A LONG, REMARKABLE JOURNEY: TANGENTIAL MIGRATION IN THE TELENCEPHALON

Oscar Marín and John L. R. Rubenstein

Recent studies on the origin of cell populations in rodent and chicken embryonic brains provide evidence for extensive tangential migration within the developing telencephalon. On the basis of these findings, a new concept of corticogenesis has emerged, which proposes that two distinct neuronal populations cooperate in the formation of the cortex. One population consists of radially migrating neurons that originate in the ventricular zone of the pallium (cortex) and give rise to the glutamatergic pyramidal neurons. The second population consists of tangentially migrating neurons that originate in the ventricular zone of the subpallium (subcortical telencephalon) and give rise to GABA (γ-aminobutyric acid)-producing local circuit neurons. The subpallium is also the origin of other cell types that follow distinct tangential trajectories to migrate to structures such as the olfactory bulb and the striatum. Here, we review evidence that supports the existence of several tangential migration pathways in the telencephalon, and summarize recent findings that describe their regulation.

DEVELOPMENT

SOMAL DISPLACEMENT
Displacement of the cell body, as opposed to migration of the whole cell. Also known as somal translocation.

Department of Psychiatry, Nina Ireland Laboratory of Developmental Neurobiology, Langley Porter Psychiatric Institute, 401 Parnassus Avenue, University of California, San Francisco, California 94143-0984, USA.
Correspondence to J.L.R.R.
e-mail: jlrr@cgl.ucsf.edu

Cell migration is a fundamental process in the development of the central nervous system (CNS), because both neuronal and non-neuronal cells are usually generated in sites that differ from those in which they eventually reside. So, most neurons migrate from the site of their last mitotic division, near the ventricle, towards the outer surface of the CNS, where they integrate into specific brain circuits.

In the telencephalon, radial migration is recognized as the primary mechanism by which developing neurons arrive at their final position[1–4]. This mode of cellular migration is, for example, essential for the proper morphogenesis of the cerebral cortex[5–11]. At early stages of cortical development, SOMAL DISPLACEMENT of immature neurons into the overlying mantle zone seems to be an important mechanism of radial movement[4,12]. As the cortex thickens, radial migration is largely dependent on the interactions of migrating neurons with radial glial fibres[13–17]. Molecular and cellular studies are rapidly elucidating many of the mechanisms that regulate radial migration processes[5–11,18].

Despite the radially orientated disposition of most of the migratory neurons in the cortex, early studies using Golgi-stained sections or electron microscopy revealed the existence of tangentially orientated cells in the intermediate zone of the developing cortex[12,19,20]. The idea that radial migration is the only significant mode of neuronal translocation in the developing cortex was challenged further when retroviral lineage experiments showed that many cortical neurons disperse tangentially[21–25]. A similar conclusion was reached from the observation of migrating neurons in slice cultures[26] and from the analysis of cell dispersion patterns in X-INACTIVATED TRANSGENIC MOSAICS[27,28].

The coexistence of two different modes of cell migration in the developing cortex began to be clarified when lineage analysis provided evidence that radially and tangentially migrating cells in the developing cortex arise from different progenitor cells[29,30]. Moreover, analysis of the distribution of the transcription factor *Dlx2* in the embryonic mouse telencephalon led to the suggestion that cells that originate in the subpallial

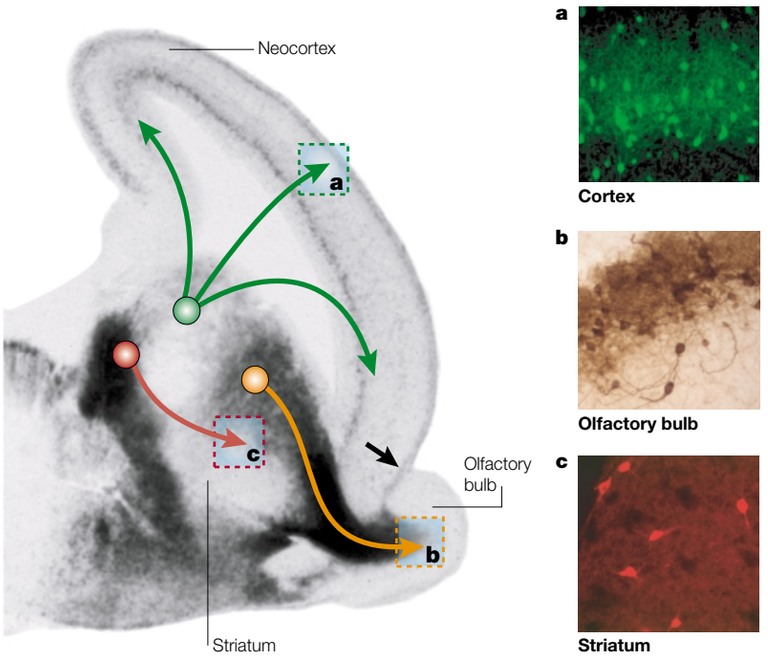

Figure 1 | **Streams of tangentially migrating interneurons from the subpallial telencephalon.** The subpallial telencephalon (the lateral ganglionic eminence, medial ganglionic eminence, caudal ganglionic eminence, septum and anterior entopeduncular region) is the origin of multiple streams of tangentially migrating interneurons that express Dlx genes. **a** | Superimposed on a parasagittal section of the mouse telencephalon at embryonic day 15.5, which shows β-galactosidase expression driven by a *Dlx5/Dlx6* enhancer, are arrows indicating the three main tangential migration pathways that have been identified in this region: the latero-caudal migration from the subpallial telencephalon to the cortex (green), the medio-rostral migration from the subpallial basal telencephalon to the olfactory bulb (orange), and the latero-caudal migration from the basal telencephalon to the striatum (red). These migratory pathways are temporally and spatially distinct, and give rise to a variety of GABA (γ-aminobutyric acid)- and non-GABA-containing interneurons that are shown in panels **b**, **c** and **d** (taken from the regions of the boxes shown in panel **a**). For example, the subpallial telencephalon generates **b** | parvalbumin-containing interneurons in the neocortex, **c** | dopaminergic interneurons in the olfactory bulb and **d** | cholinergic interneurons in the striatum. Also note the continuity of expression between the olfactory bulb and the marginal zone of the cerebral cortex (black arrow), which points to the existence of a further migratory route, as suggested previously[62].

(subcortical) telencephalon might migrate tangentially into the PALLIUM[31]. This idea was based on three observations: first, the embryonic cortex contained *Dlx2*-expressing cells in several of its layers; second, the expression in the cortex was continuous with expression in the SUBPALLIUM; and third, the *Dlx2*-expressing cells were excluded from the cortical ventricular zone, but were present in the progenitor zones of the subpallium (FIGS 1 AND 2). Consistent with this hypothesis, several laboratories showed that cells derived from the subpallial telencephalon contribute to the population of tangentially migrating cells in the cortex[32–34] (FIG. 1).

X-INACTIVATED TRANSGENIC MOSAICS
Based on the process of X-linked gene inactivation, the analysis of X-linked transgenic markers (e.g. LacZ) provides a method to distinguish between clonally related cell populations in the developing brain.

Fate of tangentially migrating cells in the cortex

There is now compelling evidence that most cortical GABA (γ-aminobutyric acid)-producing neurons (BOX 1) are born in the subpallial telencephalon and reach the cortex in several tangentially migrating streams. The idea that GABA neurons migrate tangentially in the developing cortex derives from early morphological and birth-dating studies. First, the morphology and distribution of GABA-containing neurons in the developing cortex led to the suggestion that many GABA neurons in the marginal zone, subplate and lower intermediate zone of the cortex constitute different populations of tangentially migrating neurons[35]. Similarly, birth-dating studies showed that GABA-containing cells that are born at a particular embryonic stage occupy progressively more medial regions in the lower intermediate zone of the cortex, indicating that they migrate tangentially in a lateral to medial direction[36]. In agreement with these results, lineage analysis revealed that clones that disperse tangentially in the cortex consist of GABA neurons[29,30]. Although none of these studies addressed the origin of the cortical GABA neurons, it was tacitly assumed at that time that cortical GABA-containing cells arise from cortical proliferative regions.

Anderson *et al.*[33] provided the first evidence that, in fact, many cortical GABA neurons originate in the subpallial telencephalon and migrate tangentially to reach their final destination. Subsequently, a variety of experimental approaches has supported the idea that GABA neurons derived from the subpallial telencephalon populate all areas of the cortex, including the neocortex[37–39], piriform cortex[40] and hippocampus[41]. In addition, genetic manipulations have provided further evidence for the subpallial telencephalic origin of cortical GABA-containing interneurons. For example, mice lacking transcription factors that regulate either differentiation (*Dlx1*, *Dlx2* or *Mash1*) or regionalization (*Nkx2.1*) in the basal telencephalon have reduced numbers of cortical GABA neurons at the time of birth[33,38,41–43].

Although the experiments described above indicate that the subpallial telencephalon contributes to several of the GABA-containing cell populations present in the developing cortex, it has been unclear to what extent the migrating cells contribute to the final population of interneurons in the adult cortex. Recently, three different experimental approaches have shed light on this issue. First, fate-mapping methods involving *in vivo* transplantation of subpallial telencephalic cells have shown that the tangentially migrating neurons give rise to cortical interneurons in adult rodents and birds[44,45]. Second, using β-galactosidase expression driven by a *Dlx5/Dlx6*

Box 1 | **Interneurons in the telencephalon**

On the basis of their neurotransmitter content, several interneuron subtypes can be distinguished in the cortex, olfactory bulb and striatum. The most common type of telencephalic interneuron contains GABA (γ-aminobutyric acid) as its main neurotransmitter. GABA interneurons can be further subdivided on the basis of their content of calcium-binding proteins (calbindin, calretinin and parvalbumin) and neuropeptides (for example, neuropeptide Y)[132–136]. In addition, some interneurons of the olfactory bulb and striatum do not use GABA as their principal neurotransmitter, but instead use dopamine or acetylcholine[132,137]. It is also worth noting that 'GABA neuron' is not synonymous with 'interneuron'. For example, most striatal neurons are projection neurons, and they also use GABA as their main neurotransmitter[132].

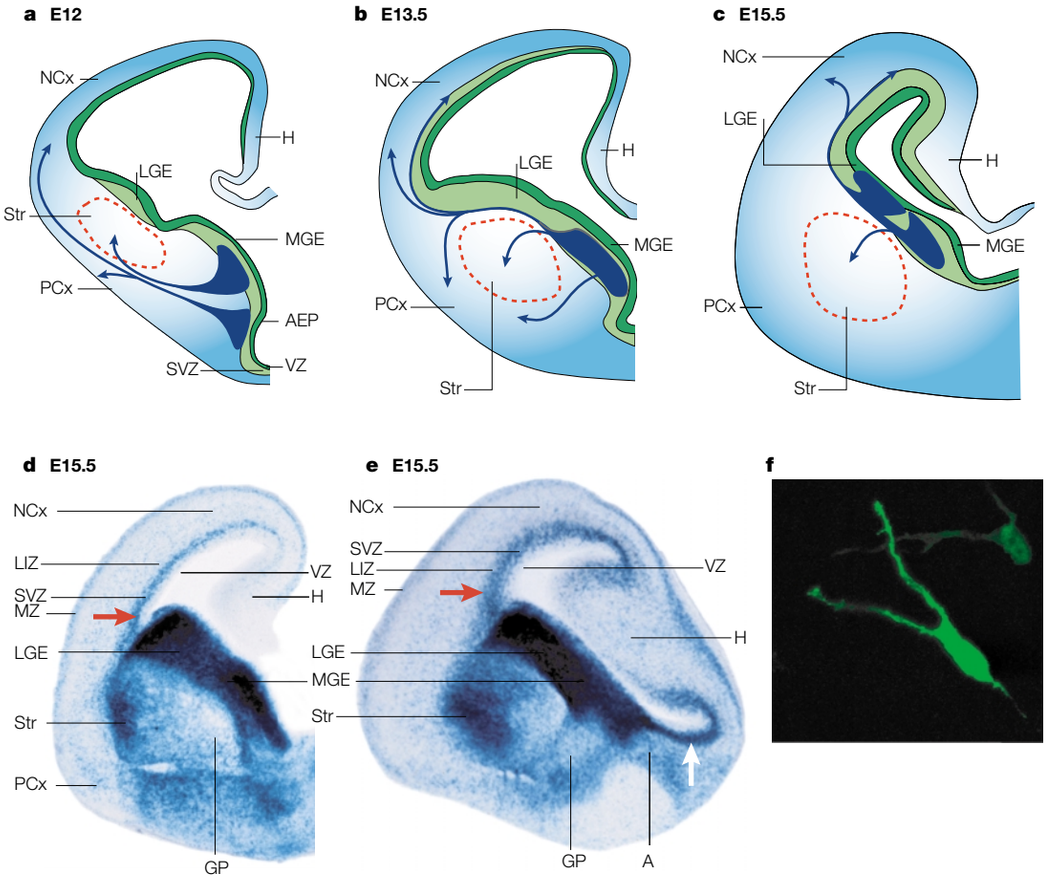

Figure 2 | **Routes of tangential migration of immature interneurons from the subpallial telencephalon to the cortex.** At least three spatially and temporally distinct routes can be distinguished, as depicted here in schemas of transverse sections through the embryonic telencephalon. **a** | Early during development (embryonic day (E) 12), interneurons that migrate to the cortex arise primarily from the medial ganglionic eminence (MGE) and the anterior entopeduncular area (AEP), and follow a superficial route. **b** | At the peak of migration (E13.5), interneurons migrating to the cortex arise primarily from the MGE and follow a deep route to the developing striatum (Str). Some interneurons also migrate superficially. **c** | At later stages (E15.5), cells migrating to the cortex might also arise from the lateral ganglionic eminence (LGE) and follow a deep route. **d**,**e** | Analysis of both coronal (**d**) and sagittal (**e**) sections from mice in which β-galactosidase expression is driven by a *Dlx5/Dlx6* enhancer indicates that cell migration to the cortex by the deep route occurs primarily through the subventricular zone (SVZ), or in the boundary between the SVZ and the intermediate zone (red arrows). In addition, interneurons might reach the cortex by a caudal migratory stream that courses through the primordium of the amygdala (A; white arrow). **f** | Migrating interneurons are typically bipolar or multipolar, with several leading processes, which are orientated in roughly the same direction, and a short trailing process. GP, globus pallidus; H, hippocampus; LIZ, lower intermediate zone; MZ, marginal zone; NCx, neocortex; PCx, piriform cortex; VZ, ventricular zone.

enhancer[46], Stühmer *et al.*[47] have provided evidence that virtually all cortical GABA interneurons in the adult brain are derived from cells that express the Dlx genes. This result is consistent with the idea that most GABA cortical interneurons derive from subpallial telencephalic progenitors. Data from a third approach — *in vivo* labelling of telencephalic progenitors by focal microinjection of tritiated thymidine in ferrets — also supports the idea that few, if any, GABA cells in the adult cortex are generated in the cortical neuroepithelium (S. A. Anderson, C. E. Kaznowski and S. K. McConnell, personal communication).

There is now compelling evidence that, in addition to giving rise to GABA interneurons, the subpallial telencephalon also generates oligodendrocytes that migrate tangentially to the cortex[48,49]. So, the subpallial telencephalon seems to generate both GABA-producing interneurons and oligodendrocytes with tangential migratory properties.

PALLIUM
The roof of the telencephalon. It contains both cortical structures (e.g. hippocampus and neocortex) and deep-lying nuclear structures (e.g. claustrum and parts of the amygdala). Pallium is not synonymous with cortex.

SUBPALLIUM
The base of the telencephalon. It consists primarily of the basal ganglia; for example, the striatum, globus pallidus, and parts of the septum and amygdala.

Other tangential migrations in the telencephalon

In addition to the migration of cells from the subpallial telencephalon to the cortex, other tangential migratory routes have been described in the telencephalon (FIG. 1). For example, it has been recognized for some time that progenitor cells in restricted regions of the telencephalic subventricular zone (SVZ) continue to proliferate in the adult, and generate granule and periglomerular cells in the olfactory bulb[50–57]. More recently, direct evidence for this rostral migratory stream (RMS) was provided in both neonatal and adult rodents and primates[56–58]. The olfactory bulb derivatives of the RMS are GABA-containing interneurons (granule and periglomerular cells)[44,51–54]. The onset of migration through the RMS

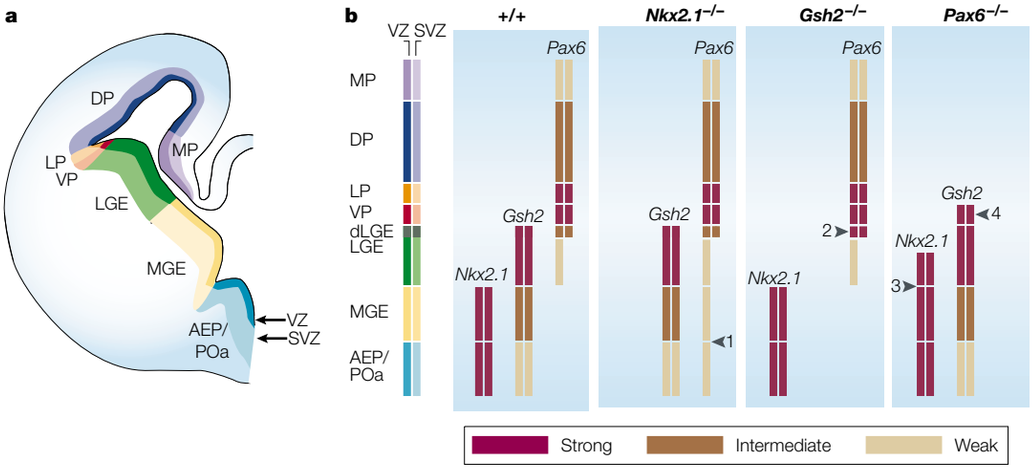

Figure 3 | **Interactions between regulatory genes contribute to the generation of subpallial progenitor domains in the telencephalon. a** | A coronal hemisection through a brain at embryonic day 14.5, showing in different colours the distinct progenitor cell domains of the telencephalon. **b** | The expression of *Nkx2.1*, *Gsh2* and *Pax6* is required to define independent progenitor cell populations in the lateral ganglionic eminence (LGE) and medial ganglionic eminence (MGE). Interactions between these genes define boundaries between the different progenitor zones. In *Nkx2.1* mutants, *Pax6* expression is expanded ventrally into the MGE and anterior entopeduncular area (AEP) (arrowhead 1). In *Gsh2* mutants, *Pax6* expression is expanded ventrally into the dorsal LGE (dLGE), along with other pallial markers (arrowhead 2). Finally, in *Pax6* mutants, *Nkx2.1* expression is expanded dorsally into the LGE (arrowhead 3) and *Gsh2* expression is expanded dorsally into the ventral pallium (VP) (arrowhead 4). DP, dorsal pallium; LP, lateral pallium; MP, medial pallium; POA, anterior preoptic area; SVZ, subventricular zone; VZ, ventricular zone.

seems to occur prenatally, as recent studies have shown that cells derived from the subpallial telencephalon migrate rostrally during embryonic stages and seed the olfactory bulb SVZ[44] (FIG. 1).

Striatal GABA-containing and cholinergic interneurons are other examples of cells that migrate tangentially within the telencephalon (FIG. 1; see also BOX 1). These interneurons derive from progenitor zones of the subpallial telencephalon, which are located outside the striatal anlage[59]. These studies reinforce the idea that the subpallial telencephalon is the origin of a chemically diverse population of tangentially migrating interneurons. In addition, it has recently been shown that the subpallial telencephalon seems to be the origin of a population of GABA interneurons that migrates caudally into the dorsal thalamus, although it has been proposed that this caudal migration might only be present in humans[60,61].

Origins and molecular specification

The evidence reviewed above indicates that the developing subpallial telencephalon is the origin of several tangential migratory streams that distribute cells to other regions of the telencephalon, including the cortex, olfactory bulb and STRIATUM. Which progenitor zones generate these tangentially migrating cells?

Experimental embryological analysis. The lateral ganglionic eminence (LGE) was originally identified, by DII-labelling experiments *in vitro*, as the likely source of cells that migrate tangentially from the subpallial telencephalon to the cortex[32–34]. However, more recent studies indicate that cells that migrate to the cortex originate in several proliferative regions of the subpallial telencephalon, including the LGE, medial ganglionic eminence (MGE), anterior entopeduncular area (AEP) and perhaps the area around the base of the olfactory bulb (retrobulbar area)[37–40,44,45,49,62,63]. These observations are based on different experimental methods, including DiI-labelling techniques in slice cultures[37,38,63] and several transplantation paradigms[39,40,44,45,49,63]. So, the properties and behaviour of the tangentially migrating cells seem to be closely related to the place and timing of their production. On the basis of these factors, three general and partially overlapping phases of migration can be distinguished (FIG. 2).

First, the MGE and AEP seem to be the primary sources of tangentially migrating cells during early stages of telencephalic development. Early migration from the MGE and AEP begins around embryonic day 11.5 (E11.5) in the mouse. These streams course primarily superficially to the developing striatum, and invade the cortical marginal zone and subplate[37,40,63]. Cells migrating from the MGE and AEP also invade the striatum at this stage[40].

Second, at mid-embryonic stages (E12.5–14.5), the MGE seems to be the principal source of cells that migrate tangentially into the cortex. MGE-derived cells migrate either deep or superficially to the developing striatum, and they populate both the SVZ/lower intermediate zone (BOX 2) and the subplate, from where they extend into the cortical plate[37,40,44,63]. During this period, a population of MGE-derived cells also migrates into the developing striatum [38,40,59]. LGE-derived cells, on the other hand, migrate profusely to the olfactory bulb at this stage[44], but do not seem to contribute to the population of cells migrating into the cortex[44,63]. This rostral migration of cells from the SVZ of the LGE to the olfactory bulb proceeds continuously into adulthood[44,56,57].

STRIATUM
Part of the subpallium and one of the components of the striatopallidal complex. It comprises deep (caudate nucleus, putamen and nucleus accumbens) and superficial (olfactory tubercle) parts.

DII
DiI is a lipophilic carbocyanine dye that emits an intense fluorescence when incorporated into cell membranes. It is commonly used to track cell migration, or for the retrograde or anterograde tracing of axons. It can be used on both live and fixed tissue.

Box 2 | **Laminar location of tangentially migrating cells in the cortex**

There is continuing controversy concerning the specific laminar location of the migrating cells that course tangentially in the cortex. Although most studies agree on the distribution of tangentially migrating cells in the cortical marginal zone and in the subplate, the laminar position of deeper migrating cells is still a matter of debate. In particular, it is unclear whether GABA (γ-aminobutyric acid)-producing interneurons invade the cortex through the lower intermediate zone, in close contact with fibres of the corticofugal projection[36,37,96,98], or whether they travel in a deeper layer that is adjacent to the cortical ventricular zone[44,138] (see also FIG. 2). Perhaps this deep migration contributes cells to the developing subventricular zone of the cortex in a manner analogous to that in which the rostral migratory stream contributes cells to the subventricular zone of the olfactory bulb.

Consistent with this idea, LGE-derived cells, but not MGE-derived cells, that are transplanted into the adult SVZ give rise to neurons that migrate rostrally to the olfactory bulb[39].

It has recently been shown that the AEP is the origin of a large fraction of telencephalic oligodendrocytes[49,64,65]. Nevertheless, further sources of oligodendrocytes might exist in the telencephalon[49,64].

Third, at late stages of telencephalic development (E14.5–16.5), cells that migrate tangentially into the cortex seem to derive from both the LGE and MGE[63] (D. Jiménez, L. M. López-Mascaraque, F. Valverde and J. A. De Carlos, personal communication). Interestingly, some migrating cells are directed towards the proliferative regions of the cortex at this stage[63]. Although it is possible that most of these cells derive initially from the MGE, *in vitro* experiments indicate that many of the migrating cells go through their last mitotic division while they are in the LGE[63].

So, neuroembryological analyses have identified a diverse set of temporally and spatially distinct migratory pathways, which originate in different progenitor zones within the subpallial telencephalon.

Genetic analysis. Examination of the distribution of interneurons in mice lacking transcription factors that regulate regional specification in the subpallial telencephalon, such as *Nkx2.1*, *Pax6* and *Gsh2*, has helped to clarify the anatomical origins of the different migratory streams. Through a mechanism that involves mutually repressive interactions, these transcription factors establish boundaries between different progenitor zones in the subpallial telencephalon (FIG. 3)[38,66–69]. Consequently, loss of any of these genes causes re-patterning of the subpallial telencephalon, which leads to changes in the composition of specific progenitor pools.

Specification of the MGE and AEP requires the expression of the HOMEOBOX transcription factor *Nkx2.1* (REF. 38). In the absence of *Nkx2.1*, progenitor cells from the MGE and AEP are re-specified to a more dorsal fate, similar to that of LGE progenitors[38] (FIG. 3). Re-specification of the *Nkx2.1* domain in the subpallial telencephalon results in a ~50% reduction in the number of cortical interneurons, reinforcing the idea that a large proportion of these cells originates in the MGE and AEP[38]. Furthermore, *Nkx2.1* mutants lack most striatal interneurons (GABA-producing and cholinergic cells), consistent with the evidence that these cells also migrate tangentially from the MGE/AEP[59]. On the other hand, the olfactory bulb of *Nkx2.1* mutants contains roughly normal numbers of interneurons[38], indicating that olfactory bulb interneurons derive primarily from the LGE.

The homeodomain gene *Gsh2* is required for the specification of the dorsal part of the LGE. In mice lacking *Gsh2* function, dorsal LGE progenitor cells express molecular markers that are associated with the cortex (FIG. 3), indicating that this transcription factor is necessary to establish the boundary between the LGE and the adjacent cortex[67–69]. Consistent with embryological evidence that the LGE is the source of olfactory bulb interneurons, re-patterning of the LGE in *Gsh2* mutants results in a reduction in the number of olfactory bulb interneurons at mid-embryonic stages[68,69].

Pax6 and *Nkx2.1* antagonize each other to establish the boundary between the MGE and LGE[38,66]. Accordingly, *Pax6* mutants show a phenotype that is complementary to that found in *Nkx2.1* mutants (FIG. 3). In *Pax6* mutant mice, LGE progenitor cells are re-specified to a more ventral fate, leading to an expansion of the MGE and a subsequent increase in the number of neurons that migrate tangentially into the striatum and cortex[70]. In addition, *Pax6* and *Gsh2* have opposing roles in the establishment of the boundary between the LGE and cortex[67,69]. So, loss of *Pax6* function results in the expression of dorsal LGE markers in the cortex, and severe disruption of the boundary between the cortex and basal ganglia[67,69] (FIG. 3). This defect might also contribute to the increased migration of interneurons that is observed in *Pax6* mutants[70]. In addition, *Pax6* heterozygous mice have reduced numbers of dopaminergic cells in the olfactory bulb[71] (BOX 1), indicating that this subtype of olfactory bulb interneuron arises from *Pax6* progenitors in the LGE. Interestingly, *Pax6* is strongly expressed in the dorsal LGE, a progenitor zone that does not produce many striatal cells[69,72], but instead might be the origin of cells migrating to the olfactory bulb and other structures[68,69].

In summary, genetic perturbation of the basal telencephalic pattern shows that reduced numbers of MGE and AEP progenitor cells leads to a decrease in the number of cortical GABA interneurons, whereas a reduction in the number of dorsal LGE progenitors decreases the number of olfactory bulb interneurons. These results indicate that the MGE/AEP is the source of most cortical interneurons and the LGE is the source of olfactory bulb interneurons. However, this relatively simple model does not account for the observation that 50% of cortical GABA interneurons are still present in *Nkx2.1* mutants[38], a result that indicates that many cortical interneurons might arise from a region distinct from the MGE and AEP. Anderson *et al.*[63] provided evidence that late in mouse gestation, the LGE is a source of neurons that migrate tangentially to the cortex (FIG. 2). These migrations tend to follow a subventricular course, and are present in *Nkx2.1* mutants. It is also possible that re-patterning of the MGE and AEP in *Nkx2.1* mutants is not complete, and that these regions can still produce some cortical interneurons. Arguing against this possibility is the observation that tangential migrations from the

HOMEOBOX
A sequence of about 180 base pairs that encodes a DNA-binding protein sequence known as the homeodomain.

MGE are not detectable in *Nkx2.1* mutants[63], and that subpallial telencephalic cells derived from *Nkx2.1* mutants have a migration defect *in vitro*[64]. However, there is evidence that caudal aspects of the subpallial telencephalon might be relatively spared in the *Nkx2.1* mutant, and this region might therefore be a source of some cortical interneurons[64].

Are all cortical interneurons from the subpallium?

Several lines of genetic evidence indicate that cortical projection neurons and interneurons have distinct origins. For instance, these two cell types express different sets of transcription factors. Developing cortical interneurons express members of the Dlx family[47,73], whereas cortical projection neurons express *Tbr1* and *Emx1*[74,75]. Accordingly, mice lacking *Tbr1* function show defects in the development of early-born cortical and olfactory bulb projection neurons, whereas development of interneurons seems to be normal[74,76]. Moreover, genetic evidence indicates that cortical progenitors expressing *Emx1* do not give rise to GABA-containing interneurons[77]. In these experiments, a strain of transgenic mice in which the CRE RECOMBINASE gene was inserted into the *Emx1* locus was crossed with a LacZ reporter line to assess the distribution of cells derived from *Emx1* progenitors (as shown by Cre-mediated recombination). Analysis of the distribution of LacZ-expressing cells in the cortex of Emx1–Cre/LacZ double-heterozygous mice showed no overlap of LacZ and GABA expression, indicating that *Emx1*-expressing cortical progenitors, at least, do not generate GABA neurons (REF. 77 and K. Jones, personal communication.)

The tangential migration of GABA neurons from the basal ganglia to the cortex in birds[45], and the presence of Dlx-positive cells in the cortex of birds and mammals[78], indicates that migration of interneurons from the basal telencephalon to the cortex might be a highly conserved trait in cortical evolution. Although present evidence indicates that most cortical GABA interneurons derive from the subpallial telencephalon, it is not clear whether this is true for all cortical GABA interneurons. *Mash1* is expressed in a subset of cortical progenitor cells[79], and there is evidence that *Mash1* can induce *Dlx1* (REF. 80). So, although there is postnatal Dlx expression in the cortical SVZ[47,63], it is unclear whether this expression arises from *Mash1* induction in cortical progenitors[80], or whether these Dlx-positive cells are introduced into the cortex by tangential migration from the basal telencephalon[63]. Through this latter mechanism, progenitor cells that are specified in the subpallial telencephalon might continue to proliferate after they reach the progenitor zone of the cortex, providing a secondary source of GABA neurons.

Differentiation of tangentially migrating cells

Several transcription factors have been identified that are essential for the differentiation of tangentially migrating interneurons, including *Dlx1*, *Dlx2* and *Mash1*. *Dlx1* and *Dlx2* are partially redundant, genetically linked homeobox genes, whereas *Mash1* is a BASIC HELIX–LOOP–HELIX gene. All three of these genes are expressed in some ventricular zone (VZ) and most SVZ progenitor cells in the LGE, MGE and AEP[31,81–87]. Analysis of the distribution of interneurons in mice lacking these factors has revealed that they are essential regulators of the timing of interneuron production and differentiation.

Loss of *Dlx1* and *Dlx2* function blocks the differentiation of late-born subpallial telencephalic neurons. In *Dlx1*/*Dlx2* double-mutant mice, partially differentiated interneurons (that is, cells that are able to express GABA) fail to migrate, and collect as periventricular ectopias[59,88]. Consequently, the number of GABA neurons found in the cortex, olfactory bulb and hippocampus at the time of birth is severely reduced compared with that of wild-type littermates[33,41,76]. Interestingly, loss of *Dlx1* and *Dlx2* function does not affect all cortical regions equally. So, whereas the olfactory cortex in neonatal *Dlx1/Dlx2* double mutants contains roughly normal levels of GABA neurons in the marginal zone and only slightly reduced numbers in the cortical plate, the neocortex has a 75% reduction in the number of GABA neurons and the hippocampus has a virtually complete loss[33,41]. Whereas *Dlx1/Dlx2* mutations affect late-born subpallial telencephalic neurons, loss of *Mash1* function leads to premature differentiation of several early-born cell populations[42]. In *Mash1* mutants, the lateral cortex is more severely affected than more medial cortical regions, and the overall loss of GABA interneurons in the cortex is more prominent in the marginal zone than in the intermediate zone. Together, these results support the view that early-born interneurons depend primarily on *Mash1* function, whereas late-born interneurons depend largely on *Dlx1* and *Dlx2* function[59]. In addition, gain-of-function experiments provide evidence that the Dlx and Mash genes are each sufficient to induce aspects of the GABA phenotype[73,80] (T. Stühmer, S. A. Anderson, M. Ekker and J. L. R. R., unpublished observations). So, these genes might have roles both in regulating the timing of neuronal differentiation and in inducing, and perhaps maintaining, the GABA phenotype.

Other transcription factors have also been implicated in regulating the differentiation of GABA interneurons. For instance, *Dlx5* and *Dlx6* are expressed after *Dlx1* and *Dlx2* (REFS 87,89), and are therefore candidates for later steps in the differentiation of GABA neurons. On the basis of their expression, it seems that the *Lhx6* and *Lhx7* Lim homeodomain proteins might also participate in the process of interneuron differentiation. Specifically, *Lhx6* might contribute to the development of cortical and striatal GABA interneurons[37,59], whereas *Lhx7* might regulate the development of cholinergic cells in the subpallial telencephalon[59].

Mechanisms controlling tangential migration

It is now well established that the subpallial telencephalon produces projection neurons that migrate radially and interneurons that migrate tangentially. Moreover, tangentially migrating cells from the basal telencephalon give rise to neurons that populate different telencephalic structures. It seems likely, therefore, that a variety of guidance systems is needed to direct

CRE RECOMBINASE
Part of a site-specific recombination system derived from *Escherichia coli* bacteriophage P1. Two short DNA sequences (*loxP* sites) are engineered to flank the target DNA. Activation of the Cre recombinase enzyme catalyses recombination between the *loxP* sites, leading to excision of the intervening sequence.

BASIC HELIX–LOOP–HELIX
A structural motif present in many transcription factors, which is characterized by two α-helices separated by a loop. The helices mediate dimerization, and the adjacent basic region is required for DNA binding.

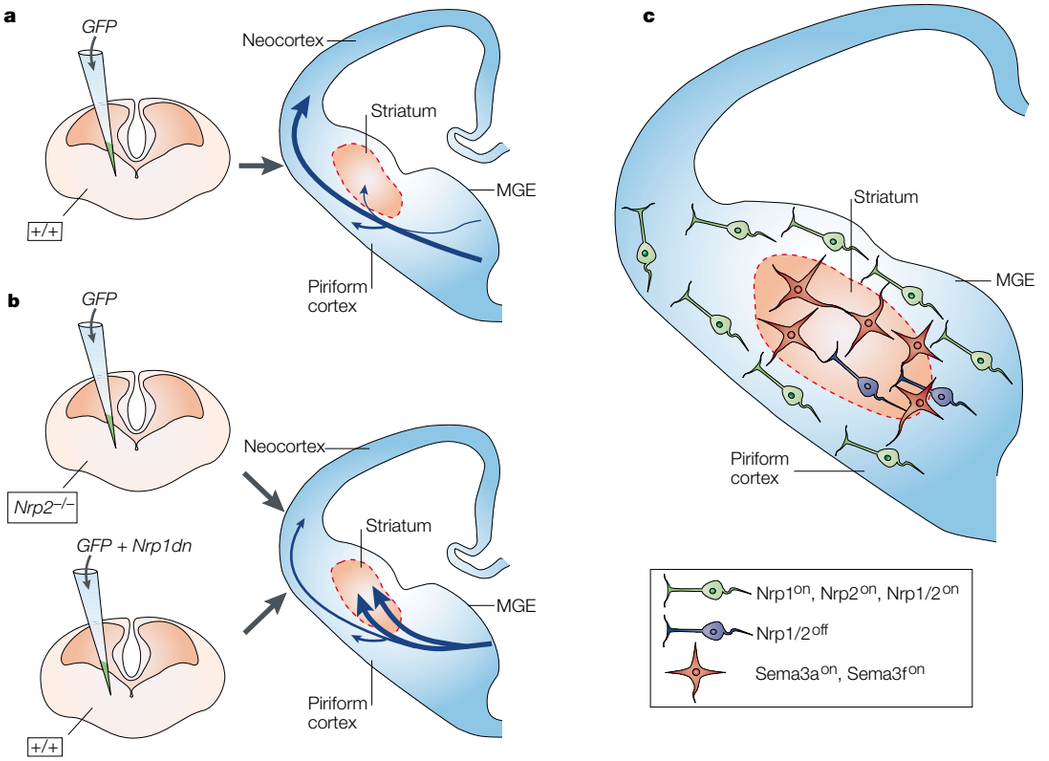

Figure 4 | **Neuropilin receptors regulate the sorting of striatal and cortical interneurons.** Focal electroporation of a green fluorescent protein (GFP) expression vector can be used to selectively label subsets of migrating cells in a normal or a mutant embryonic telencephalon *in vitro*. **a** | In wild-type embryos, most *GFP*-expressing cells derived from the medial ganglionic eminence (MGE) migrate towards the piriform cortex and neocortex, whereas only a fraction migrates into the developing striatum. **b** | In neuropilin 2 mutant embryos (*Nrp2*$^{-/-}$), most *GFP*-expressing cells that are derived from the MGE migrate towards the striatum, and only a few reach the cortex. Similarly, expression of a dominant-negative form of neuropilin 1 (*Nrp1dn*) in *GFP*-expressing wild-type MGE cells increases the number of cells that enter the striatum and decreases the number migrating to the cortex. **c** | A model for the mechanism of neuropilin-mediated sorting of striatal and cortical interneurons. Interneurons migrating into the cortex express neuropilin 1, neuropilin 2, or both (green cells), whereas interneurons migrating into the striatum do not (blue cells). Striatal cells express the semaphorins Sema3a and Sema3f (red cells), which presumably create an exclusion zone for migrating cortical interneurons and channel them into adjacent paths. All schemas depict transverse sections through the embryonic telencephalon.

these diverse migrations. Once a cell has been specified to take a tangential migratory course, there are at least three different types of factor that can regulate this process: first, factors that stimulate the movement of cells; second, factors that constitute the extracellular substrate for the migration; and third, factors that guide different migratory streams through appropriate pathways towards their targets.

Motogenic factors. Immature interneurons derived from the LGE and MGE have an impressive capacity for migration. *In vitro* experiments show that LGE cells migrate more than 100 μm per day, and MGE cells migrate almost three times faster[39,64]. Which signals are responsible for triggering this migratory behaviour? Several factors have been shown to possess motogenic activity, stimulating the undirected movement of neurons from their original position. Among these molecules, both hepatocyte growth factor/scattered factor (HGF/SF) and neurotrophic factors have been implicated in controlling the rate of migration of neurons derived from the subpallial telencephalon. For instance, exogenous HGF/SF increases the number of cells that migrate away from the subpallial telencephalon in slice cultures, whereas anti-HGF/SF antibodies inhibit cell movement[90]. Consistent with these results, mice lacking the urokinase-type plasminogen-activator receptor (uPAR), one of the factors that can cleave the inactive pro-form of HGF/SF to a biologically active protein, have fewer cortical calbindin-positive interneurons at birth[90]. Also, addition of brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT4), both of which are high-affinity ligands for the tyrosine kinase receptor TrkB, produces heterotopic accumulations of neurons in the marginal zone of the cortex both *in vitro* and *in vivo*[91]. These heterotopias are probably caused by increased migration, and they contain neurons that resemble GABA-containing subpial granule cells[62]. Consistent with the idea that TrkB receptor activation might stimulate neuronal migration in the developing telencephalon, tyrosine kinase inhibitors block BDNF-induced migration in cortical slice culture[92]. It remains to be determined whether the distinct migratory behaviour of LGE- and MGE-derived precursors depends on the differential expression of receptors for these motogenic factors.

Box 3 | **Radial versus tangential migration**

Current evidence indicates that most tangentially migrating neurons in the telencephalon become interneurons when they reach their final destination, whereas projection neurons, both in the cortex and in the subpallial telencephalon, seem to reach their final positions by radial migration. One possible explanation for the different migratory behaviours of interneurons and projection neurons might be related to the distinct functions that these two main types of neuron perform once they are integrated into specific brain circuits. Projection neurons frequently have topographically arranged patterns of connections. Regional patterning information present in neuronal progenitors in the ventricular zone might have an important role in regulating the topographical connectivity of projection neurons derived from these progenitors. Radial migration of immature projection neurons would permit the transfer of this topographical information — the protomap hypothesis of Rakic[139]. By contrast, local circuit neurons (interneurons) might not have an important role in the establishment of topographical connectivity maps, and they can therefore migrate tangentially to their final destination.

Extracellular substrates. Little is known about the substrates that are used by migrating neurons to reach the cortex. Tangential migration in the telencephalon seems to be largely independent of interactions with radial glia. In turn, tangentially migrating cells in the intermediate zone of the cortex seem to be closely associated with CORTICOFUGAL AXONS[93–96], indicating that migrating neurons might use other neuronal processes as the substrate for their migration (axonophilic migration). In agreement with this hypothesis, recent evidence indicates that the number of interneurons migrating to the cortex in slice cultures is severely reduced by adding antibodies against the neuronal adhesion molecule TAG-1 (contactin 2), which is expressed on corticofugal axons[96]. So, as described for other cell populations in the forebrain, such as the luteinizing-hormone-releasing hormone (LHRH) neurons[97], it is possible that migrating interneurons use axons as their substrate in the cortex[98]. However, it is still unclear whether most interneurons that migrate to the cortex interact with fibre tracts *in vivo*[44] (BOX 2).

Guidance factors. Although tangential migration in the telencephalon is a highly directional process, the mechanisms underlying the guidance of migrating cells are only just beginning to be understood. On the basis of their expression in the subpallial telencephalon, several families of ligands/receptors are candidates for guiding the trajectories of tangentially migrating interneurons. These include the netrin/Dcc (deleted in colorectal carcinoma), Slit/Robo and semaphorin/neuropilin systems[99–104]. So far, there is no evidence to suggest that netrin signalling participates in controlling tangential migration in the telencephalon[73], although it is implicated in regulating the radial migration of striatal projection neurons[105]. By contrast, both the Slit/Robo and semaphorin/neuropilin signalling systems have been proposed to affect tangential migration.

Slits are large extracellular matrix molecules that possess chemorepulsive activity for growing axons and migrating cells in a variety of systems[106]. In the telencephalon, Slit proteins repel most subpallial GABA neurons *in vitro*[107–110], and it has been proposed that this mechanism guides the migration of GABA interneurons to the cortex[109]. However, as the subpallial telencephalon produces both GABA-containing projection neurons (which remain in the subpallial telencephalon) and GABA interneurons (which migrate tangentially to the cortex) (see BOX 1), and both types of cell seem to respond *in vitro* to Slits, a specific role for Slit proteins in the guidance of tangentially migrating interneurons to the cortex seems unlikely. The expression of Slit proteins along the proliferative regions of the subpallial telencephalon is consistent with a repulsive activity that helps neuronal precursors to move away from the ventricular zone and prevents their movement towards the midline. Loss-of-function experiments are needed to clarify the role of Slits in the migration of interneurons to the cortex.

The mechanisms that control the segregation of migrating cells into different telencephalic structures also remain to be elucidated. Inroads towards understanding these questions have recently been made by the suggestion that neuropilin receptors mediate the sorting of striatal and cortical interneurons during their migration[40] (FIG. 4). Neuropilins are transmembrane receptors that mediate the repulsive actions of class 3 semaphorins on axons[111,112]. In the subpallial telencephalon, neuropilins are expressed by interneurons that migrate to the cortex, but not by interneurons that invade the developing striatum. Expression of neuropilins allows migrating cortical interneurons to respond to a chemorepellent activity in the striatal mantle, of which the class 3 semaphorins Sema3a and Sema3f are likely components. Loss of neuropilin function increases the number of interneurons that migrate into the striatum and decreases the number that reach the embryonic cortex. So, the final destination of tangentially migrating interneurons (striatum or cortex) is determined by the expression of the class 3 semaphorin receptors neuropilin 1 and neuropilin 2. Moreover, by channelling migrating cortical interneurons into superficial and deep pathways, the chemorepellent activity in the developing striatum might also help to distribute cortical interneurons differentially into superficial (marginal zone) and deep (SVZ/lower intermediate zone) positions within the cortex (REF. 40 and N. Tamamaki, personal communication).

Guidance of migration to the olfactory bulb. Several types of molecule that affect the rostral migration of interneuron precursors in the adult SVZ have been identified. Migrating neuroblasts in the adult RMS move in tightly associated chains[57,113,114], indicating that this type of migration is regulated by cues that act by cell–cell contacts. There is no evidence for an interaction of these cells with axons.

Cells that migrate in the RMS express high levels of the polysialylated neural cell-adhesion molecule (PSA-NCAM), which is required to maintain a permissive milieu for their migration[115–117]. Genetic deletion of PSA-NCAM[118,119], or enzymatic removal of polysialic acid from PSA-NCAM in wild-type mice[120], disrupts neuronal migration to the olfactory bulb. However, cells that lack PSA-NCAM migrate normally along the RMS of wild-type mice, indicating that the PSA-NCAM is an essential component of the migration substrate[121].

CORTICOFUGAL AXONS
Generic term to define efferent projections from the cerebral cortex.

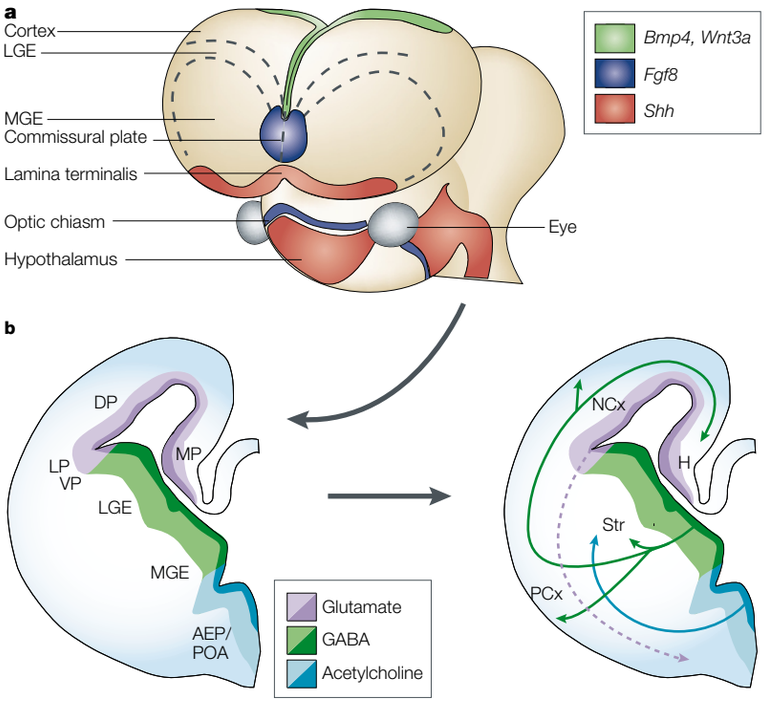

Figure 5 | **Coordination of patterning and migration mechanisms is required to achieve the cellular complexity of the telencephalon. a** | The main known signalling centres of the telencephalon are depicted in this schematic view of the mouse brain at mid-gestation. Patterning molecules include bone morphogenetic proteins (*Bmp4*) and members of the wingless-type MMTV integration site family (*Wnt3a*) (green), fibroblast growth factors (*Fgf8*; blue) and sonic hedgehog (*Shh*; red). **b** | Patterning molecules, alone or in combination, are postulated to regulate the regionalization of the telencephalic progenitor zone through the induction of transcription factors, as depicted in this schema of a coronal hemisection through a telencephalon at embryonic day 14.5. **c** | Distinct neurotransmitter phenotypes seem to be specified in different progenitor populations in the telencephalon. So, it is suggested that glutamatergic neurons are specified in the pallium (VP, LP, DP and MP), whereas GABA and cholinergic neurons are specified in the subpallium (LGE, MGE and AEP/POA). Tangential migration of glutamatergic, GABA (γ-aminobutyric acid) and cholinergic neurons to their final postmitotic destination allows different subdivisions of the telencephalon to increase their cellular complexity (note that radial migrations of projection neurons are omitted for clarity). AEP, anterior entopeduncular area; DP, dorsal pallium; H, hippocampus; LGE, lateral ganglionic eminence; LP, lateral pallium; MGE, medial ganglionic eminence; MP, medial pallium; NCx, neocortex; PCx, piriform cortex; POA, anterior preoptic area; Str, striatum; SVZ, subventricular zone; VP, ventral pallium; VZ, ventricular zone.

Cells of the SVZ express members of the Eph family of RECEPTOR TYROSINE KINASES and their ligands, the ephrins[122]. Infusion of the ectodomain of EphB or ephrin-B2 proteins into the telencephalic lateral ventricle, which abuts the SVZ, perturbs neuroblast migration[122]. These experiments indicate that attraction or repulsion between cells, mediated by Eph/ephrin signalling, might help to restrict neuroblast migration to specific routes along the RMS. As in the case of migrating cortical interneurons, diffusible factors might also help to guide neuroblast migration in the RMS. *In vitro* assays have shown that Slit proteins can repel neuroblasts derived from the anterior SVZ[107,108].

RECEPTOR TYROSINE KINASES
A family of membrane receptors, the intracellular domains of which catalyse the phosphorylation, by ATP, of specific tyrosine residues on their target proteins.

Why do they undergo this long journey?

It is now clear that progenitor cells in the ganglionic eminences not only generate the projection neurons of the basal ganglia and other subcortical structures, but, in addition, give rise to many neurons that disperse tangentially to populate different structures outside the subpallial telencephalon (BOX 3). Why do subpallial telencephalic cells migrate to other telencephalic regions? One possibility is suggested by the observation that patterning and migratory processes are intimately linked during development of the telencephalon[44,59,123]. So, dorsoventral patterning of the telencephalon, involving opposing gradients of morphogens, generates different zones of neuronal progenitors with distinct molecular properties at different dorsoventral locations (FIG. 5). As in other regions of the neuroaxis, these different progenitor zones are under the control of a specific homeobox code, which could, in turn, determine the properties of the cells derived from them. In the telencephalon, for example, certain populations of neurons with distinct neurotransmitter phenotypes seem to be derived from progenitors that are located in different regions (FIG. 5). So, glutamatergic cells might only be produced in pallial areas, whereas most or even all cells expressing GABA might be generated in the subpallium, and cholinergic neurons might derive exclusively from the ventral-most region of the subpallial telencephalon[59,123]. According to this model, the specification of forebrain cholinergic cells, for example, might occur only in the proximity of ventral signals, such as sonic hedgehog (Shh) and bone morphogenetic protein 9 (Bmp9)[124,125], and so the only way to incorporate this cell type into more dorsal regions of the telencephalon would be through tangential migration. Moreover, this hypothesis anticipates that tangential migration from the pallium to the subpallium will occur when cell types specified in dorsal regions of the telencephalon are required in ventral structures[126,127]. Such migrations are very prominent; for example, in the hindbrain[128–131]. Consequently, tangential migration in the telencephalon (and perhaps in other regions of the CNS) might be a mechanism selected through evolution to increase the cellular complexity of specific circuits, such as those of the cerebral cortex.

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