one of the X-chromosomes: in cells of female embryos one of the two X-chromosomes is stochastically inactivated (at E8.5, ref. 138), thereby generating a mosaic of precursor cells expressing the marker gene or not. The expression of the marker gene was then assessed and revealed radial columns in the cortex dominated by blue (chromosome with LacZ activated) or white (chromosome with LacZ inactivated) cells. The quantitative analysis

of the cellular composition of the radial columns revealed a two to one relation of the respective cell types, again reminiscent of the migrational data of a third of tangentially migrating cells. Taken together, these data strongly suggest that the majority of cortical cells remain within a radial column (the smallest columns in the adult were 100 μm wide), but incorporate a considerable minority of dispersing cells. Thus, the cellular majority provides a radial continuity from the ventricular zone to the cortical plate, thereby at least in quantitative agreement with the radial unit hypothesis.

Interestingly, the lateral dispersion seems to differ between preplate and cortical plate cells, since the radial columns extend only from layer 6-2 in adult cortex, whereas a different pattern is present in the marginal (layer 1) and subplate zone (layer 6b). This difference is intriguing for two reasons. First, the subplate and marginal zone are the earliest neurons generated in the cortex that form a so-called 'preplate' which is then split by the developing cortical plate, the predecessor of the later layers 2-6 [1,96,98,99,116]. Second, at the early stages of neurogenesis, when subplate and marginal zone cells are produced, hardly any tangential dispersion seems to occur as compared to later stages, when cortical plate cells are generated (O'Leary and Borngasser, Neurosci. Abstr., 1992; ref. 35). Therefore this early cell population could provide even more positional continuity than the later generated cortical plate.

In summary, a quantitative picture emerges with some cellular dispersion but predominant radial alignment in the developing cortex. Particular cell populations migrate even across different telencephalic domains and cells disperse to some extent within the neocortex. The majority of neocortical neurons, however, does not disperse far and remains within the same area or even radial column. Moreover, cellular dispersion seems to be even more restricted at earlier developmental stages when positional specification might be set up. Such a migrational pattern is consistent with both hypotheses about area specification (fig. 2): either the early cortex is homogeneous and positional specification occurs only late during development, or there is positional specification in the early developing cortex that could be maintained from development to adulthood by the majority of non-dispersing cells or specific cells types that disperse even less (for further discussion see below). Thus, the studies about migration in the cortex cannot reveal the actual mechanisms involved in regional specification, but they provide important constraints for the evaluation of potential mechanisms. For example, any positional information present at early developmental stages has to accommodate a minority of 'displaced' cells due to the tangential dispersion. This will be discussed now: first, what evidence is there for early positional specification in the cortex and then, how could the cellular dispersion fit in.

Positional specification in the ventricular zone

Despite the homogeneous histological appearance of the ventricular zone, there is increasing evidence for its heterogeneity, both at cellular and positional levels. Precursor cells in the ventricular zone differ in their specification and generate predominantly distinct cell types; exclusively astrocytes, oligodendrocytes or neurons[52,94,95,114,146]. Heterogeneity in the expression of GFAP (glial fibrillary acidic protein) and oncogenes was observed in distinct cell populations of the ventricular zone[69,84], but it is not clear how this relates to the observed cell fate restrictions. More molecular markers, however, highlight the positional heterogeneity of the ventricular zone. The expression pattern of several molecules corresponds to specific functional regions in the adult cortex and is specified already in the ventricular zone[5,6,26,29,83]. Although most of these molecules are not expressed in the ventricular zone itself, they reveal its positional specification as suggested by the protomap hypothesis.

The best characterized example is a cell surface molecule expressed on neurons of the limbic system located in various different parts of the brain, named limbic-system-associated-membrane-protein (LAMP)[61,83]. In the cortex, LAMP is detected in limbic areas comprising allo-, meso- and neocortical parts. The glycoprotein LAMP is a member of the immunoglobulin superfamily expressed from early developmental stages exclusively on postmitotic neurons and not on glial or precursor cells[32,83,149] (Pimenta et al., Neurosci. Abstr. 1993). Thus, only neurons located at particular (limbic) positions express LAMP. In vitro studies revealed that precursor cells are already specified either to express or not to express LAMP depending on their position in the developing cortex[32]. When cells from limbic cortex are dissociated before the onset of LAMP-immunoreactivity, they become LAMP-positive after a few days in vitro. In contrast, when cells are taken from more medial, neocortical regions hardly any acquire LAMP-immunoreactivity in vitro. Thus, isolated precurosr cells in vitro regulate LAMP-expression as they would have in vivo. These results indicate that LAMP-expression is specified in precursor cells and requires no further environmental influences.

As a member of the Ig-superfamily, LAMP seems to be involved in axonal growth and mediate appropriate connectivity. Whereas on adult neurons LAMP is located on cell somata and dendrites, during development it is transiently localized on axonal processes as well[149]. Thus, during formation of neuronal connectivity, LAMP is present on afferent fibers from specific thalamic nuclei and their appropriate target cells in the limbic cortex[61,83,149]. Indeed, LAMP antisera interfere with the formation of connections between limbic explants[72], and in vivo, limbic cortex apparently attracts

its appropriate, LAMP-positive thalamic innervation after transplantation to a new location[10]. Homophilic binding of LAMP on axons and target cells seems to account for these observations and suggests that LAMP could mediate the molecular match between limbic afferents and their target cells. As a homophilic adhesion molecule, LAMP could also be involved in segregation of LAMP-positive from LAMP-negative cells, thereby setting up limbic and non-limbic telencephalic domains. This is consistent with recent reaggregation experiments that revealed differences in the adhesive properties between cells derived from different telencephalic compartments, i.e. limbic (hippocampal) and non-limbic (neocortical) cells segregate in vitro suggesting they do so in vivo (Götz et al., Neurosci. Abstr. 1994). Such a mechanism of selective adhesion would contribute to keeping most cells within a given region regardless of some cells that migrate across these telencephalic areas.

Some other molecules also reveal early positional specification in the cortex, but much less is known about their functional roles. The monoclonal antibody PC3.1 recognizes a 29 kD protein expressed specifically in neurons of parietal cortical regions[5]. Despite the later onset of PC3.1 compared to LAMP-immunoreactivity, the expression pattern seems to be specified also at the precursor cell level. When ventricular zone cells are isolated in vitro more than three weeks before the onset of PC3.1 expression (at E12 when no postmitotic cells are present in rat cortex), they develop PC3.1-immunoreactivity corresponding to the cortical position they are derived from. This is particularly intriguing since only 1% of all cortical neurons, located exclusively in deeper layers, express this antigen[6]. Moreover, the small PC3.1-positive subpopulation of cortical neurons seems to be generated at a particular developmental window[6]. These findings suggest that cell type specification and positional specification, including lamina as well as area specification, occur concomitantly at least for some aspects of neuronal phenotypes.

The other striking example of early regional specification in the cortex came as a surprise from a transgenic mouse line. In mice where the expression of the transgene LacZ is driven by specific regulatory elements of a major histocompatibility complex class I gene, this construct was found to be expressed in the telencephalon exclusively in primary somatosensory cortical areas[26]. When prospective somatosensory cortex was transplanted to a different cortical region or to the cerebellum *prior* to the generation of layer 4 cells (in which the transgene is predominantly expressed later), the expression pattern occurred corresponding to the original location. Conversely, transgene expression could not be initiated in visual cortex after transplantion into somatosensory cortical areas[26]. Thus, precursor cells are already irreversibly specified to express or not to express this transgene dependent on their position (for discussion of specification and determination see below).

As we have seen, the positional expression pattern of some marker molecules is specified already in ventricular zone cells, but they do not yet express these molecules. Thus, so far, we have discussed 'invisible' specification as a developmental anlage. Studies of cell cycle dynamics performed in developing primate cortex can visualize a prominent difference between cortical precursor cells located at specific positions: ventricular zone cells in the presumptive primary visual area 17 proliferate faster than their neighbours generating the secondary visual area 18 [29]. Since area 17 contains higher numbers of neurons than area 18 [124], the cell cycle difference detected in the ventricular zone is likely to contribute to the differences in cell number of these areas in the adult. Differential cell death in specific cortical areas might contribute as well to sculpturing the final differences in cell numbers[33,34], but cannot account for the results obtained by Dehay and colleagues, because the differences in cell numbers can be detected before the peak of cell death in monkey visual cortex[29]. Particularly relevant for our discussion is their observation that the differences in the mitotic rate during development are graded, whereas the transition in cell number between cortical areas in the adult is abrupt[29,73]. Comparably, LAMP is expressed in a developmental gradient with increasing numbers of LAMP-positive cells from medial towards more lateral areas[32].

This prompts the question of how smooth transitions during development are transformed to abrupt transitions in the adult. This is asking how a minority of cells can be eliminated during further development. Cellular minorities are found at the ends of gradients and are caused by cellular dispersion. In fact, the migrational data obtained in the cortex with stochastic dispersion of fewer cells over wide distances and more cells over short distances would suggest a graded distribution with more cells derived from a given point in the ventricular zone located within a smaller area and fewer cells distributed further apart. The elimination of minorities transforms smooth to abrupt boundaries (fig. 6). Such a mechanism is required independent of the number of cells dislocated – few, as in the hindbrain, or many more, as in the telencephalon. Elimination of cellular phenotypes can be achieved either by respecification of cells or by their death. Respecification seems to occur in insects when cells cross the posterior segment boundaries[141]. What evidence for respecification or selective cell death is there in the developing mammalian telencephalon?

Plasticity of positional specification

Specification of cellular properties can be revealed by isolation in vitro, as discussed above. The specified

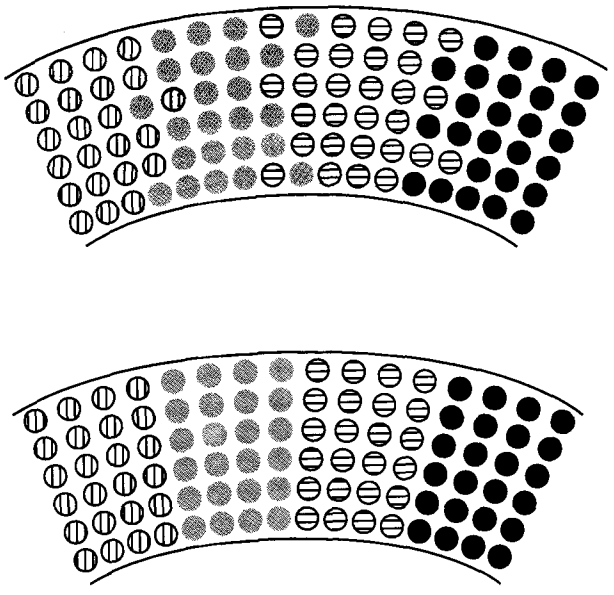

Figure 6 illustrates a model of how to encompass both positional specification and cellular dispersion. Minorities of displaced cells generate smooth positional boundaries during development (upper panel). Elimination of these cells (by respecification or cell death) can generate the abrupt positional transitions seen in the adult (lower panel). Such a mechanism has to be required for any extent of cellular dispersion during development – be it greater, as in the telencephalon, or smaller, as in the retina or hindbrain (figs 5 and 4).

phenotypes, however, could still be plastic and amenable to environmental influences. Alternatively, they could be irreversibly specified, i.e. determined. Plasticity or determination of cell fate is best assessed by manipulating environmental influences, either in vitro by varying culture conditions or in vivo by transplantation. It is important to bear in mind that plasticity observed after transplantation does not reveal the lack of specification[109], but shows the instructive role of environmental influences and the lack of determination. This has been shown for the expression of LAMP: cortical cells are specified to express or not to express LAMP according to their position, as shown by isolation in vitro[32]. However, when they are transplanted at the same time, this fate decision can still be altered in accordance to their new location[9,10]. When cortex is taken at E12 from limbic areas and transplanted to neocortical areas, the transplanted cells do not express LAMP even though they would have done at their normal location or when isolated in vitro. Conversely, when neocortical tissue is transplanted to limbic areas it becomes LAMP-immunoreactive according to its new position[9]. These results show that at a time when LAMP-expression is specified and would occur autonomously in vitro, it can still be respecified at a different cortical position. Intriguingly, the respecification can be communicated over some distance, since the transplants were relatively large pieces of 500 μm diameter[10]. The plasticity in LAMP-expression is restricted to early developmental stages, and its specification cannot be altered anymore in transplants taken two days later[9].

Such a 'critical period' raises the issue of whether other positional fate decisions would be determined simultanously or sequentially[85]. For example, transplantation of the transgenic somatosensory cortex that was found to be determined was performed at a time when LAMP-expression was already determined[26]. Would there be plasticity of the transgene expression at an earlier time and would this timing be similar for other aspects of area specification? This issue has been excellently reviewed by Levitt and colleagues who point out that various aspects of cell fate decisions related to cortical areas are made at different developmental stages and hence would be found to be plastic at different developmental stages[85]. It is intriguing, however, how many phenotypic aspects of cortical cells are already determined at their final mitotic division: the cell type[52,94,95,114,146], the lamina position[101], the transmitter specification[42] and the axonal projection (see e.g. ref. 129; the evidence for the specification of the projection pattern around the final mitosis has been reviewed by Götz and Price, 1994, Semin. devl Biol., in press). So far, the timing observed for the area specific expression patterns would also be consistent with determination during the final mitosis. Interestingly, not all cells in the transplants altered their LAMP expression pattern[10], suggesting that some might have already been determined irreversibly and others not. As suggested by Kennedy and Dehay[73], the partial plasticity might reflect in which phase of the cell cycle transplantation had been performed. Some other phenotypic aspects, however, can clearly be influenced at later developmental stages[85] (e.g. neuropeptide expression[42], barrel formation[128]).

Plasticity of cell fate decisions suggests a model of area specification combining the evidence for early positional information in the cortex (as suggested by the 'protomap' hypothesis) with the evidence for cellular dispersion and respecification (as suggested by the 'protocortex' hypothesis). A majority of cells maintaining their position could preserve positional information and respecify minorities of displaced cells (fig. 6). This is consistent with the data about LAMP-expression that reveal specification and plasticity coexisting simultaneously at least for some time. In vitro experiments, where varying proportions of cells derived from different cortical positions could be mixed, might provide a direct test for this hypothesis: would a majority of limbic derived cells influence a minority of neocortical cells to express LAMP in vitro? Once respecification takes place in vitro, the factors involved in it would be accessible and could be characterized (for comparison see refs 76, 122). Alternatively, if respecification could not be achieved in dissociated cell cultures, this would limit the cellular interactions potentially involved in respecification that occurs in vivo after transplantation;

the responsible factors would be present in vivo but absent in vitro, such as extracellular matrix molecules or diffusible molecules that might be diluted in vitro. Alternatively or concomitantly, displaced cells could be eliminated by cell death. Indeed, there is evidence for selective cell death in different cortical areas[33,34]. Moreover, the proportion of widely dispersed cells was found to decrease considerably from postnatal to adult stages[145]. Thus, cell death is likely to contribute to the elimination of inappropriately located cells, but it cannot entirely account for the observed phenomena as directly shown in the transplantation studies where cells in the transplants are still alive but have altered their phenotypes. The relative contribution and potential interaction of phenotypic respecification and cell death remains an interesting issue for future research.

Final remarks

Taken together, results obtained from different studies addressing cell migration, cell fate decisions and pattern formation might now provide the basis for addressing the cellular mechanisms involved in the regional specification of telencephalic domains as well as functional areas within the neocortex. We have seen that there is early positional information in the ventricular zone, but nothing is yet known about the cells or the molecules involved. Expression patterns of transcription factors related to those responsible for segmentation also delineate regional boundaries in the tel- and diencephalon, suggesting a similar role in setting up positional identity[17,133]. However, which cells express these genes is not known, neither in the better examined hindbrain nor in the telencephalon. The final remarks here aim to draw attention to a cell population that is central for several developmental phenomena closely related to positional specification, but that has been neglected so far, supposedly due to its 'glial' name. Radial glial cells guide neuronal migration. They are potential neuroepithelial stem cells and thereby might influence cell fate decisions. Moreover, they are the only cells in the developing cortex that provide spatial *and* temporal continuity. Therefore radial glia seem to be prime candidates for carrying positional identity.

Radial glial cells span from the ventricular zone to the cortical plate and retain their neighborhood relations despite the morphogenetic sheering or transformation during development[38,102,103,119]. Thus, even though migrating neurons disperse to some extent, radial glial cells themselves form a stable network suited to relay positional information between the ventricular zone and the cortical plate. Radial glia is derived from the earliest neuroepithelium and disappears only after neuronal migration is finished. Before any postmitotic neurons are generated, precursor cells throughout the CNS extend from the ventricular to the pial surface and mitosis is accompanied by interkinetic nuclear migration between these surfaces[59,127,131]. When the neuroepithelium thickens during further development, the only cells to maintain their contacts at both the pial and ventricular surface are the radial glial cells. Thus, they are – or are directly derived – from the earliest CNS stem cells. In fact, cell lineage analysis in the avian tectum supports the former. Radial glial cells are the earliest cells generated in a clone; most clones contain only one radial glial cell and all the descendents migrate along their own radial glial mother cell[49]. These results suggest that the radial glial cell itself is the earliest stem cell that continuously generates all the different neuronal and glial descendents and provides their migrational substrate. This would be a revolutionary observation, if true as the general lineage in various parts of the CNS and various species. So far, however, it has not been tested anywhere else. Radial glia of the mammalian neocortex do indeed continue their mitotic activity throughout periods of neurogenesis and neuronal migration[103], but their derivatives are unknown. Unfortunately, most retroviral studies have analyzed the labeled clones at times when the radial glial cells have already disappeared or been transformed into astrocytes[142]. Whatever the exact lineage of radial glial cells, they are present from the earliest stages of cortical development and hence could maintain positional information from early stages, when positional patterning seems to be set up, to later stages of neurogenesis, when cellular dispersion occurs. Despite the central role of radial glial cells in CNS development, our knowledge about their cellular and molecular properties is surprisingly limited.

Further support for radial glial cells as an essential interface in the generation, migration and specification of CNS derivatives is the striking correlation between migrational patterns and cell fate decisions. As described above, the overall pattern of cellular migration differs markedly between the telencephalon and other parts of the brain (fig. 5) – as does the cell fate specification. There seems to be an inverse correlation between restriction of migration and restriction of cell fate: in the parts of the CNS where descendents of the same precursor cell migrate strictly radially, clonal descendents differentiate into a variety of different cell types[39,46–48,139]. Conversely, in telencephalic parts, migration is less radially restricted, but precursor cells are more restricted in their potential[52,94,95,114,146]. Since this has also been demonstrated in dissociated cell cultures[146], any direct influence of the migrational pathway on the restricted cell fates of cortical precursor cells can be excluded. Rather, these comparisons prompt the speculation that a specific cell type involved in both, migration and cellular generation, differs in the more rostral parts of the CNS. These are the radial glial cells. It is tempting to speculate that changes in the same cell types, the radial glial cells, could alter migration, regional specification

and cell type specification altogether. Thus, radial glial cells would be good candidates for patterning the CNS and their properties should be further elucidated.

Interestingly, the pattern of migration seems to be comparable between the avian and mammalian telencephalon. In the avian telencephalon retrovirally labeled cells are more dispersed than in the avian midbrain[47]. This similarity is reminiscent of similarities in the functional organization. The avian telencephalon exhibits modality-specific subdivisions comparble to the ones in the mammalian neocortex[71]. The most elaborate part of the telencephalon in birds is the lateral pallium, the dorsoventricular ridge (DVR). This receives the major sensory input and its input is organized in a modality-specific manner: distinct parts of the thalamus that relay different sensory modalities from the tectum (in birds the major sensory projection is relayed via the tectum as opposed to the direct thalamic projection in mammals) innervate specific parts of the DVR and the efferent projections from the DVR are modality-specific as well[71,140]. The organization in the DVR is nuclear rather than tangential as in mammalian neocortex, but both are well comparable in various detailed aspects[71]. (Compared to the functional subdivisions in the mammalian and avian telencephalon, the functional organization of the mammalian and avian midbrain is markedly different: different modalities are processed in different horizontal layers.) Since these functional subdivisions have evolved after the separation from a common ancestor, they must have evolved several times during phylogeny. This suggests that allocation of distinct regions to specific functional aspects is a successful strategy for achieving more and more sophisticated information processing. A further analogy is that the overall radial cytoarchitectonics of the cortex (including the dispersion we have discussed so far) also seems to have evolved convergently (homplastic) in birds and mammals[43,50]: species closer to the common root have poor radial cytological patterns in the developing pallium[43] and in both mammals and birds radial arrangements of cells in the developing telencephalon become more and more pronounced during phylogeny.

These considerations close the circle and return to the radial unit hypothesis, originally prompted by the radial migration and organization of developing primate cortex. Two phylogenetic trends seem to continue in parallel: the radial arrangement of cells during development and the functional compartmentalization. The multiplication of functional parcellation is still ongoing: the more evolved a sensory system is, the higher the number of areas devoted to analyzing particular aspects of this modality (as e.g. the primate's visual cortex or the bat's acoustic cortex). The parallel phylogeny of two aspects, however, does not implicate that one depends on the other. Positional specification occurs throughout the CNS and involves cellular dispersion to varying extents in almost any system. The two phenomena, however, might interact and lead secondarily to different developmental strategies. Species differences and similarities help in understanding ontogenetic as well as phylogenetic questions that, after all, are closely related. Phylogenetic alterations can be achieved only via developmental mechanisms. The cells at the hub of it appear to be the radial glial cells.

Acknowledgements. I would like to thank in particular Jack Price, Marika Nosten-Bertrand, Roger Morris and Henry Kennedy for their contribution to the long formation of this 'penelopian tapestry'. They provided important individual combinations of helpful comments, criticism, discussions, corrections of the manuscript, patience and motivation that were essential for the completion of the manuscript. This work was supported by a Human Frontiers Science Program postdoctoral fellowship.

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