

Telencephalic cells take a tangent: non-radial migration in the mammalian forebrain

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During development of the mammalian telencephalon, cells migrate via diverse pathways to reach their final destinations. In the developing neocortex, projection neurons are generated from cells that migrate radially from the underlying ventricular zone. In contrast, subsets of cells that populate the ventral piriform cortex and olfactory bulb reach these sites by migrating long distances. Additionally, it has been recently established that cells migrate tangentially from the ventral ganglionic eminences to the developing cortex. These tangentially migrating cells are a significant source of cortical interneurons and possibly other cell types such as oligodendrocytes. Here we summarize the known routes of migration in the developing telencephalon, with a particular focus on tangential migration. We also review recent genetic and transplantation studies that have given greater insight into the understanding of these processes and the molecular cues that may guide these migrating cells.

The mammalian telencephalon, the anterior-most aspect of the neuraxis, is the most complex division of the brain^{1,2}. The telencephalon is broadly subdivided into dorsal (pallial) and ventral (subpallial) domains. The two primary structures of the pallium are the cerebral cortex and the hippocampus. The main subpallial structure is the basal ganglia, which arises from two bulges in the wall of the lateral ventricle, the medial (MGE, primordial globus pallidus) and lateral (LGE, primordial striatum) ganglionic eminences^{3,4} (Fig. 1). A third eminence, the caudal ganglionic eminence (CGE), is believed to primarily give rise to the amygdaloid region of the limbic system. The telencephalon is the seat of all higher brain function in mammals; it is involved in such diverse tasks as integration of sensory and motor processing, memory, thought and emotion. Furthermore, a number of devastating disorders such as Parkinson's disease, Huntington's disease and schizophrenia are primarily caused by defects in telencephalic function. A detailed knowledge of how the brain's cytoarchitecture is assembled is essential for our understanding of both normal and abnormal brain function. In this regard, fundamental issues that must be addressed include determining the relationship between where a cell is born and how it migrates to its final destination, and how this process is tied to cell-type specification and, ultimately, neuronal interconnections. (For a review of cortical patterning, see Monuki and Walsh in this issue.)

Cell migration within the telencephalon can broadly be divided into two categories, radial and non-radial. The substrate for radial migration is the radial glia, which in the developing neocortex extend long, unbranched processes from the ventricular zone lining the lateral ventricle out to the cortical pial surface. Neocortical cells that are born in the cortical ventricular zone use these radial glia as a scaffold upon which to migrate to the

developing cortical plate. In the neocortex, radially migrating cells primarily give rise to projection neurons that express the neurotransmitter glutamate. In contrast, non-radially migrating cells that are generated in the ganglionic eminences give rise to a majority of interneurons, and possibly other cell types, such as oligodendrocytes, in the dorsal telencephalon. Here we summarize how early work in this field (dating back over 35 years) has provided the framework for our current understanding of the modes of migration in the developing brain. We will also review the more recent findings that have dramatically reshaped our view of how regional cell diversity within the telencephalon is generated.

Historical perspective

The cerebral cortex has a modular organization that can roughly be divided into 52 distinct functional regions in humans⁵. The protomap hypothesis, which posited that the columnar organization of the cortex arises through large numbers of neuronal precursors using a 'point to point' radial migration from the ventricular zone to the cortical plate, was proposed as an explanation for the generation of this organization⁶. The foundation for this hypothesis was based on observations that cells migrate in a direct radial manner to positions in the overlying cerebrum⁷⁻⁹. Support for the protomap hypothesis has also come from both chimeric^{10,11} and retroviral lineage tracing¹²⁻¹⁵ studies, which revealed that radially oriented cells within a cortical column can be lineally related. In this way, positional information regarding the location of a neuron within a functional subunit of the cortex is apparently established in the ventricular zone.

In addition to this direct migration, birthdating studies beginning in the 1960s suggested that not all radially migrating

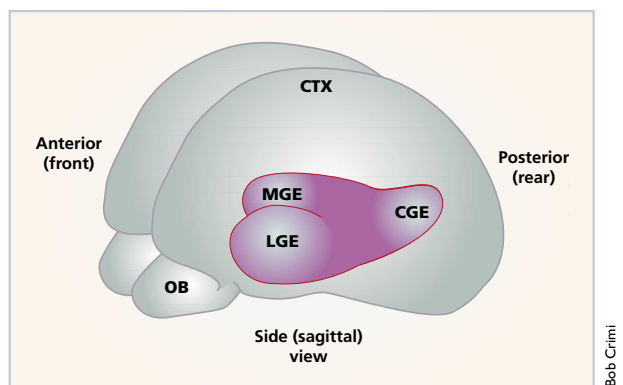


Fig. 1. Basic anatomy of the embryonic telencephalon. Sagittal view of the embryonic vertebrate telencephalon as a transparent structure to reveal the ganglionic eminences. All three eminences (MGE, LGE and CGE) are shown in relation to their relative position within the telencephalon. CGE, caudal ganglionic eminence; CTX, neocortex; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; OB, olfactory bulb.

telencephalic cells take such simple routes to their final destinations. By using radioactive tracers to label dividing progenitors, it seemed that numerous cells that ultimately reside in the ventrolateral telencephalon (piriform cortex) originated a considerable distance away in a region close to the cortical–striatal (C–S) boundary^{16,17}. This migratory pathway was termed the lateral cortical stream (LCS), and has been confirmed by elegant cell tracing studies in which DiI-labeled cells were observed migrating from the C–S boundary to the ventrolateral telencephalon¹⁸. This path of migration is traversed by a long palisade of radial glia emanating from the C–S boundary^{3,16,18–20}, suggesting that cells of the LCS also use a radial glial scaffold as a guide²¹. Therefore, it seems that unlike the ‘point to point’ mode of migration used by cells of the developing neocortex, not all radially migrating cells take direct routes.

Another early suggestion that cells can migrate long distances in the developing telencephalon came from the analysis of neurogenesis in the mammalian olfactory bulb. Early birthdating studies suggested that a population of thymidine-labeled cells found in the olfactory bulb originated in the wall of the lateral ventricle²². Subsequent studies revealed that both periglomerular and granule interneurons of the olfactory bulb are, in fact, generated in the subventricular zone (SVZ) of the striatum^{23–26} and migrate to the olfactory bulb. Because of the rostral path that these cells take, this route has been dubbed the rostral migratory stream (RMS). Unlike the other hypothesized routes of migration, this pathway is devoid of radial glia. More recent experiments have determined that in absence of this scaffold, the cells of the RMS migrate via ‘chain migration,’ using their migrating neighbors to provide a foothold for their movement²⁷. Cells of the RMS migrate faster than radially migrating cells, suggesting that the chain migration strategy may, in part, account for their rapid ability to transit from the SVZ to the olfactory bulb²⁸.

Concurrent with the early studies of neurogenesis in the olfactory bulb, observations from anatomical studies of the developing human brain suggested that the ventral telencephalon is also the source of cells that tangentially migrate to the pulvinar nucleus of the thalamus^{29,30}. Although this migratory stream was observed in humans, this early observation seeded the idea for the more recent finding that the ganglionic eminences also seem to be the source of most of the interneurons

in the cerebral cortex and hippocampus in a variety of species. The initial proposal of this ventral to dorsal route of migration was put forth to explain the pattern of GABA immunoreactivity observed in the developing rodent telencephalon³¹. Results from subsequent BrdU birthdating studies combined with immunohistochemical analysis were also consistent with the then contentious notion that developing interneurons arose from extracortical sources³². This hypothesis was further supported by work showing that severing the developing neocortex from the ventral telencephalon not only resulted in the expected accumulation of neurons on the ventral side of the cut, but also in a concomitant loss of intermediate zone cells on the dorsal side of the cut³³. The observation by this same group that DiI-labeled cells from the LGE later appeared in the neocortex provided further strong evidence in support of the existence of this novel migratory route. Because GABAergic interneurons account for approximately 15–25% of all neocortical neurons³⁴, this represents a significant route of migration. However, it is currently not yet clear if all neocortical GABAergic cells arise from the ventral telencephalon or if the neocortex is also a source of these cells, as suggested previously³⁵.

The results of these histological and anatomical studies suggesting a massive ventral to dorsal tangential migration were remarkably consistent with the results of both cell tracking and cell lineage studies ongoing at the same time. Cell tracking studies using video microscopy to track fluorescently labeled cells revealed that cells of both the neocortical ventricular zone and the cortical plate can undergo long-distance tangential movements^{36–38}. Furthermore, chimeric¹¹ and retroviral lineage tracing^{39,40} studies suggested that both glutamatergic and GABAergic cells are derived from separate lineages. Therefore, the hypothesis that dorsal telencephalon is host to a huge immigrant population of ventral telencephalic cells was proven by two independent but convergent experimental approaches: those using anatomical and classical cell tracing approaches, and those using state of the art video microscopy and retroviral cell lineage tracing techniques.

The ventral origins of tangentially migrating cells

A more detailed understanding of the sources of these tangentially migrating cells has come from recent genetic and transplantation studies. Investigation of mice carrying null alleles of various transcription factors essential for the development of distinct ventral regions has proved invaluable in understanding the contribution of the ganglionic eminences as a source of tangentially migrating cells^{41–48}. The analysis of mice lacking the transcription factor-encoding genes *Dlx1* and *Dlx2* provided insight into this subject⁴¹. In the telencephalon, these genes are first expressed exclusively in the ganglionic eminences (MGE, LGE and CGE) and are only later found in more dorsal regions. The ablation of *Dlx1/2* resulted in a loss of most interneurons in the developing cortex and hippocampus^{41,47}. As a result of these studies, it was initially suggested that cortical *Dlx* positive cells originated in the LGE⁴¹. Subsequent transplantation⁴⁹ and genetic^{43,44,48} analyses, however, have supported the notion that the MGE is the source of most neocortical interneurons, including a subpopulation of cells in the marginal zone (MZ), the most superficial layer of the developing neocortex which contains the future layer I cells of the cerebral cortex. Furthermore, recent *in vivo* fate mapping studies directly demonstrated that cells from the MGE can undergo robust migration to the neocortex (including the MZ) *in vivo*, whereas the LGE does not⁵⁰. Interestingly, the MGE also seems to be a major source of striatal interneurons^{50,51}.

The LGE, in contrast, seems to be the source of interneurons within the olfactory bulb⁴⁹, a role carried on into adulthood by the proliferative striatal SVZ. Genetic support for this hypothesis has come from analysis of mutant mice lacking the gene encoding the ventrally expressed homeodomain transcription factor *Gsh2* (refs. 52–54). In these mice, development of the LGE was affected and the MGE was spared. Although the generation of cortical interneurons was normal in these animals, there was a disruption of the RMS that delayed the appearance of interneurons in the olfactory bulb^{52,54}. In accordance with this genetic evidence, large numbers of homotopically transplanted E13.5 LGE cells migrated to the olfactory bulb, but not to the neocortex⁵⁰. However, the idea that the LGE also contributes to the cortical interneuron population cannot be discounted. Analysis of mice lacking *Nkx2.1*, in which the MGE is lost, and *in vitro* transplantation studies, have suggested that a second, later wave of tangential cell migration may arise from the LGE^{47,48}.

There are still gaps in our knowledge concerning the source and diversity of cells that undergo tangential migration. For example, little is known regarding the contribution of the third eminence, the CGE, to these migratory routes. Nevertheless, a picture is beginning to emerge in which distinct ventral structures contribute significant populations of cells to different regions of the developing telencephalon (Figs. 2 and 3). Further transplantation studies and analyses of genetic mutants in which ventral telencephalic structures are specifically affected will likely shed light on these issues.

Is the ventral telencephalon a source of multiple cell types?

Although it seems undeniable that tangentially migrating cells emigrate from the ventral eminences, there is still much to be learned concerning the cell types produced from these areas. Numerous studies support the notion that most interneurons are derived ventrally, but it is not yet clear if other cell types, such as glutamatergic neurons or glial cells, are generated from this region. For example, studies have suggested that similar to the generation of interneurons, telencephalic oligodendrocytes may also arise in specific foci that are located ventrally^{55–58}. This would be analogous to the mechanism used for generation of oligodendrocytes in the spinal cord, which are specified in a discrete ventral foci and subsequently disperse throughout the tissue⁵⁹. This putative migratory route is supported by the observation that markers of oligodendrocyte development initially appear restricted to the ventral forebrain. Furthermore, grafting studies in chick have suggested that cells of the anterior entopeduncular area (AEP) region of the ventral telencephalon (located between the MGE and hypothalamus) is a localized source of oligodendrocytes⁵⁸. In the spinal cord, both oligodendrocytes and motor neurons arise from a common progenitor^{60–62}. Perhaps similarly in the telencephalon, interneurons and oligodendrocytes also share a common lineage⁵⁷ (W.C. He, C. Ingraham and S. Temple, *Soc. Neurosci. Abstr.* 26, 505.16, 2000). Currently, because of the perinatal lethality of mice lacking the ventrally expressed homeodomain genes, *Nkx2.1* and *Dlx1/2*, more definitive answers to these questions await conditional knockouts as well as more detailed *in vivo* fate and lineage analyses.

Factors controlling non-radial migration

From the studies mentioned above, it is clear that cells undergoing non-radial migration must travel long distances to their sites of residence. This raises the question as to the identity of the molecular cues that guide these cells to their ultimate destinations.

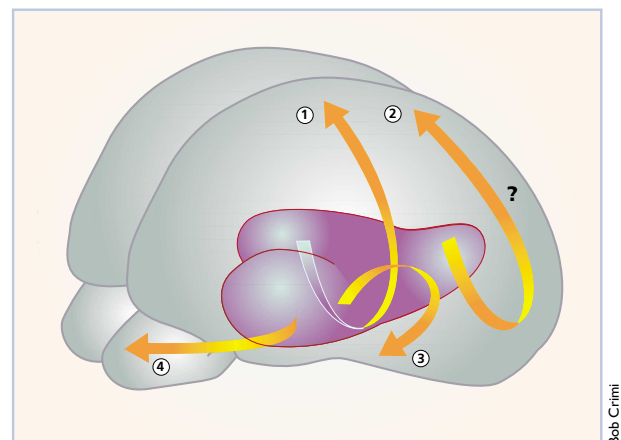


Fig. 2. Major routes of tangential migration. Numbered arrows are superimposed on Fig. 1 to broadly depict the major routes of cell migration in the developing telencephalon. The question mark on arrow (2) indicates that this route is less well characterized than the others. Key to migratory routes: (1) MGE to the dorsal telencephalon (2) CGE to dorsal telencephalon (3) Cortical-striatal boundary to the ventrolateral telencephalon (lateral cortical stream) (4) LGE to the olfactory bulb (rostral migratory stream).

In contrast to radial migration, where genetic analyses have begun to provide a framework for the molecular mechanisms underlying this mode of migration⁶³, much remains unknown about the cues that guide non-radial migration. Recently, however, some clues have begun to emerge.

Remarkably, tangentially migrating cells may also use many of the guidance molecules used to guide the outgrowth of neuronal growth cones. To date, the most compelling results have implicated members of the Slit and Semaphorin families, which act as repulsive cues for axon guidance in the murine central nervous system⁶⁴. In the telencephalon, *Slit1* and *Slit2* are expressed postnatally in the septum, a structure close to the striatum from which the RMS emanates, and *Slit1* is expressed at high levels embryonically in the ventricular zone of the MGE and LGE⁶⁵. Consistent with this expression, *in vitro* experiments have suggested that Slit1 can repulse LGE neurons out of the ventricular zone⁶⁶, as well as prevent cells of the RMS from ectopically entering the septum as they move to the olfactory bulb⁶⁷. Additionally, work combining both gain and loss of function approaches has strongly suggested that Semaphorin 3A and 3F can perform a similar repulsive role to inhibit subsets of migrating MGE cells from entering the striatum as they migrate to the cerebral cortex⁶⁸. In combination, these studies suggest a model in which chemorepellants, which seem to be used repeatedly for multiple aspects of CNS development, act to repulse cells from the structures from which they either emanate (MGE) or pass by (septum, striatum) while in transit to their final destinations.

Less well understood is the role that positive or permissive factors play in regulating tangential cell migration. A number of factors including ephrins⁶⁹, which guide axonal outgrowth, NT-4 (ref. 70), a neurotrophic factor most closely associated with neuronal survival and differentiation, and hepatocyte growth factor/scatter factor⁷¹, a secreted molecule typically associated with chemotaxis of mesodermally derived cells, have been suggested to chemotactically influence tangential migration. However, from these studies it is not yet clear whether these factors act by affecting the degree of motility or the direction of cell

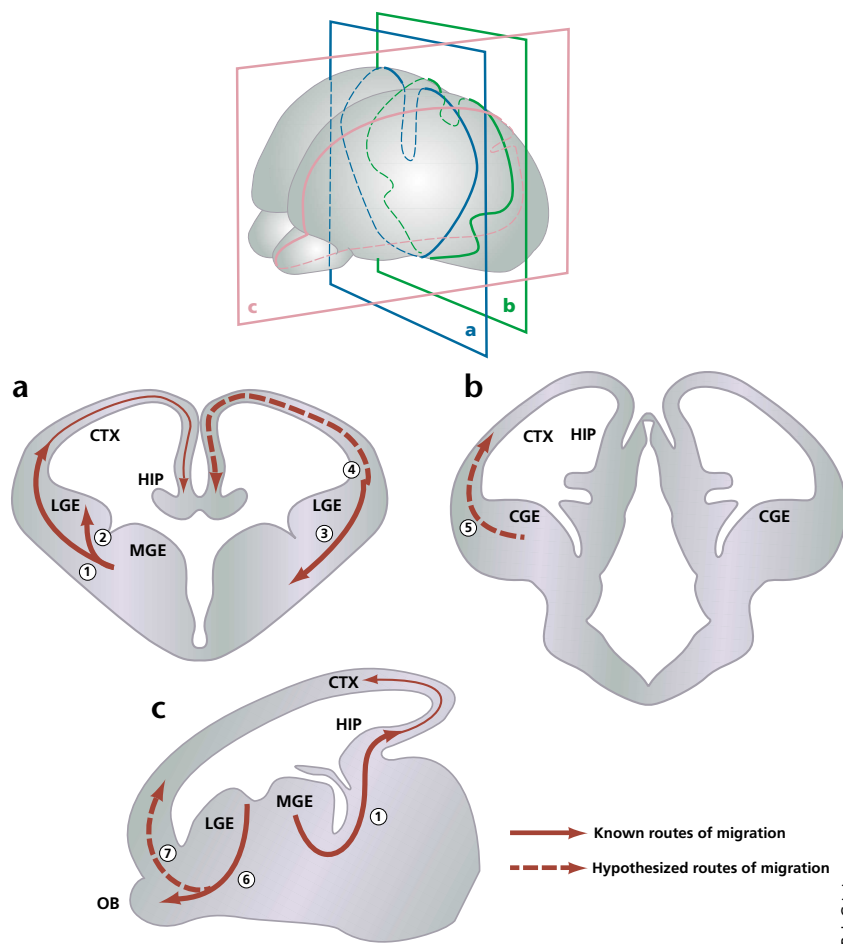


Fig. 3. Detailed overview of the known and hypothesized routes of tangential cell migration. The embryonic telencephalon is shown in coronal (**a**, **b**) and sagittal (**c**) cutaways to reveal the multiple pathways of migration. Well characterized routes of migration are shown as a solid arrow; less well characterized routes are shown by a dashed arrow. Key to migratory routes: (1) MGE to neocortex and hippocampus (2) MGE to LGE (3) cortical–striatal boundary to ventrolateral telencephalon (lateral cortical stream) (4) LGE to neocortex and hippocampus (5) CGE to dorsal telencephalon (6) LGE to olfactory bulb (rostral migratory stream) (7) Retrobulbar region to marginal zone^{75,76}. HIP, hippocampus.

migration. In this regard, it is notable that the identification of true chemoattractants that regulate tangential migration have remained elusive. For instance, mutations in the netrin signaling pathway, which can act as a chemoattractant for growing axons, have not been shown to have an effect on tangential cell migration^{45,46}. Therefore, the isolation of novel factors, in addition to detailed analyses of mutant mice that lack either the ligands or receptor molecules for many of the factors mentioned above, will no doubt prove informative.

Given the diversity of routes used by different populations of tangentially migrating cells, it seems inevitable that some cues will only act upon the migration of specific subpopulations. For example, the differential migration of cells from the MGE and LGE may be regulated by specific cue(s) that act as a chemoattractant to one population and chemorepellant to the another. Indeed, the suggestion that the absence or presence of expression of the semaphorin receptors, the neuropilins, determines whether an individual MGE cell migrates to the striatum or to the cerebral cortex⁶⁸, respectively, is consistent with such a model.

Substrates for non-radial migration

Although elegant work has demonstrated that cells of the RMS migrate in chains to the olfactory bulb, the substrates for other modes of tangential migration have yet to be clearly identified. It has been speculated that cells tangentially migrating from the ganglionic eminences to the cortex use the incoming cortico–fugal fibers as a guide¹⁶. Contrary to this hypothesis is the observation that many cells that migrate from the ventral ganglionic eminences are restricted to the cortical SVZ (ref. 50 and S.N., J.C. and G.F., unpublished observations). These cells are, in fact, a considerable distance from the outgrowing cortical–fugal fibers that are found in the intermediate zone, making it unlikely that they are guided by these fibers. Although these cells may attach themselves to the existing neocortical radial glial scaffold after they enter the cortical plate, no such guide exists as they migrate out of the ventral telencephalon. It is possible that cells of the cortical SVZ may provide molecules that allow for cell–cell interactions to facilitate migration. These cells may migrate by using many of the same molecules used by growing axons (such as N-cadherins, NCAM, TAG-1 and NrCAM). These types of interactions would then allow these cells to migrate in the absence of a radial glial substrate or the formation of chains. Alternatively, these migrating cells may use as of yet uncharacterized modes of migration, and/or proteins, to facilitate their movement.

Future directions

There are many unresolved questions regarding tangential migration in the developing telencephalon. Nonetheless, it is already apparent that this type of migration is extremely widespread, and there probably are further pathways of migration yet to be discovered. Among the outstanding issues, two broad theoretical questions stand out. First, why do specific populations need to be born at such a distance from their final destination? Second, how do the region-specific genes expressed by migratory cells instruct these cells to migrate along distinct routes and differentiate into specific cell types?

The most parsimonious explanation to the first of these questions is that locally expressed factors, which are required to pattern the telencephalon along the dorsal–ventral axis, could also be involved in specifying distinct cell fates. For example, sonic hedgehog (Shh) is required for ventral patterning and may be involved in the generation of interneurons and oligodendrocytes. In support of this suggestion, interneurons and oligodendrocytes are generated close to Shh sources. Moreover, the misexpression of Shh resulted in the ectopic expression of ventral telencephalic markers⁷² and the generation of oligodendrocytes in the cerebral cortex⁵⁷. Conversely, dorsally expressed bone morphogenetic proteins may be inhibitory to the development of interneurons and oligodendrocytes, while promoting the

development of other cell types such as astrocytes^{73,74}. Consistent with the notion that discrete cell types are derived from separate regions are the results from retroviral lineage^{15,39,40} and chimeric¹¹ analyses suggesting that tangentially migrating cells represent distinct lineages from those that migrate radially.

With regard to the second question, it is currently unknown how genes that are expressed in regional patterns affect cell fate and/or migratory behavior. Mutations of ventrally expressed homeodomain transcription factor genes such as *Dlx1/2*, *Nkx2.1* and *Gsh2* have unique and profound effects on telencephalic development. However, it is not yet clear as to whether these gene(s) function only in the establishment of regional structure or are part of the genetic cascade that leads to the specification/differentiation of specific cell types. Alternatively, perhaps unique combinations of these intrinsic determinants in each of the ganglionic eminences endows those cells with the capacity to respond differentially to similar extrinsic inductive or migratory cues. With so many questions remaining to be answered, it is clearly a very exciting time to be studying this subject. Despite their non-classical mode of migration, non-radially migrating cells clearly are of more than just tangential interest.

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