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Cell-autonomous and cell-to-cell signalling events in normal and altered neuronal migration

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Abstract

The cerebral cortex is a complex six-layered structure that contains an important diversity of neurons, and has rich local and extrinsic connectivity. Among the mechanisms governing the cerebral cortex construction, neuronal migration is perhaps the most crucial as it ensures the timely formation of specific and selective neuronal circuits. Here, we review the main extrinsic and extrinsic factors involved in regulating neuronal migration in the cortex and describe some environmental factors interfering with their actions.

Introduction

The cerebral cortex is a complex six-layered structure that contains an important diversity of neurons, and has rich local and extrinsic connectivity. This structure forms through tightly regulated processes, including proliferation of neural precursors and specification of neuronal subtypes, migration of young neurons, and establishment of synaptic contacts (Rakic, 2007; Clowry *et al.*, 2010). Because migrating neurons are long-distance travellers, precisely regulating their journey is crucial to ensure an appropriate final positioning within developing neuronal networks, and consequently prevent cortical malformations. Improper neuronal migrations are indeed important causes of malformations of cortical development that lead to mental retardation, epilepsy and other neurological syndromes (Guerrini & Parrini, 2010).

In addition to being generated in different germinal zones, distinct neuronal subtypes also use different migratory modalities to reach their final destinations. Pyramidal glutamatergic neurons originate in the pallial ventricular zone (VZ) and migrate radially to reach the cortical plate (Kriegstein & Noctor, 2004). γ-Aminobutyric acid (GABA)ergic interneurons mainly originate in the subpallium and migrate tangentially over long distances (Corbin *et al.*, 2001). It must be noted that migrating interneurons have to switch from tangential to radial migration and leave their migratory streams to reach their final destination in the cortical plate (Ang *et al.*, 2003).

If the direction of migration differs, the migratory modes used by both pyramidal cells and interneurons, however, share striking similarities: they both rely on tightly regulated movements of their guiding and trailing processes, as well as on those of their nuclei, they require cell-to-cell contacts and have to interpret guiding cues while migrating. Early generated pyramidal neurons migrate independently of radial glial fibres by shortening their leading processes as their soma move rapidly toward the pial surface. This mode of migration is known as somal translocation (Nadarajah *et al.*, 2001). When the distance between their birthplace and their final destination increases as corticogenesis continues, pyramidal neurons generated later migrate along radial glial fibres by using a three-step migratory mode (Kriegstein & Noctor, 2004). In this 'standard' three-step migratory mode utilized by both pyramidal cells and interneurons, neurons first extend a leading process, then translocate their nucleus into the leading process (i.e. nucleokinesis) and finally retract their trailing process, before they repeat this three-step cycle in a saltatory manner (Ayala *et al.*, 2007). Locomotion requires attachment to radial glial fibres, and is used by pyramidal neurons after they leave the intermediate zone and change their morphology from a multipolar to a bipolar shape (Nadarajah & Parnavelas, 2002; Tabata & Nakajima, 2003). Whereas pyramidal neurons usually have a single leading process while undergoing locomotion, tangentially migrating interneurons extend leading process branches – a feature that reflects an intense exploratory behaviour (Métin *et al.*, 2006; Valiente & Marín, 2010). Even though they do not seem to require contacts with radial glial cells, direct interactions with other cell types (including other migrating interneurons) have been proven crucial for interneuronal navigation toward their target fields, as well as external guiding cues.

Here, we review mechanisms that enable a precise regulation of pyramidal cells and interneuronal migrations by focusing on the cell-autonomous events controlling leading process dynamics and branching, nuclear movement, as well as on the cell-to-cell signalling events modulating cell adhesion and guidance (Fig. 1). Finally, among the modulatory signals involved in regulating neuronal migrations, we choose to emphasize the crucial role played by neurotransmitters and to illustrate the adverse effects of some environmental factors interfering with their actions.

Cell-autonomous events

Leading process dynamics and branching

Migrating neurons harbour a highly specialized process that, by its polarized location at the leading edge of the cell, is considered as a

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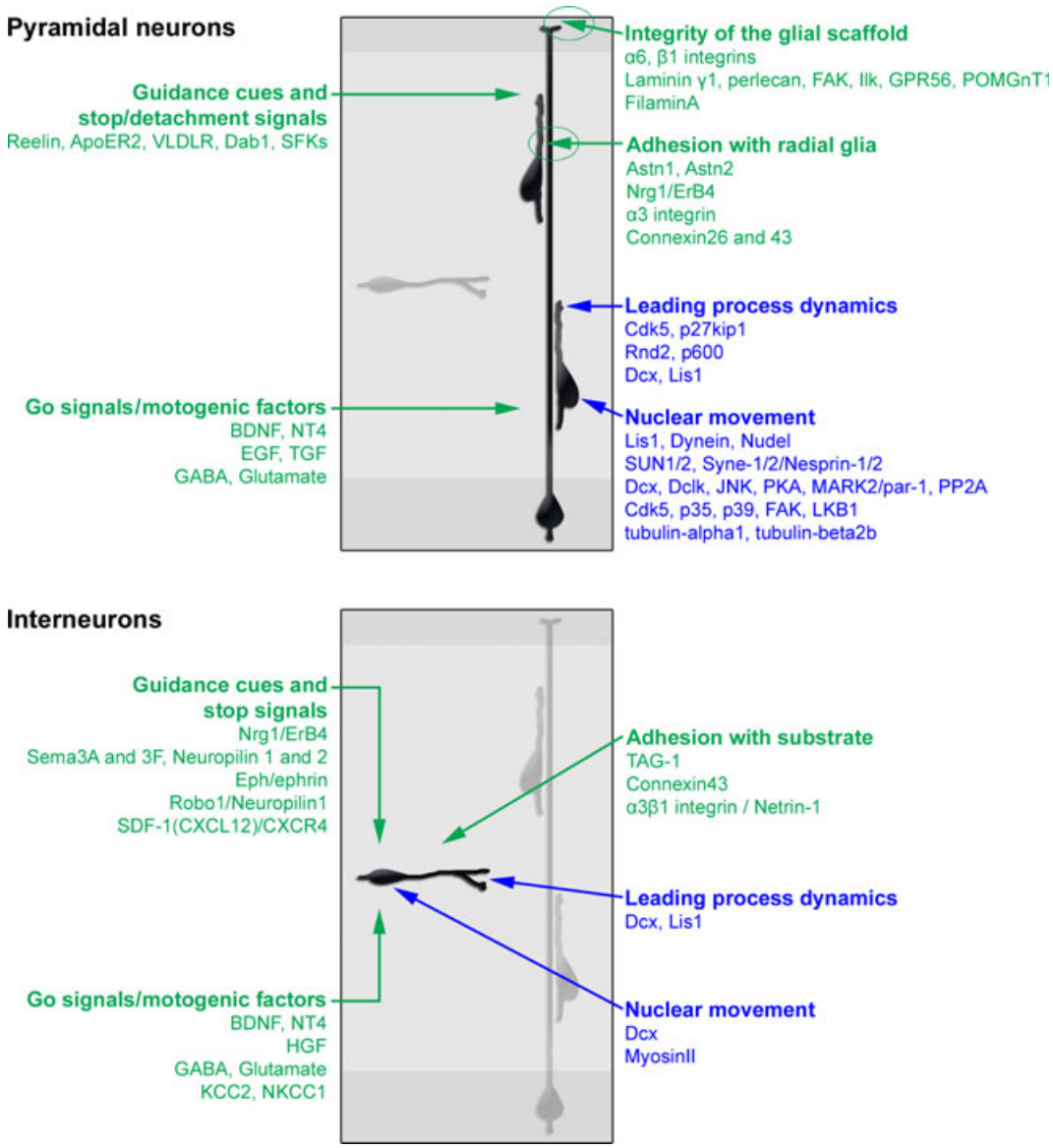

FIG. 1. Mechanisms controlling pyramidal cell and interneuron migration in the cerebral cortex. Molecular actors involved in radial migration (pyramidal neurons migrating along a radial glial cell, top panel) and tangential migration (interneurons, bottom panel) are listed in relation to their roles/functions. Blue colour refers to cell-autonomous mechanisms and green colour to cell-to-cell signalling events. Note that a large number of listed molecules are involved in both radial and tangential migration. For interpretation of color references in figure legend, please refer to the Web version of this article.

crucial sensing organ. This so-called leading process is an extremely dynamic entity utilized by migrating neurons to sense their surrounding environment and to determine the directionality of movement. Leading process morphological properties differ in migrating pyramidal neurons and interneurons. Whereas migrating pyramidal neurons display a typical bipolar morphology characterized by a single and unbranched leading process oriented forward, interneurons extend leading process branches when migrating. This difference is most likely due to the fact that pyramidal neurons undergoing locomotion are highly dependent to radial glial fibres that might impose the presence of a single guiding entity. Interneurons instead navigate in a more exploratory fashion and have to interpret guidance cues to determine what direction to follow. They thus frequently extend or retract branches, and change direction when receiving attractive or repulsive signals. Nevertheless, the leading process dynamics appears crucial for both migrating pyramidal cells and interneurons as altering this dynamics is associated with impaired migration. Although the molecules and mechanisms involved in regulation of the leading process dynamics are mostly unknown, some actors have been identified. Among them, the cyclin-dependent kinase Cdk5 was found to be crucial in modulating the leading process extension in migrating pyramidal neurons. Migrating pyramidal neurons expressing a dominant-negative form of Cdk5 (DN-CDK5) after *in utero* electroporation do not migrate to the cortical plate, and their leading processes morphology is found to be severely affected (Kawauchi *et al.*, 2006). In addition to being unable to exhibit the typical multipolar morphology in the lower intermediate zone, DN-CDK5-expressing neurons remain round-shaped and extend thinner processes compared with controls. Moreover, whereas control neurons normally transition from multipolar to bipolar shape in the upper Intermediate Zone (IZ), DN-CDK5-expressing neurons in the upper IZ often lose their leading processes or, when present, their leading processes appear abnormal. RNAi-mediated knockdown of $p27^{kip1}$ further revealed this effect to be mediated via Cdk5-dependent phosphorylation of $p27^{kip1}$, leading

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to its stabilization in migrating neurons and resulting in the maintenance of appropriate levels of F-actin in leading processes.

Another important protein is the small GTP-binding protein Rnd2, a Rho GTPase of the Rnd subfamily. Rnd2 is expressed in the cortical subventricular zone (SVZ) and intermediate zone, and is absent in the cortical plate (Nakamura *et al.*, 2006; Heng *et al.*, 2008). Migrating pyramidal neurons expressing after *in utero* electroporation a wild-type form or a constitutively active form of Rnd2, but not a mutant form, fail to reach the cortical plate and adopt an abnormal morphology (Nakamura *et al.*, 2006). Similarly, RNAi-mediated knockdown of Rnd2 in migrating pyramidal neurons after *ex vivo* electroporation and slice culture reveals an altered radial migration (Heng *et al.*, 2008). In Rnd2-RNAi transfected brains, transfected pyramidal neurons fail to reach the cortical plate and accumulate in the cortical VZ/SVZ. In addition, Rnd2 knockdown increases the amount of transfected pyramidal cells exhibiting a multipolar morphology in the IZ, as well as the number of uni/bipolar pyramidal cells displaying highly atypical branched leading processes in the upper IZ and cortical plate (CP), a phenomenon never seen in controls.

The microtubule-associated protein p600 is another crucial regulator of the leading process dynamics in migrating pyramidal neurons. RNAi-mediated p600 knockdown in migrating pyramidal neurons results in an abnormal neuronal migration, with cells failing to reach the cortical plate and accumulating in the SVZ and IZ (Shim *et al.*, 2008). In addition, p600-deficient uni/bipolar neurons in the IZ exhibit a highly abnormal morphology compared with controls, with thinner and undulated leading processes.

The lissencephaly-associated genes Lis1 and DCX, in addition to their roles during nucleokinesis (see below), are also involved in regulating the leading process dynamics and branching in both pyramidal cells and migrating interneurons. *In utero* RNAi-mediated knockdown of DCX in rat embryos results in pyramidal neurons accumulated at the multipolar stage in the IZ (Bai *et al.*, 2003). Similarly, *in utero* RNAi-mediated knockdown of Lis1 in rat embryos prevents migrating pyramidal neurons to transition from the multipolar to the bipolar stage and, consequently, multipolar cells with increased numbers of branches accumulate at the VZ/SVZ (Tsai *et al.*, 2005). Migrating interneurons also require proper DCX and Lis1 functions. First, *Dcx*-deficient migrating interneurons in *Dcx* knockout mice extend leading processes that branch more frequently and remain unstable compared with wild-type ones (Friocourt *et al.*, 2007; Kappeler *et al.*, 2006). Second, migrating interneurons in heterozygous *Lis1* knockout mice, unlike controls, extend long leading processes that never branched (Nasrallah *et al.*, 2006).

Nuclear movement

Nuclear movement, or nucleokinesis, comprises two phases that characterize the typical saltatory movement of migrating neurons: first, a cytoplasmic dilation forms in the leading process, followed by a forward movement of the centrosome (and the Golgi apparatus) into this swelling. This first step is associated with the leading process extension. Second, the nucleus moves forward, following the centrosome. This second step is usually associated with a leading process arrest or branching. A large amount of proteins are known to participate in nuclear movement, which requires coordinated pulling and pushing forces controlled by motor and cytoskeleton-related proteins, and organized around a perinuclear microtubule network. Among these, a major actor is Lis1, a protein that binds microtubules and promotes their stability. *Lis1* gene is part of a highly conserved family of genes that in lower eukaryotes control nuclear distribution, a phenomenon sharing striking similarities with nucleokinesis. Lis1 interacts, among other proteins, with cytoplasmic dynein, its regulatory complex dynactin and proteins in the dynein pathway such as Nudel. Analysis of migrating cerebellar neurons expressing a RFP-tagged version of Lis1 together with a green fluorescent protein (GFP)-tagged version of the centrosome-associated protein centrin-2 reveals Lis1 is associated with the centrosome in migrating neurons (Tanaka *et al.*, 2004a). In addition, nucleus-to-centrosome coupling in *Lis1*-deficient neurons is found to be affected in heterozygous knockout mice, and similar defects are observed in wild-type neurons when cytoplasmic dynein function is inhibited (Tanaka *et al.*, 2004a). *In utero* RNAi-mediated knockdown of Lis1, dynein and Nudel in migrating pyramidal neurons further confirmed these observations, and reveals that these three proteins operate synergistically (Shu *et al.*, 2004). First, in both transfected cortical neurons in culture and migrating pyramidal neurons after *in utero* electroporation, Lis1, dynein and Nudel1 loss-of-function results in a defective nucleus-to-centrosome coupling leading to abnormal migration. Second, rescue experiments show that improper neuronal migration in Nudel1-RNAi animals is partially rescued by concomitant Lis1 overexpression, whereas this rescue is not observed in dynein-RNAi animals. However, migration defects in Lis1-RNAi animals are not rescued by concomitant overexpression of Nudel1. These observations suggest that coordinated actions of Lis1, dynein and Nudel are essential for regulating nuclear translocation, and may explain lamination deficits in lissencephalic patients with *LIS1* mutations.

Recent observations highlighted the role of SUN (Sad1p/UNC-84)–KASH (Klarsicht/ANC-1/Syne Homology) proteins during nucleokinesis and nucleus-to-centrosome coupling (Zhang *et al.*, 2009). Interestingly, the SUN–KASH proteins SUN1/2 and Syne-1/2 were proposed to transmit the forces from the microtubule motor proteins to the nucleus via molecular complexes involving SUN1/2, Syne-1/2, dynein/dynactin/Lis1 and nuclear lamins, thus clarifying how dynein-mediated pulling forces are transferred to the nucleus.

DCX and Dclk are microtubule-associated proteins with partially redundant functions that interact with microtubules and promote their polymerization and stabilization (Horesh *et al.*, 1999; Koizumi *et al.*, 2006). *DCX* mutations are responsible for X-linked lissencephaly in males, and for subcortical band heterotopia or double cortex syndrome in female patients (Gleeson *et al.*, 1998; des Portes *et al.*, 1998). *DCX* and *Dclk* knockout mice show no cortical lamination deficits, except minor hippocampal abnormalities (Corbo *et al.*, 2002), whereas DCX and Dclk double knockout mice show an exacerbated phenotype confirming the redundancy of the two genes function (Deuel *et al.*, 2006; Koizumi *et al.*, 2006; Tanaka *et al.*, 2006). Analysis of nucleokinesis in *DCX*-deficient migrating interneurons reveals that these cells display enlarged centrosome-containing cytoplasmic dilations that, instead of moving gradually forward as controls, move forward and backward in the leading process (Kappeler *et al.*, 2006). Moreover, whereas movement of the cytoplasmic dilations is tightly associated with a forward movement of the nucleus in controls, this coordinated forward movement is lost in *DCX*-deficient migrating interneurons. In line with this, analysis of the centrosome dynamics in GFP-expressing pyramidal neurons transfected with *DCX* shRNAs and expressing a RFP-tagged centrosomal protein revealed an exacerbated but mostly random centrosomal motility (Sapir *et al.*, 2008). Interestingly, defective nucleus to centrosome coupling in *Lis1*-deficient migrating neurons is rescued when DCX is concomitantly expressed (Tanaka *et al.*, 2004a). Additional control of DCX function is obtained through multiple kinases and phosphatases (JNK, CDK5, PKA, MARK2/PAR-1 and PP2A) that, via phosphorylation/dephosphorylation cycles, regulate DCX affinity to microtubules (Schaar *et al.*, 2004; Tanaka *et al.*, 2004b; Sapir *et al.*, 2008). In addition to its function for regulating DCX affinity to microtubules (Tanaka *et al.*,

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2004b), Cdk5 is known to phosphorylate other targets, such as the microtubule-associated protein MAP1B (Kawauchi *et al.*, 2005), or kinases like the focal adhesion kinase (FAK; Xie *et al.*, 2003). For the latter, migrating pyramidal neurons overexpressing a non-phoshorylatable form of FAK after *in utero* electroporation fail to migrate to the cortical plate and accumulate in the IZ. In addition, these cells exhibit an abnormal nuclear morphology and organization of the perinuclear microtubule network. To note, Cdk5 function depends on activation by its neuronal-specific activators p35 and p39 (Ko *et al.*, 2001).

Another actor is the Ser/Thr kinase LKB1, an orthologue of the *C. elegans* polarity protein Par4. RNAi-mediated LKB1 knockdown in migrating pyramidal neurons after *in utero* electroporation results in impaired migration with neurons accumulated in the cortical IZ (Asada *et al.*, 2007). Analysis of centrosome-to-nucleus distance in LKB1-RNAi neurons further revealed an increased distance in migrating neurons compared with controls, associated with an increased number of differentiated neurons with an upside-down orientation.

Most of the molecular actors cited above are involved in regulating the nucleus forward movement via pulling forces organized around the perinuclear microtubule network. Pushing forces at the rear of the nucleus are also required, the major actor being myosin II. Myosin II is found accumulated at the rear of migrating interneurons, and its inhibition by blebbistatin abolishes saltatory nuclear movements (Bellion *et al.*, 2005). In addition, inhibiting nuclear movements with blebbistatin causes perinuclear protrusions to form laterally, and nuclei could occasionally move into them. This further reveals that, in addition to its crucial role for the nucleus forward movement, myosin II is also essential for maintaining the nucleus aligned with the centrosome in the leading process. More recently, time-lapse analysis of actin dynamics in migrating interneurons expressing a GFP-fused reporter peptide interacting with F-actin provided an interesting description of actin remodelling during nuclear movement (Martini & Valdeolmillos, 2010). Whereas actin is homogeneously distributed around the nucleus when interneurons are stationary, actin was found to transiently condense at the rear of the nucleus concomitantly to the forward displacement of the nucleus. Moreover, F-actin and myosin II were observed to display a similar expression pattern at the rear pole of the nucleus and, consistently with this, blebbistatin treatment abolished both actin condensations and nuclear movement, thus confirming that actomyosin contraction controls nuclear translocation as already proposed by Bellion *et al.* (2005).

To note, the microtubule subunit composition is another crucial element for neuronal migration as exemplified by identified mutations in tubulin-alpha1 (Keays *et al.*, 2007) and tubulin-beta2b (Jaglin *et al.*, 2009) in human lissencephalic or polymicrogyric patients.

Cell-to-cell signalling events

Cell-to-cell interactions

Adhesion with radial glial cells/integrity of the glial scaffold

Radial glial cells have a dual role during corticogenesis in the sense they both are the progenitors of cortical pyramidal neurons and their guide when they migrate to the cortical plate. Interactions between migrating pyramidal neurons and radial glial fibres are thus extremely crucial for neuronal locomotion and acquisition of the appropriate laminar positioning. Large amounts of proteins belonging to the class of membrane-bound cell adhesion molecules have been described, as well as proteins that control interactions between membrane-bound proteins and the cytoskeleton. Among them, Neuregulins and Astrotactins were the first molecules identified as mediating, together with their receptors, neuron-to-glia interaction in migrating cerebral and/or cerebellar neurons (Anton *et al.*, 1997; Rio *et al.*, 1997; Adams *et al.*, 2002). Astrotactin (Astn1) is expressed on the surface of migrating cerebellar neurons, and treatment with antibodies against astrotactin blocks their migration *in vitro* (Fishell & Hatten, 1991). Time-lapse microscopy analysis of Astn1 localization in migrating cerebellar neurons expressing a Venus-tagged version of Astn1 reveals this protein constantly accumulates at the front of the soma and in the base of the leading process when neurons migrate. This protein accumulation could correspond to a new site of adhesion between the migrating neuron and its glial guide as migration proceeds (Wilson *et al.*, 2010). Astn2, another member of the Astrotactin family, was recently identified as a potential regulator of Astn1 protein levels on the membrane of migrating neurons (Wilson *et al.*, 2010). Neuregulins and their receptors are expressed by both migrating cortical and cerebellar neurons and radial glial cells (Anton *et al.*, 1997; Rio *et al.*, 1997). Incubation with exogenous neuregulins was found to promote cortical neuron migration on radial glial fibres in an *in vitro* assay, while incubation with blocking antibodies drastically retards migration (Anton *et al.*, 1997). In addition, cerebellar neurons migration on glial cells expressing a dominant-negative form of the neuregulin receptor Erb4 *in vitro* is impaired compared with migration on wild-type glial cells (Rio *et al.*, 1997).

Several integrin subunits expressed in the developing brain have also been found to be crucial for neuronal migration and adhesive interactions between migrating neurons and glial cells. α_3 integrin subunit is expressed by migrating neurons in the cortical VZ/IZ, decorating their leading and trailing processes, and surrounding their plasma membrane. α_V integrin subunit is primarily expressed by radial glial cells (Anton *et al.*, 1999). In an *in vitro* assay, incubation with anti-α_3 antibodies reduces cortical neuron migration on radial glia, without affecting their attachment. In contrast, incubation with anti-α_V antibodies leads to reduced migration, retraction of both leading and trailing processes, and eventually detachment from radial glia (Anton *et al.*, 1999). Consistent with this, α_3 mutant mice show an abnormal cortical lamination (Anton *et al.*, 1999; Schmid *et al.*, 2004). Time-lapse microscopy analysis further reveals both radial and tangential abnormal migrations, associated with an impaired leading/trailing process dynamics due to a disrupted regulation of actin microfilaments in migrating neurons (Schmid *et al.*, 2004).

Integrins are expressed as heterodimers composed of α- and β-subunits, and α_3- and α_6-subunits are known to interact with β_1-subunits. Consistent with this, incubation with antibodies against β_1 alters migration *in vitro* (Anton *et al.*, 1999). Moreover, conditional removal of β_1 from neural precursors in transgenic mice results in major brain development defects that include a reduced size of the cerebral hemispheres and cerebellum, altered cortical lamination with marginal zone ectopias, and simplified and distorted cerebellar folia (Graus-Porta *et al.*, 2001). These defects, however, appear rather as a consequence of abnormal glial fibres endfeet at the pial surface, associated with an abnormal positioning of Cajal-Retzius cells, than a direct defect in neuron-to-glia interactions that appear mostly normal (Graus-Porta *et al.*, 2001). Interestingly, mice lacking α_6-subunits display a mostly similar brain phenotype, with disrupted cortical lamination and appearance of leptomeningeal heterotopia secondary to a disrupted basal membrane at the pial surface (Georges-Labouesse *et al.*, 1998), a phenotype that is exacerbated in α_3 and α_6 double knockouts (De Arcangelis *et al.*, 1999).

Overall, these observations illustrate that maintaining the integrity of the radial glial scaffold is crucial for neuronal migration. In line with this, disruption of the pial membrane in mice with a targeted deletion of the nidogen-binding site of laminin γ1 results in retracted radial glia endfeet at the pial surface, mislocalized Cajal-Retzius cells,

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and abnormally undulated cortical layers with leptomeningeal heterotopia (Halfter *et al.*, 2002; Haubst *et al.*, 2006). Strikingly similar brain phenotypes are observed in several knockout mice with constitutive or conditional deletions of genes resulting in disrupted pial basal lamina integrity, such as α_3, α_6 and β_1 integrin subunits (Georges-Labouesse *et al.*, 1998; De Arcangelis *et al.*, 1999; Graus-Porta *et al.*, 2001), perlecan (Costell *et al.*, 1999), FAK (Beggs *et al.*, 2003), integrin-linked kinase Ilk (Niewmierzycka *et al.*, 2005), GPR56 (Li *et al.*, 2008a) and POMGnT1 (Hu *et al.*, 2007). It is worth stressing that defects in radial glial endfeet at the ventricular surface are also induced when β_1 integrin signalling is blocked at the VZ on cultivated neocortical explants (Loulier *et al.*, 2009). This last observation suggests that maintaining the integrity of pial and ventricular radial glial endfeet, as well as basal lamina at the pial and ventricular border, are crucial for neuronal migration. In line with this, the actin cross-linking protein FilaminA, in addition to its role for promoting neuronal migration (reviewed in Sarkisian *et al.*, 2008), has been suggested to play a role in maintaining the VZ surface integrity. FilaminA mutations are responsible for periventricular nodular heterotopias, where neurons that failed to migrate accumulate on nodules lining the ventricular surface. Two genes involved in FilaminA regulation, FILIP (Nagano *et al.*, 2002) and MEKK4 (Sarkisian *et al.*, 2006), have been found to induce in rodents, when respectively overexpressed or knocked-down, an accumulation of cortical pyramidal cell neuroblasts in the VZ, reminiscent of the nodules observed in human patients. Preliminary data from our laboratory obtained after *in utero* knockdown of FilaminA expression strongly support the notion that periventricular nodules could involve a disruption of the germinative field including radial glial cells, so that FilaminA would impact neuronal migration rather indirectly (A. Carabalona, S. Beguin, E. Pallesi-Pocachard, E Buhler, C. Pellegrino, P. Hubert, M. Oualha, J.P. Siffroi, S. Khantane, I. Coupry, C. Goizet, A. Bernabe Gelot, A. Represa & C. Cardoso, unpublished data).

Finally, more recently identified actors are the gap junction subunits connexin26 and 43. Both are expressed during corticogenesis (Nadarajah *et al.*, 1997; Cina *et al.*, 2007), and are found enriched at the contact points between migrating neurons and radial glial cells (Elias *et al.*, 2007). RNAi-mediated knockdown of connexin26 or 43 in migrating pyramidal neurons after *in utero* electroporation causes improper neuronal migration, and rescue experiments further revealed that the migration phenotype is prevented when connexin mutants that make connexions, but not channels, are coexpressed (Elias *et al.*, 2007). These results suggest that adhesion between migrating cortical neurons and radial glia via gap junction hemichannels, but not the presence of a pore channel, is necessary for migration. Similar observations were made in constitutive (Fushiki *et al.*, 2003) and conditional (Cina *et al.*, 2009) connexin43 knockout mice.

Adhesion with substrate

If migrating pyramidal neurons are extremely dependent on interactions with radial glial fibres along their way toward their fated layer, they have to detach from their migratory guide when the final destination is reached. Dulabon *et al.* (2000) proposed that this gliophilic to neurophilic adhesion switch involves the extracellular matrix protein Reelin (see below) through a direct interaction with $\alpha_3\beta_1$ integrins leading to their internalization. Consistent with this view, radial migration of wild-type cortical neurons in an *in vitro* assay is inhibited when exposed to Reelin, whereas migration of $\alpha_3\beta_1$-deficient neurons is unaffected (Dulabon *et al.*, 2000). Interestingly, Dab1, an essential intracellular component of the Reelin signalling pathway, was also found to interact with β1 integrin in a Reelin-dependent manner (Schmid *et al.*, 2005).

Tangentially migrating interneurons have to navigate onto various substrates and interact with other cell types before they reach their final destination. Along their migratory routes, some migrating interneurons appear to be associated with corticofugal axons (Métin *et al.*, 2000; Denaxa *et al.*, 2001), which suggests these fibres may serve as a migratory substrate. TAG-1, a neural adhesion molecule of the Ig superfamily, is expressed by corticofugal axons, and blocking TAG-1 with antibodies in cultivated brain slices impairs interneuronal migration (Denaxa *et al.*, 2001). However, interneuronal migration and interneurons final distribution were both found unaffected in *TAG-1*-deficient mice (Denaxa *et al.*, 2005), which suggests that adhesion through TAG-1 is dispensable for migrating interneurons.

Several groups have suggested that radial glia is important for migrating interneurons (Polleux *et al.*, 2002; Poluch & Juliano, 2007; Yokota *et al.*, 2007), by observing the behaviour of migrating interneurons in contact to radial glia or after radial glia ablation. Elias *et al.* (2010) recently reported the presence of gap junctions between radial glial cells and migrating interneurons, and observed that RNAi-mediated connexin43 knockdown in migrating interneurons electroporated on cultivated slices does not inhibit their tangential migration, but strongly affects their tangential to radial orientation switch. This suggests that interactions between interneurons and radial glia via gap junctions are crucial and may contribute to the proper distribution of interneurons within cortical layers.

Lastly, a recent study from Stanco *et al.* (2009) revealed that interactions between netrin-1 and $\alpha_3\beta_1$ integrin control interneuronal navigation throughout the developing cortex, and are required for the interneurons appropriate positioning in the cerebral cortex.

Modulatory signals: guidance cues, go and stop/detachment signals

Go signals and motogenic factors

The initiation of cortical neuron migration is modulated mainly by trophic factors [brain-derived neurotrophic factor (BDNF), neurotrophin (NT)4, epidermal growth factor (EGF) and transforming growth factor (TGF)α] and neurotransmitters (GABA and glutamate), which acting as chemoatractants will stimulate the neuronal motility.

BDNF and NT4, acting on TrkB receptors, were the first factors shown to be important in stimulating migration, thanks to a simplified experiment using dissociated cortical pyramidal neuroblasts in multi-well microchemotaxis assay (Behar *et al.*, 1997). Years later Polleux *et al.* (2002) demonstrated that migrating interneurons on organotypic explants were also stimulated to migrate by these neurotrophins, and that the effects were linked to the activation of TrkB receptors, as the stimulation of migration was attenuated by the Trk-family inhibitor K252a and the number of tangentially migrating calbindin-positive neurons was significantly decreased in the cortex of TrkB-null mice.

The role of EGF and/or TGFα, well known mitogenic factors for neural precursors, on cortical neuronal migration was first suggested by Threadgill *et al.* (1995). Their phenotype analysis of animals defective for EGF receptors depicted a clear impact on cell survival and cortical anomalies, suggestive that cellular migration may have been slowed or blocked (Threadgill *et al.*, 1995). Caric *et al.* (2001) demonstrated then that migrating neuroblasts in the rostral migratory stream (RMS), the lateral cortical stream and the radial pathway might express high levels of EGF receptors while the targets of these pathways express the ligands HB-EGF and/or TGFα. These authors challenged the notion that EGF receptors (EGFRs) mediate chemotactic migration by increasing the size of the population of cells expressing threshold levels of EGFRs *in vivo* by viral transduction.

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Their results suggest that EGFRs triggered the migration of neurons in any investigated field, with the exception of the RMS.

The effects described here showing that molecules with complex pleiotrophic activities regulate neuronal migration increase the possibility that many other similar factors would also contribute to promote neuronal migration, thus opening the way for investigations of new candidates as, for example, hepatocyte growth factor/scatter factor, which has been found to be motogenic for GABA interneurons in cortical explants (Powell *et al.*, 2001).

Neurotransmitters GABA and glutamate are important chemoattractants for migrating neuroblasts, as explored by Behar *et al.* (1998, 1999, 2001). These authors evaluated in dissociated cells and cortical explants the impact of these transmitters by testing the impact of receptor antagonists, and thus illustrated that radial migration was triggered by *N*-methyl-D-aspartate (NMDA) and $GABA_B$ receptors. The role of these transmitters is described in more detail below.

Guidance cues and stop/detachment signals

Large amounts of proteins have been identified as regulators of both radial and tangential migrations. Among them, secreted molecules from Slits, Netrins and Semaphorins families are known to modulate both cell types migration; however, their roles are more clearly defined for migrating interneurons (see below). One extremely well characterized actor involved in the modulation of radial migration is the extracellular matrix protein Reelin, a large glycoprotein mainly secreted by Cajal-Retzius cells located in the cortical marginal zone. Reelin binds to two lipoprotein receptors, ApoER2 and VLDLR (D'Arcangelo *et al.*, 1999; Hiesberger *et al.*, 1999), and this binding leads to phosphorylation of its intracellular adapter Dab1 by Src-family tyrosine kinases SFKs (Howell *et al.*, 1997). Dab1 phosphorylation subsequently leads to the activation of multiple downstream targets instructing neurons to settle down into appropriate layers via mostly unknown mechanisms. Cortical lamination defects found in *reeler* mice lacking Reelin expression are very similar to those observed in *ApoER2* and *VLDLR* double mutants (Trommsdorff *et al.*, 1999), as well as those seen in *scrambler* and *yotari* mice, carrying mutations in Dab1 (Sheldon *et al.*, 1997). Recent observations revealed that the Reelin signalling pathway ability to modulate radial migration appears to rely on the actin cytoskeleton stabilization after Reelin-induced n-cofilin phosphorylation mediated by Dab1, SFK and PI3K (Chai *et al.*, 2009). Accordingly, phosphorylated cofilin was found expressed on the leading processes of migrating neurons reaching the marginal zone (Chai *et al.*, 2009). However, how Reelin provides positional information to migrating pyramidal neurons is still mostly unclear. Many other mechanisms that involve interactions with adhesion molecules such as integrins (Dulabon *et al.*, 2000; see above), ephrins (Sentürk *et al.*, 2011), among others, may also be important. Interestingly, the laminar distribution of interneurons and their morphology was found affected in the *reeler* forebrain (Yabut *et al.*, 2007), suggesting the Reeling signalling pathway to be important for interneurons as well.

Many guidance cues controlling interneuronal migration have been identified, mediating either attractive or repulsive signals. Among those, Neuregulin1 (Nrg1) and its receptor ErB4, in addition to their roles during radial migration (as described above), are also involved in interneuronal migration. Complementary expression of the two Nrg1 isoforms Nrg1-CRD and Nrg1-Ig, as well as their receptor ErB4, is observed in the developing telencephalon during the interneuronal migration period (Flames *et al.*, 2004). Nrg1 is a chemoattractant for migrating interneurons *in vitro*, and its ectopic expression on brain slices redirects interneuronal migration toward the source of Nrg1 (Flames *et al.*, 2004; Martini *et al.*, 2009). Moreover, loss-of-function experiments with a dominant-negative form of Nrg1 (Flames *et al.*, 2004), combined with the analysis of *Nrg1* (Flames *et al.*, 2004) and *ErB4* (Neddens & Buonanno, 2010) mutant mice revealed impaired interneuronal migration and altered interneuron distribution.

Repellent actions mediated by class 3 Semaphorins and their receptors were also found to be crucial for interneuronal migration. Complementary expression of Sema3A and 3F, as well as their receptors Neuropilin1 and 2, is observed in the developing telencephalon during the interneuronal migration period (Marın *et al.*, 2001). Grafting experiments and slice cultures revealed that migrating interneurons avoid entrance into the developing striatum expressing Sema3A and 3F, and ectopic expression of these molecules blocks interneuronal migration on cultivated explants (Marın *et al.*, 2001). Recently, members of the Eph/ephrin system were identified as additional repulsive signals preventing migrating interneurons to enter in the developing striatum (Rudolph *et al.*, 2010). Similarly, Robo1 receptor via Neuropilin1 was recently found to be involved in preventing interneurons to enter the striatum (Hernández-Miranda *et al.*, 2011).

Lastly, another important class of molecules involved in regulating interneuronal migration is the chemokines. The CXC chemokine receptor 4 (CXCR4), a receptor for stromal cell-derived factor-1 (SDF-1/CXCL12), was found to be expressed by migrating interneurons (Stumm *et al.*, 2003). Analysis of late-generated interneurons distribution in *CXCR4* and *SDF-1*-deficient mice revealed alterations suggesting a regulatory role for SDF-1/CXCR4 on interneuronal migration (Stumm *et al.*, 2003). SDF-1 expression was initially described as restricted to meningeal cells in the marginal zone (Stumm *et al.*, 2003), but a more careful analysis revealed that SDF-1 is also expressed by upper-layer fated migrating pyramidal neurons in SVZ/IZ (Tissir *et al.*, 2004; Tiveron *et al.*, 2006). Analysis of interneurons migratory routes in *CXCR4*-deficient mice revealed a reduced preference for the major routes in the SVZ/IZ and MZ described in wild-type animals and, importantly, revealed a premature invasion of the cortical plate by migrating interneurons (Tiveron *et al.*, 2006; Li *et al.*, 2008b; Lopez-Bendito *et al.*, 2008).

Neurotransmitters

As mentioned before, neuronal migration develops under intrinsic and cell population-dependent constraints. Among the later, neurotransmitters have been largely investigated and documented. It was thus proposed that transmitters, by impacting neuronal proliferation and migration control final positioning, timing and numbers of neurons reaching the appropriate target fields (Manent & Represa, 2007). In this section we will review these data and provide new evidence for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors modulation of GABAergic neurons migration.

GABA and glutamate acting mainly on $GABA_A$ and NMDA receptors have been shown to modulate the migration of different neuronal subtypes, including, among others, cerebellar granule cells (Komuro & Rakic, 1993, 1998), olfactory bulb neurons migrating in the RMS (reviewed in Platel *et al.*, 2010), cortical and hippocampal pyramidal cell neuroblasts and interneurons (reviewed in Manent & Represa, 2007). Interestingly, the regulation of migration by neurotransmitters and receptors depends on the type of migration (radial, tangential or chain migration), the type of cells (principal glutamatergic neurons, cortical GABAergic interneurons, olfactory granule cells) and the brain area (neocortex, cerebellum, RMS). For example, pyramidal neurons migration is modulated by GABA and glutamate acting on NMDA receptors but not AMPA (Manent *et al.*, 2005), while the migration of interneurons appears to be mediated by AMPA but not NMDA receptors (Manent *et al.*, 2006).

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The case of cortical/hippocampal interneurons

Different data support the notion that AMPA receptors modulate interneuronal migration. Thus, AMPA receptor activation affects the length of their processes (Poluch *et al.*, 2001; Fig. 2) as well as their GABA content (Poluch & König, 2002). Using cortico-hippocampal explants from GAD67–EGFP knock-in embryos, we previously reported that AMPA receptor blockade prevents the migration of GAD67–EGFP interneurons, which fail to populate the hippocampal primordium (Manent *et al.*, 2006). Time-lapse experiments confirmed this observation. In these experiments acute slices (400 μm thick) were analysed using a Zeiss LSM 510 laser-scanning microscope. Slices were perfused with an artificial cerebrospinal fluid solution as described before (Manent *et al.*, 2006). Under application of AMPA receptor antagonist NBQX (10 μM; Tocris Bioscience, Bristol, UK), a dramatic reduction in the number of GAD67–EGFP cell bodies moving during the 30-min recording period was observed; this was associated with a clear reduction on the mean distance travelled by the cells still motile. A careful analysis of the body of affected neurons indicates that opposite to cells in the control condition, the cells exposed to this AMPA receptor antagonist failed to accomplish the nuclear translocation and displayed only a movement of soma balance and deformation (Fig. 2A). Treatment with this receptor antagonist did not affect in contrast the motility of the leading process, as the number or distance travelled remained similar to that recorded before treatment (Fig. 2C and D). These effects were also reproduced by the application of the calcium-permeable AMPA receptor antagonist IEM1460 (50 μM; kindly provided by Magazanik *et al.*, 1997), chosen because receptors expressed by migrating GABA neurons are lacking GluR2 subunit and are therefore permeable to calcium (Métin *et al.*, 2000). In conclusion, it can be proposed that glutamate acting through AMPA receptors modulates nuclear translocation without affecting the motility of the leading process. The actions of glutamate on migrating interneurons are apparently independent of NMDA receptors, as these neurons do not express functional NMDA receptors (Métin *et al.*, 2000) and the treatment of GAD67–EGFP cortical sections with NMDA receptor antagonists failed to modify motility and migration of interneurons.

It has been well illustrated that migrating cortical interneurons express functional $GABA_A$ (Métin *et al.*, 2000; Soria & Valdeolmillos, 2002) and $GABA_B$ (Lopez-Bendito *et al.*, 2003) receptors. A blockade of $GABA_B$ receptors results in an accumulation of tangentially migrating interneurons in the VZ/SVZ of cortical explants, but the mechanisms of this action are presently not known (Lopez-Bendito *et al.*, 2003). In our experimental paradigm the blockade of $GABA_A$ receptors did not produce any significant effect on interneuronal migration. However, it was recently reported that GABA will induce interneuron migration arrest when migrating neurons increase their expression of the potassium/chloride co-transporter KCC2 (Bortone & Polleux, 2009). It is well established that KCC2 lowers the intracellular chloride and thereby renders GABAergic transmission hyperpolarizing. It was thus proposed that a shift in the type of actions of GABA from depolarizing to hyperpolarizing would explain these results. Interestingly, a recent report by Miyoshi & Fishell (2011) indicates that interneurons generated in the medial and caudal

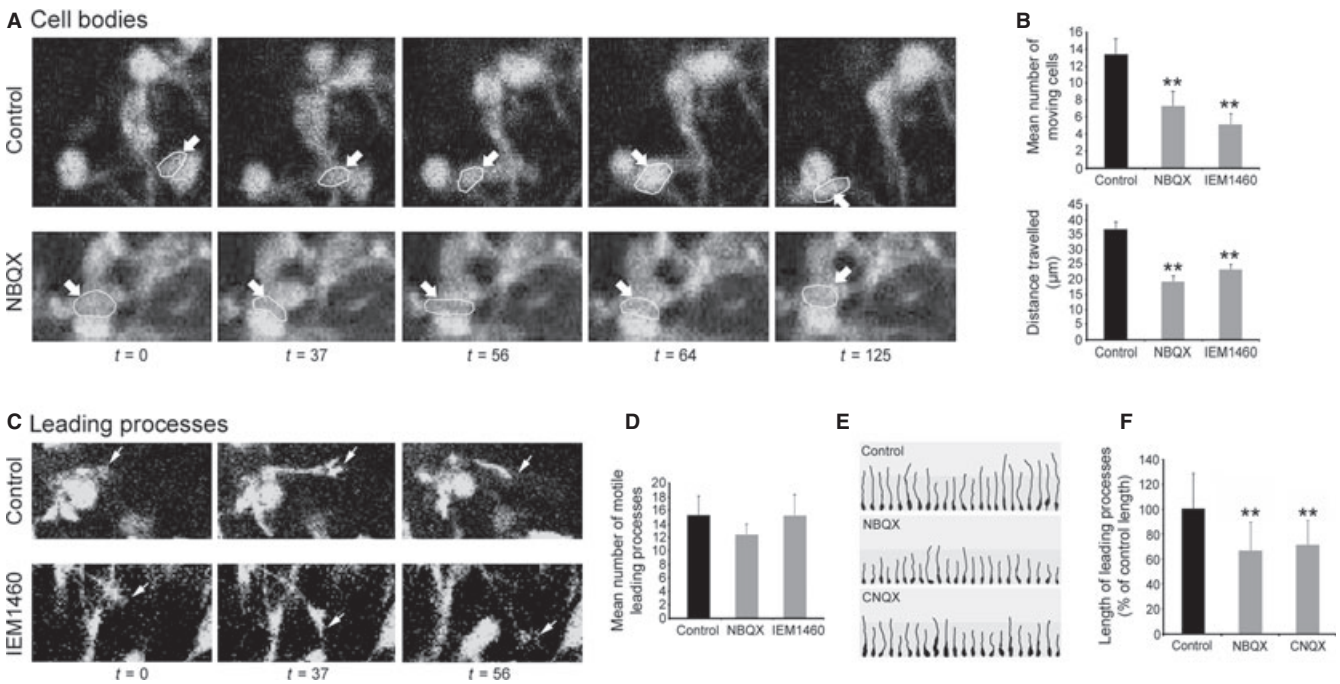

FIG. 2. AMPA receptors modulate interneuron's motility. (A and B) Effect of NBQX (10 μM) on interneuron's cell body motility. (A) Time-lapse imaging on brain sections from knock-in embryos GAD67-EGFP (E15–E17) with a biphoton microscope (Zeiss LSM). For analysis, investigations were performed in 400-μm-thick coronal sections of parietal cortex, along the deep migratory stream. Recordings of the speed of interneuron's cell body (white arrow) in both control and NBQX conditions over 1250 s (T). (B) Decreased number of both cell body moving and distance travelled by them in the focal field in the presence of AMPA receptor antagonists (10 μM NBQX or 50 μM IEM1460). Experiments were repeated five–seven times, and a total of 14 slices were analysed. (C and D) Effects of 50 μM IEM1460 on interneuron leading processes motility. (C) Experimental conditions similar to that shown in (A); white arrows point motile leading process under both control and drug conditions over 1250 s. (D) The number of motile leading processes, as well as the mean distance travelled (not shown), in the presence of AMPA receptor antagonists was not modified compared with control (n = 14 slices). (E and F) Effects of NBQX on the length of leading processes. (E) Migrating cortical interneurons were measured in fixed sections with IMAGEJ software under control or drug conditions. For quantitative analysis we only considered cells displaying unbranched leading processes; in this figure only a few representative cells were shown for comparison. (F) Histograms illustrating the impact of AMPA receptor antagonists on the mean length of leading process of migrating interneurons in the presence of NBQX (10 μM) or CNQX and compared with control conditions. For comparisons, SIGMA STAT software was used; after evaluation of the 'normal' distribution of data, Wilcoxon-test was used (**$P < 0.001$).

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ganglionic eminences by E12.2 initiate the radial sorting from their tangential pathway at the time when KCC2 is upregulated. These data together indicate that GABA/KCC2 modulates later migration steps of interneurons, when they settled into the appropriate cortical layer.

KCC2 has also been shown to impact neuronal maturation independently of its role as a co-transporter, likely through a cytoskeleton interaction (Li *et al.*, 2007; Horn *et al.*, 2010). It was thus shown a reduced migration of a neural cell line over-expressing after transfection of either transport-active or transport-inactive KCC2, indicating an ion transport-independent effect on migration (Li *et al.*, 2007). In line with these data, a premature expression of transport-inactive KCC2 displayed a perturbed neural crest migration in transgenic embryos (Li *et al.*, 2007). Therefore, it is plausible that the effects of KCC2 on interneuron migration described by Bortone & Polleux (2009) would also be related to some extent to a cytoskeleton alteration. However, these authors demonstrated that the transport properties of KCC2 are required for its effect on inducing responsiveness to GABA as a stop signal in migrating interneurons.

Intracellular chloride homeostasis is also dependent on the action of Na-K-2Cl co-transporter NKCC1, which intrudes [Cl^-] contributing to regulate the resting membrane potential and the depolarizing actions of GABA (Ben-Ari *et al.*, 2007; Blaesse *et al.*, 2009). An interesting recent report by Mejia-Gervacio *et al.* (2011) indicated that NKCC1 is highly expressed in migrating GABAergic neuroblasts in the RMS, but decreases at the time these neurons reach the olfactory bulb. Though NKCC1 activity was apparently necessary for maintaining normal migratory speed, the effect was independent of $GABA_A$ signalling. In fact, $GABA_A$ receptor antagonists induced, as expected for these cell types (Platel *et al.*, 2010), an increase of the average migration speed in control conditions, and the effect was maintained in the presence of NKCC1 blocker Bumetanide or after knockdown of the transporter after transfection with shNKCC1. These observations reinforce the notion that ion co-transporters impact neuron development though multiple functions, in this case olfactory GABA neurons through an impact on resting membrane potential (Blaesse *et al.*, 2009). There are at present no proper investigations on the action of NKCC1 on the migration of other neuronal populations.

Finally, though most efforts were devoted to GABA and glutamate, it has also been reported that dopamine and serotonin might be modulators of interneuron migration. Thus, analysis on slice preparations of embryonic mouse forebrain (Crandall *et al.*, 2007) revealed that dopamine D1 receptor activation promotes and D2 receptor activation decreases GABA neuron migration from the medial and caudal ganglionic eminences. Analysis of mouse knockout for D1 or D2 dopamine receptors confirmed these results: D1-knockout mice displayed a decreased number of cortical GABA neurons in E15 intermediate zone, while D2-knockout mice displayed a significant increase of GABA neurons in this field (Crandall *et al.*, 2007). These effects appear to be motogenic, though an effect on migration guidance is not excluded. Similarly to the effects induced by the activation of D1 receptors, time-lapse analysis of the migration of interneurons in embryonic mouse cortical slices revealed that the application of 5-HT decreased interneuron migration in a reversible and dose-dependent manner, and that this effect was due to the activation of 5-HT6 serotonin receptors (Riccio *et al.*, 2009).

Environmental factors

It is widely accepted that environment interacts with intrinsic genetically determined factors to modulate brain development, including neuronal migration. Gressens *et al*., in a quite complete review published in 2001, segregated these environmental factors into several classes, including recreational drugs, maternal diseases and maternal conditions. The mechanisms of actions of these factors are not all elucidated, and unfortunately there has not been that much progress on the topic over the last decade.

We described in the previous section that neurotransmitters are main players in neuronal migration, so that an altered activity of migrating neuroblasts can modify the process and lead to migration defects. Three main pathological conditions can be included in this section: foetal alcohol syndrome (FAS); cocaine and drug abuse; and anti-epileptic drugs (AEDs), as their adverse impact on brain development are linked to their actions on receptors for neurotransmitters.

FAS

Alcohol exposure during pregnancy remains one of the leading causes of non-genetic mental retardation, and is responsible for a syndrome characterized in addition with craniofacial and cardiovascular defects (Jones & Smith, 1973). FAS represents the severe end of the Foetal Alcohol Spectrum Disorders continuum, and is typified by the presence of several neuroanatomical malformations, including microencephaly, lissencephaly, heterotopias and loss of inter-hemispheric fibre tracks. Children with FAS experience ataxia, deficits in intellectual functioning, learning and memory deficits, and problem solving and attention impairments.

Experimental analysis in laboratory animals demonstrated that the more characteristic brain alterations were the defects in organization of the cortical layers, the presence of ectopic neurons and reduction of the thickness of the cortical wall. Ethanol consumption by pregnant rats causes many types of cortical malformations in embryos exposed, including leptomeningeal and periventricular heterotopia, indicating that ethanol alters neuronal migration (Komatsu *et al.*, 2001; Sakata-Haga *et al.*, 2002). Ethanol also disrupts cortical neurogenesis and gliogenesis in embryos exposed (Miller, 1986; Gressens *et al.*, 1992b; Miller & Robertson, 1993). Finally, administration of ethanol in the rodent newborn, what grossly corresponds to the third trimester of human gestation, causes significant neuronal death in the neocortex (Ikonomidou *et al.*, 2000; Olney *et al.*, 2002).

As described in many reports, both the severity and types of anatomical defects depend on the timing of ethanol exposure (Livy *et al.*, 2003). It was thus described that a particularly susceptible period for ethanol exposure is the third trimester (West *et al.*, 1986; Hamre & West, 1993), the period during which ethanol causes cell death (Cheema *et al.*, 2000; Mooney & Miller, 2003). *In vitro* analyses have shown that ethanol exposure during neurogenesis, grossly corresponding to the second trimester of gestational life, increases subsequent neuronal migration and neurite extension (Camarillo & Miranda, 2008). *In vivo* analysis confirmed that the disposition of tangentially migrating GABAergic neurons in the cortex was altered in mice embryos exposed to ethanol; ethanol apparently induces a premature tangential migration of interneurons into the cortical anlage. Interestingly this effect was associated with increased ambient levels of GABA and increased sensitivity to GABA of cells derived from the medial ganglionic eminences (Cuzon *et al.*, 2008), suggesting that migration perturbations were resulting from both cell intrinsic and cell population effects.

The presence of abnormal foetal brain was also dependent on the alcohol dosage: it was observed in 100% of mothers who had high consumption of ethanol during pregnancy (100–500 mL per day, four–seven times per week), in 80–90% of mothers who had moderate consumption (100–200 mL per day, one–four times per week), and in 30% of mothers who had occasional consumption of ethanol (35–100 mL, three times during pregnancy; Konavalov *et al.*, 1997).

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The deleterious effects of ethanol are related to its action on NMDA and GABA receptors. Indeed, ethanol plays a role of $GABA_A$ receptor agonist (Wafford *et al.*, 1991; Harris *et al.*, 1995) and NMDA receptor antagonist (Hoffman *et al.*, 1989). The administration of ethanol in 7-day-old rat pups days leads to significant neuronal death in the neocortex, induced by the combination of two mechanisms: excessive activation of GABA receptors; and inhibition of NMDA receptors. Indeed, administration of phenobarbital, which potentiates $GABA_A$ receptor activation, or the administration of MK801, a NMDA receptor antagonist, in rat pups cause a similar neuronal death, though of a lesser extent; the combination of the two drugs causes damage similar to that caused by ethanol alone (Ikonomidou *et al.*, 2000). Similar results were obtained in mice (Olney *et al.*, 2002). Ethanol consumption by pregnant rats causes many types of cortical malformations in embryos, suggesting migration defects (Komatsu *et al.*, 2001; Sakata-Haga *et al.*, 2002). Migratory defects associated with the administration of ethanol have also been reported by Miller (1986) and Miller & Robertson (1993). Altered migration of cerebellar granule cells was also induced by intraperitoneal administration of ethanol in raccoon (Kumada *et al.*, 2006). Finally, ethanol disrupts cortical neurogenesis and gliogenesis (Miller, 1986; Gressens *et al.*, 1992a,b; Miller & Robertson, 1993).

Cocaine

The question of the potential teratogenicity of cocaine has been raised after the increasing frequency of its abuse in the USA, where the National Institute of Drug Abuse (NIDA) estimates that 1.1% of pregnant women consume cocaine. Different reports concluded that exposure to cocaine during pregnancy results in increased spontaneous abortion, placental abruption, prematurity, intrauterine growth retardation and neurological deficits. Consequently, research has been investigating cocaine impact on foetal development in laboratory animals, while longitudinal studies of cocaine-exposed babies have been developed in order to determine how prenatal exposure would influence their development from birth through adolescence.

Exposure of the foetal brain to cocaine disrupted the cytoarchitecture of the cerebral cortex in primates, rodents and lagomorphs (Gressens *et al.*, 1992a; Jones *et al.*, 2000; Lidow & Song, 2001a,b). Cocaine decreases neurogenesis (Lidow & Song, 2001a) associated with a reduction in the cortical neuronal density and cortical volume (Lidow & Song, 2001b) and altered layering (Lidow *et al.*, 2001). Furthermore, Crandall *et al.* (2004) have reported that recurrent, transplacental exposure of mouse embryos to cocaine from embryonic day 8–15 (the treatment was thus covering the period of genesis of most GABAergic neurons) alters tangential neuronal migration resulting in deficits in GABAergic neuronal populations in the embryonic cerebral wall. Interestingly, this treatment seems to be specific for neocortical neurons, as olfactory GABA cells were not affected. In contradiction with these data, Wang *et al.* (1995) previously reported that cocaine exposure resulted in an increased number of GABAergic neurons in the anterior cingulate cortex of rabbits exposed *in utero* to cocaine. However, the distribution of parvalbumin-immunoreactive cells has been demonstrated to be altered (Wang *et al.*, 1996), which is still compatible with an altered terminal migration of these cells.

The mechanisms of cocaine action are likely to be related to an impact on monoamine extracellular levels in the foetus (Akbari *et al.*, 1992; Clarke *et al.*, 1996; Jones *et al.*, 2000). Thus, it has been suggested that monoamines can influence neurogenesis and neuronal and glial cell differentiation (Reinoso *et al.*, 1996; Vitalis *et al.*, 1998; Ohtani *et al.*, 2003).

Brain alterations in humans are most likely due to similar perturbations of neuronal proliferation and migration, which remains to be determined. Interestingly, histological analysis of a case where cocaine abuse during pregnancy was assessed by drug analysis revealed a thin cortex containing many apoptotic cells, with altered architecture due to anomalies in vascular penetration associated with anomalies in neuronal migration, cortical histogenesis and cerebral microcirculation development (Kesrouani *et al.*, 2001). Also, cell culture analysis of highly enriched human foetal brain-derived neural precursor cells indicates that cocaine treatment impacts the proliferation, migration and differentiation of these cells (Hu *et al.*, 2006).

What are the consequences if brain construction is altered upon cocaine exposure? Longitudinal studies of exposed offspring have confirmed that some children with prenatal cocaine exposure have problems with aspects of motor skills, IQ, fussiness and attention span (http://archives.drugabuse.gov/NIDA_Notes/NNVol14N3/Prenatal.html). Executive function (i.e. the ability to gather and use information in pursuit of one's own aims) may also be compromised. In general, these findings are consistent with results from studies with laboratory animals. These studies, however, indicate that severe impact is restricted to some children tempering the initial concerns but still demonstrating the need for prevention campaigns. NIDA also stresses that relatively slight even undetected alterations can have potential negative consequences that are important over the long term, interfering with integration and success at the school of affected offspring or yielding societal concerns.

AEDs

AEDs belong to a large class of chemical compounds (Perucca, 2005) that: (i) facilitate the action of the inhibitory transmitter GABA by blocking degradation systems (vigabatrin) or capture (tiagabine) GABA, or potentiating the action of GABA on the $GABA_A$ receptor subtype (benzodiazepines, phenobarbital, topiramate); (ii) decrease the action of the neurotransmitter glutamate, in particular by inhibiting its release and its interaction with glutamate receptors (carbamazepine, felbamate, topiramate, valproate); and (iii) modulate neuronal activity by blocking sodium channels and voltage-gated calcium (carbamazepine, oxcarbazepine, ethosuximide, felbamate, lamotrigine, phenytoin, topiramate, valproate, zonisamide). Some compounds also have broader targets, modulating for example enzyme systems, hormones and trophic factors. For some AEDs, the mode of action is still incompletely understood (levetiracetam, gabapentin, valproate, zonisamide).

AEDs through their modes of action are likely to affect the construction of the foetal brain. Thus, the administration of AEDs in the newborn rat pup (covering a period equivalent in humans to the third gestational trimester) causes neuronal death by apoptosis, particularly after treatment with phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin and valproate (Bittigau *et al.*, 2002). Administration of high doses of valproate at the end of the first week of gestation in mice causes defects in neural tube closure in the embryo (Ehlers *et al.*, 1992), recalling the case of spina bifida encountered in humans (Bjerkedal *et al.*, 1982; Robert & Guibaud, 1982; Lindhout & Schmidt, 1986). Our team (Manent *et al.*, 2007, 2008) studied the effects of several AEDs (carbamazepine, diazepam, lamotrigine, levetiracetam, phenobarbital, topiramate, valproate, vigabatrin) administered intraperitoneally in the last week of gestation in the rat, thus covering the period of genesis/migration of cortical and hippocampal neurons. By administering AEDs at doses comparable to those used clinically, we observed an increased incidence of cortical and

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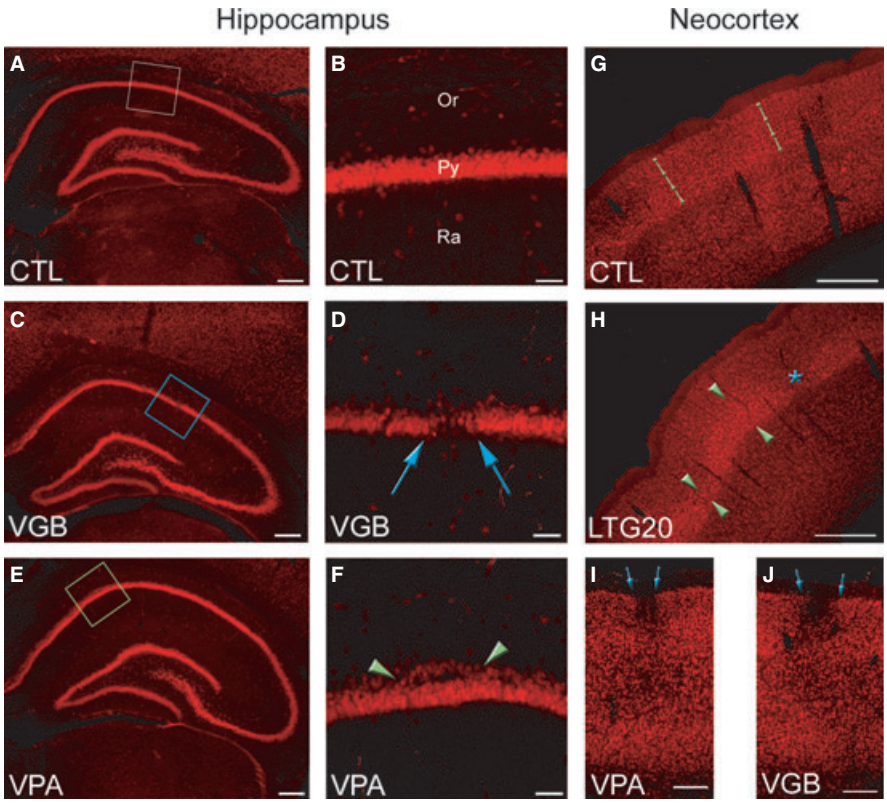

FIG. 3. AEDs generate hippocampal and cortical dysplasias. Hippocampal (C–F) and cortical (H–J) malformations induced by foetal exposure to vigabatrin (VGB), valproate (VPA) and lamotrigine (LTG) compared with controls (A, B and G). Coronal brain sections were stained with the neuronal marker NeuN for evaluating cortical and hippocampal cytoarchitectonic alterations. Examples of interruptions of lamination (blue arrows) in the hippocampus (C and D) or cortex (I and J, and asterisk in H). Examples of dispersions (green arrows) of neuronal layers resulting in the formation of a supernumerary pyramidal layer in the hippocampus (E and F) and variations in thickness of cortical layers (H). Scale bar: 200 μm. For interpretation of color references in figure legend, please refer to the Web version of this article.

hippocampal dysplasia, suggesting defects in neuronal migration in pups born to treated females. These developmental anomalies (Fig. 3) were observed after treatment with valproate (100 mg/kg/day), vigabatrin (200 mg/kg/day) and lamotrigine (5–20 mg/kg/day). They include: (i) the presence of areas of neuronal depletion, causing disruptions of hippocampal or cortical lamination; and (ii) changes in compaction of cortical layers (neuronal dispersion areas, associated with the presence of ectopic neurons). In the hippocampus, the dispersion may lead to the presence of a supernumerary pyramidal layer (Fig. 3). Neuronal death by apoptosis, albeit limited, was also observed, but neuronal proliferation was not affected by AEDs treatments.

It is interesting to note that the effects of lamotrigine are dependent on the dose administered and are also associated with maternal–foetal toxicity, shown by a weight loss in females during treatment and a reduction in the number of newborn rats. Maternal–foetal toxicity was also observed after treatment with vigabatrin and carbamazepine.

The observation of the adverse impact of vigabatrin and valproate to induce cortico-hippocampal dysplasia in animals exposed *in utero*, in contrast to carbamazepine, at least at the doses studied, supports the notion that disruption of GABA levels is more deleterious than blocking voltage-dependent sodium channels. Molecules that target these channels would therefore be more suitable in the treatment of epilepsy during pregnancy. These results are consistent with the role played by GABA during the early stages of development, as well as the immature sodium channels in migrating neurons (Manent *et al.*, 2005).

Taken together the findings summarized here clearly reveal the need for in-depth studies evaluating the impact of AEDs, and eventually other related drugs, on brain maturation. Experimental approaches in laboratory animals are in that sense a powerful tool for identifying these risks.

Launched in Europe in 1999 by a consortium of independent research groups and later extended to several other nations worldwide, EURAP consortium (http://www.eurapinternational.org/) has been created to collect data on the risk of AEDs during pregnancy and share it in an international registry. EURAP is involving physicians from 40 countries in Europe, Australia, Asia and South America, and have recorded more than 16 100 pregnancies. The differences in use of individual AEDs across countries probably reflect, among other factors, the lack of evidence concerning the optimal treatment of epilepsy in women of childbearing age. This register has not yet reached clear conclusions, but their 2006 report indicates that among the pregnancies followed, 6% of them had major congenital malformations, including 22 cases of defects in neural tube closure and seven cases of abnormal CNS. Note that subtle alterations are likely to be under evaluated, and cognitive outcomes of offspring are not necessarily investigated.

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Abbreviations

AED, anti-epileptic drugs; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; BDNF, brain-derived neurotrophic factor; CP, cortical plate; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; FAS, foetal alcohol syndrome; GABA, γ-aminobutyric acid; GFP, green fluorescent protein; IZ, intermediate zone; MZ, marginal zone; NMDA, *N*-methyl-D-aspartate; NT4, neurotrophin 4; RMS, rostral migratory stream; SDF-1, stromal cell-derived factor-1; SVZ, subventricular zone; TGF, transforming growth factor; VZ, ventricular zone.

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