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Review

Integration of GABAergic Interneurons into Cortical Cell Assemblies: Lessons from Embryos and Adults

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In the forebrain, cortical structures consist of networks of excitatory and inhibitory neurons born in distant locations. Understanding how these two major classes of neurons integrate into unique functional cell assemblies may shed light on the organization of cortical circuits. In this review, we provide an overview of the mechanisms used by GABAergic interneurons to reach their final position, with an emphasis on the final steps of this process. To this end, we analyze similarities and differences between the integration of GABAergic interneurons in the developing cerebral cortex and in the postnatal brain, using the neocortex and the olfactory bulb as model systems.

Introduction

From a reductionistic perspective, many brain circuits have evolved as hierarchical networks of excitatory glutamatergic neurons and γ-aminobutyric acid-containing (GABAergic) interneurons. In the telencephalon, for example, cortical structures consist of excitatory and inhibitory neuronal assemblies independent of their complexity and function. Accordingly, functional circuits in regions as disparate as the olfactory bulb, hippocampus, and neocortex rely on relatively similar cell assemblies of glutamatergic neurons and GABAergic interneurons. Glutamatergic neurons are the main excitatory units in these networks, typically linked through multiple recurrent connections that are critical for computational performance (Binzegger et al., 2004; Somogyi et al., 1998). GABAergic interneurons, on the other hand, comprise a highly heterogeneous group of neurons that maintain the stability of cortical networks through synaptic inhibition. In addition, interneurons modulate network activity by shaping the spatiotemporal dynamics of different forms of synchronized oscillations (Klausberger and Somogyi, 2008).

The organization of neuronal assemblies in the cortex seems to obey certain rules that guarantee a critical balance between excitation and inhibition while maximizing their computational ability. In the cerebral cortex, for example, the ratio between excitatory and inhibitory neurons is relatively constant across regions and species (Fishell and Rudy, 2011; Hendry et al., 1987; Sahara et al., 2012). In the adult olfactory bulb, where interneurons are continuously added throughout life, the proportion of newborn neurons that integrates into the mature network is tightly regulated (Kohwi et al., 2007; Winner et al., 2002). In addition, GABAergic interneurons in the cerebral cortex and olfactory bulb come in a rich variety of classes, each having highly stereotypical laminar arrangements, unique patterns of connectivity, and functions (Fishell and Rudy, 2011; Klausberger and Somogyi, 2008; Lledo et al., 2008). This enormous variety of interneuron classes provides cortical circuits with the required flexibility to carry out complex computational operations during information processing.

Considering the highly stereotypical organization of cortical networks, the most striking aspect of their assembly is that their cellular ingredients are born in separate locations. While glutamatergic neurons of the olfactory bulb and the cerebral cortex are generated locally by progenitor cells in the developing pallium (Molyneaux et al., 2007; Rakic, 2007), GABAergic interneurons populating these structures derive from the subpallium, the base of the telencephalon (Batista-Brito and Fishell, 2009; Gelman and Marín, 2010; Wonders and Anderson, 2006). Consequently, glutamatergic neurons and GABAergic interneurons follow very different strategies to reach their final destination. Glutamatergic neurons migrate radially to form the different layers of cortical structures (Rakic, 2006). In contrast, interneurons first migrate tangentially from their birthplace to the cerebral cortex and olfactory bulb and subsequently switch their mode of migration to radial to adopt their final position in these structures (Marín and Rubenstein, 2001). How these apparently disconnected processes synchronize during development is arguably one of the most fascinating questions on the assembly of neuronal circuits in the mammalian brain.

The purpose of this review is to summarize our current understanding of the mechanisms controlling the coordinated integration of glutamatergic neurons and GABAergic interneurons into cortical networks. The emphasis is on those aspects related to the final settlement of GABAergic interneurons in the cerebral cortex and olfactory bulb, and not so much on the mechanisms controlling their tangential migration to their target structures (reviewed in Belvindrah et al., 2009; Marín, 2013). The developing neocortex is used here as a model for the coordinated integration of glutamatergic neurons and GABAergic interneurons into nascent cortical circuits, while the adult olfactory bulb illustrates the ability of newborn GABAergic interneurons to integrate into fully mature networks.

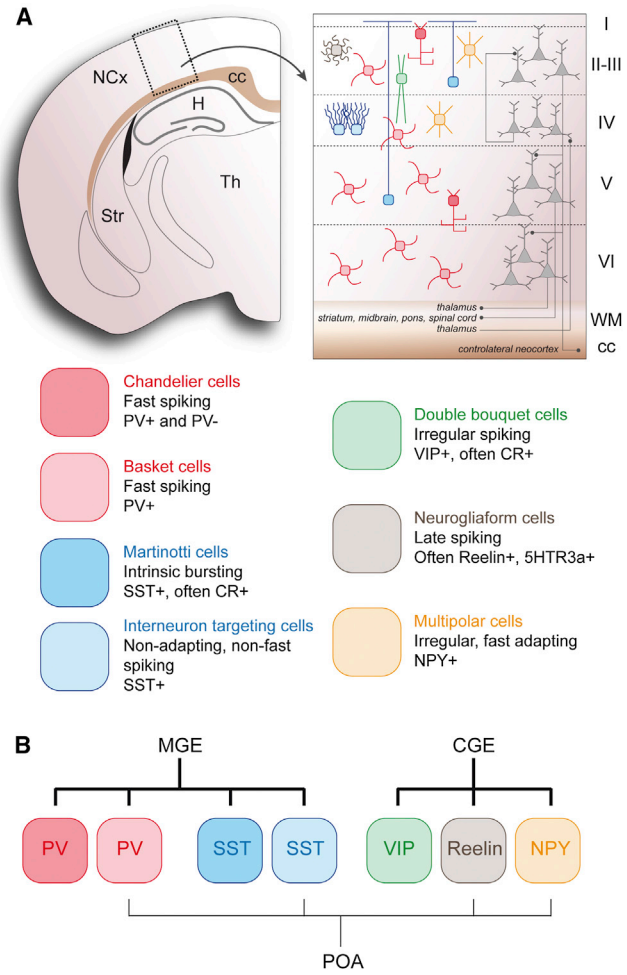

Figure 1. Major Classes of Neocortical Interneurons and Their Developmental Origins

(A) Schematic of a coronal section through the mouse cerebral cortex showing the main classes of GABAergic interneurons and their respective laminar allocation. Fast-spiking PV^+ basket cells are distributed throughout all cortical layers except for layer I. Chandelier cells localize primarily to the border between layers I and II/III, and in layer V. SST^+ Martinotti cells are mainly found in layers II/III and V and extend their axon toward layer I. Non-fast-spiking, nonadapting SST^+ interneurons are restricted to layer IV. Rapidly adapting VIP^+ interneurons and late-spiking neurogliaform cells are particularly abundant in layer II/III. Finally, multipolar cells that often contain NPY are found through layers II/III and IV. The laminar organization of pyramidal cells is also schematically represented.

(B) Grouping of the main classes of cortical interneurons according to their developmental origins. cc, corpus callosum; HC, hippocampus; NCx, neocortex; Str, striatum; Th, thalamus; WM, white matter; MGE, medial ganglionic eminence; CGE, caudal ganglionic eminence; POA, preoptic area; I–VI, cortical layers I to VI; 5HTR3a, ionotropic serotonin receptor 3a.

Integration of GABAergic Interneurons in the Developing Cortex

Glutamatergic pyramidal cells and inhibitory GABAergic interneurons constitute the main cellular elements of each of the individual modules or microcircuits of the cerebral cortex. Pyramidal cells represent about 80% of the neurons in the cortex and specialize in transmitting information between different cortical areas and to other regions of the brain. GABAergic interneurons, on the other hand, control and orchestrate the activity of pyramidal cells.

Pyramidal cells are a highly heterogeneous group of neurons with different morphological, neurochemical, and electrophysiological features. A basic classification of pyramidal cells is based on their connectivity, which is roughly linked to their laminar location in the cortex (Jones, 1984) (Figure 1). Subcortical projection pyramidal cells are the main neurons in layers V and VI. They target the thalamus (layer VI) and other telencephalic and subcerebral regions, such as the striatum, midbrain, pons, and spinal cord (layer V pyramidal cells). Pyramidal cells in layer IV, the granular layer, are associative neurons that project to pyramidal cells in layers II/III. Finally, callosal projection pyramidal cells project to the contralateral cortex and are particularly abundant in layers II/III. Some of these pyramidal cells are also present in layers V and VI. Layer II/III pyramidal cells also project abundantly to infragranular pyramidal cells.

More than 20 different classes of interneurons have been identified in the hippocampus and neocortex, each of them with distinctive spatial and temporal capabilities to influence cortical circuits (Fishell and Rudy, 2011; Klausberger and Somogyi, 2008). The classification of interneurons is a remarkably complicated task because their unequivocal identification requires a combination of morphological, neurochemical, and electrophysiological properties (Ascoli et al., 2008; DeFelipe et al., 2013). For the purpose of this review, neocortical interneurons can be broadly classified into five categories (Figure 1). The most abundant group consists of interneurons with the electrophysiological signature of fast-spiking neurons. It includes two main classes of interneurons: basket cells and chandelier cells (Markram et al., 2004). Most fast-spiking interneurons express the calcium binding protein parvalbumin (PV), although many chandelier cells do not (Taniguchi et al., 2013). A second group of interneurons is characterized by the expression of the neuropeptide somatostatin (SST). It includes interneurons with intrinsic-burst-spiking or adapting nonfast-spiking electrophysiological profiles and includes at least two different classes of interneurons. Martinotti cells, with a characteristic axon extending into layer I, are the most abundant SST^+ interneurons (Ma et al., 2006; Xu et al., 2013). In addition, a second class of SST^+ interneurons with axons that branch abundantly near the cell soma has been identified (Ma et al., 2006; Xu et al., 2013). The third major group of neocortical interneurons includes rapidly adapting interneurons with bipolar or double-bouquet morphologies, which typically express the vasointestinal peptide (VIP) and may also contain the calcium binding protein calretinin (CR) (Rudy et al., 2011). Neurogliaform cells constitute a fourth large group of neocortical interneurons (Armstrong et al., 2012). They have a very characteristic morphology, with highly branched short dendrites and a defining dense local axonal plexus. Neurogliaform cells have a late-spiking firing pattern, and many express Reelin and the ionotropic serotonin receptor 3a. Finally, a fifth group of interneurons consists of multipolar cells with irregular or rapidly adapting electrophysiological properties that often contain neuropeptide Y (NPY) (Lee et al., 2010). As explained below, the different classes of interneurons distribute through the cerebral cortex following highly specific regional and laminar patterns. This remarkable degree of organization suggests that the functional

integration of interneurons into specific neuronal circuits is largely dependent on their precise positioning within the cortex.

Pyramidal cells and interneurons are organized along two main dimensions in the cerebral cortex. The first axis divides the cortex into a variable number of layers depending on the cortical area. Neurons within the same cortical layer share important features, including general patterns of connectivity (Dantzker and Callaway, 2000; Molyneaux et al., 2007). The second axis reflects the vertical organization of neuronal circuits within a column of cortical tissue. Neurons within a given column are stereotypically interconnected in the radial dimension, share extrinsic connectivity, and function as the basic units underlying cortical operations (Mountcastle, 1997). Thus, any given cortical area consists of a sequence of columns in which their main cellular constituents, pyramidal cells and interneurons, share a common laminar organization. From this perspective, the integration of GABAergic interneurons within the organized matrix of layers and columns that compose the cortex might be better understood as a sequence of events that first determine the specific rostrocaudal and mediolateral coordinates of interneurons in the tangential plane (i.e., regional distribution) and subsequently determine their precise layering within the radial axis (i.e., laminar distribution).

Regional Distribution of Cortical Interneurons

As local circuit neurons, interneurons could be potentially incorporated in any cortical region. The question is whether interneurons are specified to migrate to precise locations or they just colonize the cerebral cortex without being targeted to specific coordinates. In other words, is there a correlation between their site of origin within the subpallium and their distribution along the rostrocaudal and mediolateral dimensions of the cortex?

Multiple lines of evidence suggest that the different classes of cortical interneurons are born in specific regions of the subpallium (Gelman and Marín, 2010; Wonders and Anderson, 2006) (Figure 1). In brief, the embryonic subpallium has five major proliferative regions: the lateral, medial, and caudal ganglionic eminences (LGE, MGE, and CGE, respectively), the preoptic area (POA), and the septum. The large majority of PV^+ and SST^+ interneurons derive from the MGE (Butt et al., 2005; Flames et al., 2007; Fogarty et al., 2007; Inan et al., 2012; Taniguchi et al., 2013; Wichterle et al., 2001; Xu et al., 2004, 2008). In turn, the CGE gives rise to most of the remaining interneurons, including bipolar VIP^+ interneurons, most neurogliaform neurons, and NPY^+ multipolar interneurons (Butt et al., 2005; Miyoshi et al., 2010; Nery et al., 2002; Xu et al., 2004). Finally, the POA generates a small, but diverse, contingent of PV^+, SST^+, and NPY^+ interneurons (Gelman et al., 2009, 2011).

Although the vast majority of cortical interneurons originate in the embryonic subpallium and migrate as postmitotic cells toward the cortex, postnatal sources of cortical interneurons seem to exist. One of these has been identified in the dorsal white matter and comprises what seems to be an expanding pool of progenitor cells possibly derived from the LGE and/or CGE (Riccio et al., 2012; Wu et al., 2011). Interestingly, these interneurons appear to follow a unique specification program and differentiate later than interneurons born in the embryo. Interneurons from this source populate primarily the lower layers of the anterior cingulate cortex. In addition, the adult subventricular zone (SVZ), the main postnatal source of olfactory bulb interneurons, also seems to give rise to some interneurons that populate forebrain structures other than the olfactory bulb, including the neocortex, caudoputamen nucleus, and nucleus accumbens (Inta et al., 2008). Intriguingly, some of the SVZ-derived interneurons that populate the deep layers of the frontal cortex share some morphological and functional features with olfactory bulb interneurons. They are small, axonless neurons that establish dendrodendritic synapses and integrate into the network in an experience-dependent manner (Le Magueresse et al., 2011).

These studies suggest that specific classes of interneurons derive from distinct regions of the subpallium to later colonize multiple cortical structures. Fast-spiking interneurons are a clear example of this circumstance. Transplantation and genetic fate-mapping studies have shown that the MGE is the origin of fast-spiking interneurons found in the amygdala, striatum, piriform cortex, hippocampus, and neocortex (Marín et al., 2000; Pleasure et al., 2000; Tricoire et al., 2011; Wichterle et al., 2001; Xu et al., 2008). Several lines of evidence suggest that distinct pools of progenitor cells within the MGE are specified to produce interneurons for each of these telencephalic structures. For instance, striatal and cortical interneurons seem to derive from different progenitor pools within the MGE (Flandin et al., 2010). Consistent with this notion, striatal and cortical interneurons are specified to reach their targets by expressing different complements of guidance receptors (Marín et al., 2001; Nóbrega-Pereira et al., 2008; van den Berghe et al., 2013). In addition, the hippocampus contains certain classes of interneurons that do not seem to have a clear homolog in the neocortex, such as PV^+/SST^+ bistratified cells (Buhl et al., 1994). Similarly, VIP^+ interneurons populate the cortex and the hippocampus but are absent from the striatum. Thus, it is conceivable that different pools of progenitor cells within the subpallium are specified to generate interneurons that migrate to specific subdivisions of the telencephalon (i.e., striatum, amygdala, neocortex, hippocampus).

Does the same rule apply for different neocortical regions? If this were the case, then one would expect to observe a topographical relationship between the origin of a specific class of interneurons within the subpallium and their final distribution in the neocortex. Transplantation experiments in slices have shown that the mediolateral distribution of GABAergic interneurons in the neocortex is not topographically related to their birthplace. So, irrespective of the site of origin in the MGE, interneurons tend to colonize the neocortex following a lateral to medial progression (Lourenço et al., 2012), in parallel to the normal maturation gradient of pyramidal cells (Bayer and Altman, 1987). Consistent with this notion, PV^+ interneurons within the same layer are, on average, younger in the lateral third of the somatosensory cortex than in the medial third (Rymar and Sadikot, 2007).

The mechanisms that control the regional distribution of neocortical interneurons are presently unclear, but several lines of evidence suggest that this process is related to the transition of interneuron migration from tangential to radial or, more precisely, to its timing (Figure 2). On their entry into the pallium, interneurons do not immediately target the cortical plate, where developing pyramidal cells are beginning to differentiate. Instead, interneurons continue their tangential spread using the

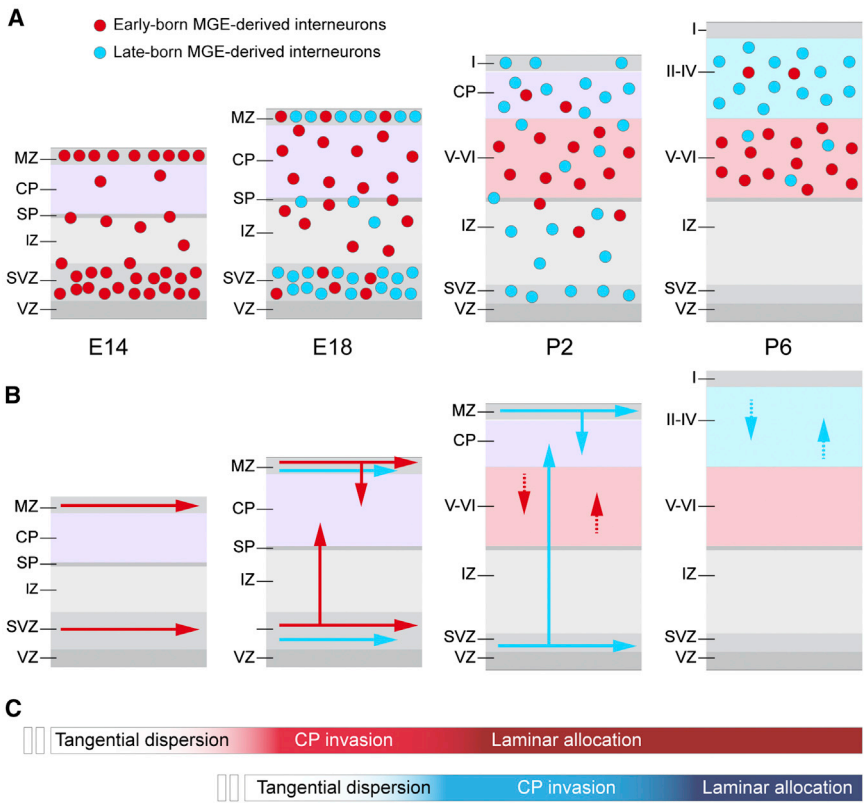

Figure 2. Integration of MGE-Derived Interneurons into Cortical Layers

(A–C) Schematic representation of the different phases underlying the integration of GABAergic interneurons in the neocortex. Circles in (A) schematically represent the distribution of MGE-derived interneurons, while arrow lines in (B) represent the migratory trajectories followed by interneurons. Early- and late-born MGE-derived interneurons are depicted in red and blue, respectively. The figure shows schematic representations of the mouse neocortex at different developmental stages (E14, E18, P2, and P6). Three distinct phases can be observed for each cohort of interneurons: tangential dispersion, cortical plate (CP) invasion, and laminar allocation. These consecutive phases seem common to all MGE-derived interneurons, but their timing varies depending on the age of interneurons (C). Sorting of interneurons into different layers of the cortex seems to follow a two-step process. First, interneurons seem generally attracted to the CP (purple); subsequently, they restrict their distribution to particular layers (light blue and light red), so that early-born MGE-derived interneurons primarily settle in infragranular layers, while late-born MGE-derived interneurons populate the superficial layers. This later phase appears to depend on signals released by pyramidal cells. MZ, marginal zone; SP, subplate; IZ, intermediate zone; SVZ, subventricular zone; VZ, ventricular zone; I–VI, cortical layers I to VI.

marginal and subventricular zones of the cortex (Lavdas et al., 1999; Marín and Rubenstein, 2001; Wichterle et al., 2001). Eventually, interneurons switch their mode of migration from tangential to radial and invade the cortical plate, where they take residence. This suggests that the mediolateral and rostrocaudal position of an interneuron during this transition determines its final coordinates in the neocortex.

The chemokine Cxcl12 regulates the tangential dispersion of interneurons throughout the neocortex. This molecule is expressed by the meninges and intermediate progenitor cells in the subventricular zone of the cortex and contributes to maintain interneurons within the tangential migratory streams (Daniel et al., 2005; Stumm et al., 2003; Tham et al., 2001; Tiveron et al., 2006). Interneurons respond to Cxcl12 using two G protein couple receptors, Cxcr4 and Cxcr7. In mouse mutants for these receptors, interneurons leave the migratory streams and enter the cortical plate prematurely, which disrupts their regional distribution within the neocortex (Li et al., 2008; López-Bendito et al., 2008; Meechan et al., 2012; Sánchez-Alcañiz et al., 2011; Tanaka et al., 2010). These studies strongly suggest that the timing of exit from the migratory streams—and so the final distribution of neocortical interneurons—is directly linked at a molecular level with the loss of responsiveness to Cxcl12.

Laminar Allocation of Cortical Interneurons

The laminar organization of pyramidal cells has been studied for several decades, and important progress has been made in understanding the mechanisms controlling their ordered allocation into specific layers. The characteristic six-layered structure of the neocortex emerges during development in an inside-out pattern that is universal among mammalian species (Rakic, 2007). Newborn pyramidal cells always migrate through previous cohorts of pyramidal neurons, so that early-born cells end up located in deep (i.e., infragranular) layers, and late-born cells populate superficial (i.e., supragranular) layers of the cortex. A signaling pathway elicited by Reelin, a glycoprotein expressed by Cajal-Retzius cells at the surface of the cortex, controls the ordered migration of pyramidal cells (Franco and Müller, 2011; Soriano and Del Río, 2005). This pattern of migration allows the organization of particular classes of pyramidal cells into coherent groups with similar functional properties. In other words, pyramidal cells exhibit comparable—although not necessarily identical—patterns of axonal connections within each of the cortical layers, which contribute to the establishment of reproducible circuits within each column of the cerebral cortex.

A superficial analysis of the distribution of GABAergic interneurons may lead to the premature conclusion that these cells distribute uniformly throughout all layers of the cerebral cortex. There is, however, a remarkable degree of sophistication in the laminar distribution of neocortical GABAergic interneurons (Figure 1). For instance, PV^+ interneurons are absent from layer I (Rymar and Sadikot, 2007), while Martinotti cells are particularly abundant in layers V and VI, and to a minor extent in layers II/III, but nearly absent from layer IV (Ma et al., 2006). In addition, most bipolar or double-bouquet interneurons reside in the supragranular layers of the cortex (Rymar and Sadikot, 2007), while chandelier cells are almost exclusively found in layers II and V

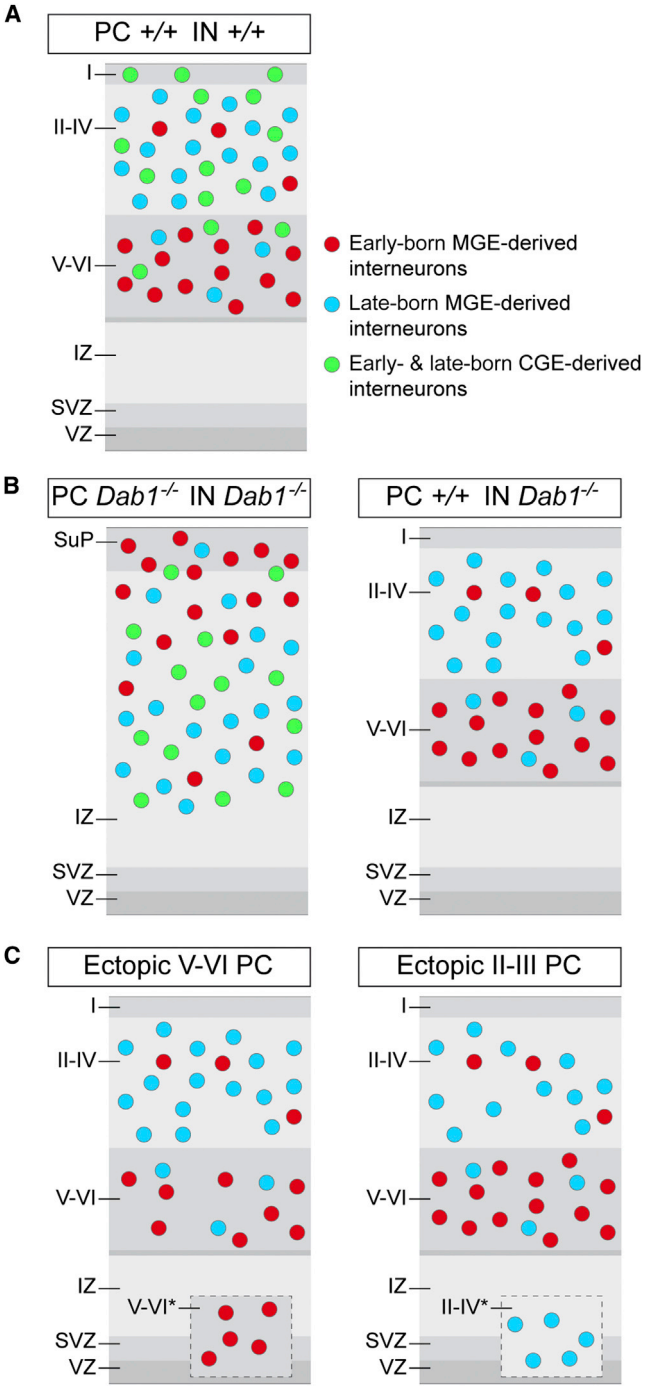

Figure 3. Pyramidal Cells Control the Distribution of GABAergic Interneurons in the Neocortex

(A) Schematic diagram illustrating the laminar distribution of MGE- and CGE-derived interneurons in the neocortex. Similar to pyramidal cells, MGE-derived interneurons distribute in a roughly inside-out pattern: early-born MGE-derived interneurons (red circles) are mainly located in infragranular layers, while late-born MGE-derived interneurons (blue circles) occupy the superficial layers. CGE-derived interneurons (green circles) distribute primarily throughout supragranular layers independently of their birthdate.

(B) Abnormal distribution of pyramidal cells in *Dab1*$^{-/-}$ mice disturbs the laminar organization of MGE-derived interneurons (left panel). This phenotype is due to the abnormal location of PN in *Dab1*$^{-/-}$ mice, because when *Dab1*$^{-/-}$ interneurons are transplanted into wild-type mice, they adopt a normal distribution (right panel).

(C) Pyramidal cells selectively recruit local interneurons based on their subtype-specific identity. The generation of ventricular zone (VZ) ectopias containing infragranular (left panel) or supragranular (right panel) pyramidal cells is sufficient to recruit early- and late-born interneurons, respectively, to this abnormal location. IN, interneurons; IZ, intermediate zone; PC, pyramidal cells; SuP, superplate; SVZ, subventricular zone; VZ, ventricular zone; I–VI, cortical layers I to VI; V–VI* and II–IV*, ectopic infragranular and supragranular pyramidal cells, respectively.

in the rodent neocortex (Taniguchi et al., 2013). Even those interneurons that seem to distribute more or less uniformly through most cortical layers, such as PV^{+} basket cells, display distinct patterns of connectivity according to their laminar position (Tremblay et al., 2010). This remarkable degree of organization suggests that precise developmental mechanisms control the laminar distribution of cortical interneurons.

The laminar distribution of MGE-derived interneurons follows a sequence that is similar to that followed by pyramidal cells. Thus, early-born MGE-derived interneurons primarily populate the infragranular layers of the neocortex, while late-born interneurons colonize the supragranular layers (Fairén et al., 1986; Miller, 1985; Pla et al., 2006; Rymar and Sadikot, 2007; Valcanis and Tan, 2003) (Figure 3). This seems to imply that the time of neurogenesis largely determines the laminar allocation of interneurons. However, several lines of evidence suggest that this is actually not the case. First, CGE-derived interneurons largely concentrate in supragranular layers of the cortex, independently of their birthdate (Miyoshi et al., 2010; Rymar and Sadikot, 2007; Xu et al., 2004). This indicates that the birthdate is not a universal predictor of laminar allocation for interneurons. Second, the distribution of MGE-derived interneurons is directly influenced by the position of pyramidal cells (Hevner et al., 2004; Lodato et al., 2011; Pla et al., 2006). For example, the laminar distribution of interneurons is abnormal in *reeler* mice (Hevner et al., 2004), and this is not due to the loss of Reelin signaling in interneurons (Pla et al., 2006) (Figure 3). These studies led to an alternative hypothesis to explain the laminar distribution of interneurons, according to which interneurons would adopt their laminar position in response to cues provided by specific classes of pyramidal cells. Direct support for this idea derives from experiments in which the laminar position of MGE-derived interneurons was specifically altered by disrupting the laminar distribution of specific classes of pyramidal cells, independently of their birthdate (Lodato et al., 2011) (Figure 3). Thus, MGE-derived interneurons appear to occupy deep or superficial layers of the cortex in response to specific signals provided by pyramidal cells located in these layers. Consequently, this process is perhaps only correlatively, but not causally, linked to the time of neurogenesis.

Recent studies on the generation of cortical lineages have shed further light on the chemical matching hypothesis for the laminar distribution of neocortical interneurons. The classical view of cortical development is based on the premise that pyramidal cells in all layers of the neocortex originate from the same lineage (Woodworth et al., 2012). In other words, cortical progenitors are multipotent and give rise to any class of pyramidal cell, but are gradually restricted to producing neurons for

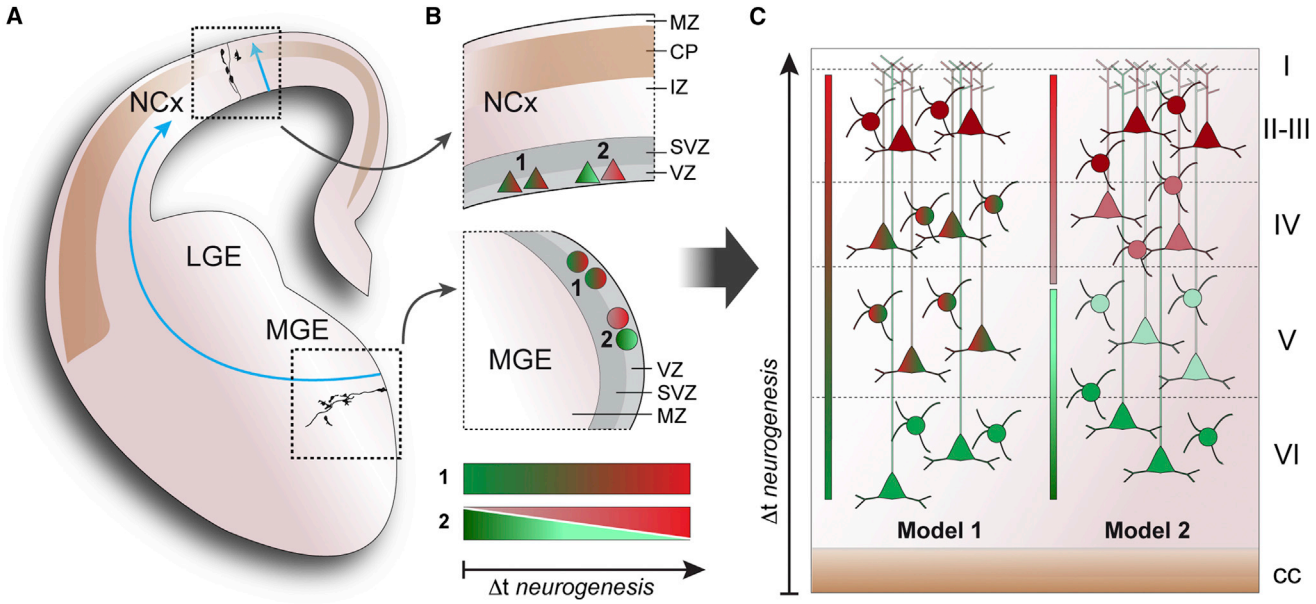

Figure 4. Lineages and Ontogenic Organization of the Neocortex

(A and B) Schematic diagram of a coronal section through the mouse telencephalon during embryonic development. The boxed areas in (A) correspond to the schemas shown in (B), which illustrate two models (1 and 2) of neurogenesis for pyramidal cells and MGE-derived interneurons. According to the classical model (model 1), progenitor cells in the embryonic cortex (triangles) and in MGE (circles) are multipotent. Each progenitor cell in these regions has the potential to generate pyramidal cells and interneurons, respectively, for all cortical layers. The fate potential of progenitor cells is progressively restricted along neurogenesis so that they give rise first to deep cortical neurons and later on to progressively more superficial neurons (transition from green to red in model 1). Model 2 is based on the observation that at least two classes of progenitor cells seem to exist for pyramidal cells (triangles) and interneurons (circles), each one committed to generate neurons with specific laminar allocations. In this model, the two lineages coexist in the proliferative regions, but their relative proportion and/or neurogenic potential changes during development.

(C) Schematic diagram of a coronal section through the adult neocortex, showing lineage relationships and neuron distributions for model 1 (left) and model 2 (right). In model 1, lineages of pyramidal cells and interneurons are organized along the columnar dimension of the neocortex. In model 2, lineages of pyramidal cells and interneurons are primarily organized along the laminar dimension of the neocortex. Color codes in the figure do not represent any developmental program but simply reflect the fate of cells according to their laminar position. In addition, note that both models are not incompatible. cc, corpus callosum; NCx, neocortex; MGE, medial ganglionic eminence; LGE, lateral ganglionic eminence; MZ, marginal zone; CP, cortical plate; IZ, intermediate zone; SVZ, subventricular zone; VZ, ventricular zone; I–VI, cortical layers I to VI.

progressively more superficial layers (Noctor et al., 2001; Rakic, 1988). Recent work on the organization of interneuron lineages also led to the conclusion that MGE-derived interneurons that extend throughout multiple layers of the cortex derive from the same progenitor cells (Brown et al., 2011) (Figure 4, model 1).

This view of cortical neurogenesis has recently been challenged by the identification of different classes of progenitor cells for both pyramidal cells and interneurons (Ciceri et al., 2013; Franco et al., 2012; Stancik et al., 2010) (Figure 4, model 2). In the pallium, two classes of progenitor cells in the neocortex might exist: one largely responsible for the generation of pyramidal cells in deep (V and VI) layers and another one for pyramidal cells in superficial (II and IV) layers (Franco et al., 2012). Similarly, recent work on the organization of progenitor cells in the subpallium suggests that MGE-derived interneurons originate from at least two separate lineages: one that primarily produces interneurons for deep (V and VI) layers of the cortex and another one that generates interneurons for superficial (II and IV) layers (Ciceri et al., 2013) (Figure 4). According to this model, the relative proportion of the different types of progenitor cells varies with time, and this determines the classes of pyramidal cells and interneurons that are being produced at a particular developmental stage. Furthermore, these experiments suggest that MGE-derived interneurons might be generated to mirror the laminar organization of pyramidal cells.

Early Functional Interactions

The distribution of GABAergic interneurons into the cerebral cortex also relies on functional interactions between these cells and the networks into which they integrate. Initially, these interactions rely on the ability of migrating interneurons to sense the combined extracellular levels of GABA and glutamate, and so they precede the onset of synaptogenesis in the cortex. Both neurotransmitters enhance neuronal migration in the embryo because they depolarize the membrane of interneurons and stimulate the generation of calcium transients (Cuzon et al., 2006; Manent et al., 2005). However, the reversal potential for chloride ions changes in interneurons as they mature, and so GABA becomes hyperpolarizing when this occurs. This change turns ambient GABA into a stop signal for migrating interneurons, because hyperpolarizing GABA decreases the frequency of intracellular calcium transients (Bortone and Polleux, 2009). The potassium/chloride exchanger KCC2 mediates the reversal potential of chloride ions in maturing neurons (Ben-Ari, 2002), and so the mechanisms controlling the upregulation of this transporter are likely linked to the termination of migration (Bortone and Polleux, 2009). Consistently, interneurons upregulate

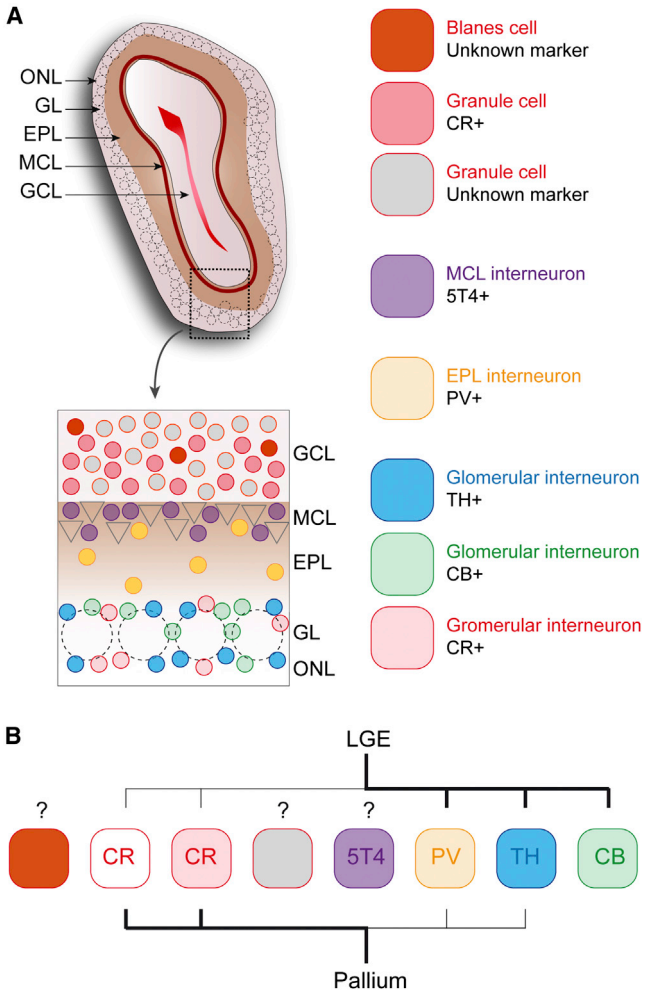

Figure 5. Major Classes of Olfactory Bulb Interneurons and Their Developmental Origins

(A) Schematic of a coronal section through the mouse olfactory bulb showing the main classes of GABAergic interneurons and their respective laminar allocation. Granule cells include at least three different classes: Blanes cells, CR^+ granule cells preferentially located in the most superficial aspect of the granule cell layer, and granule cells without a known specific marker. The mitral cell layer contains interneurons that express the glycoprotein 5T4. The external plexiform layer contains PV^+ interneurons. Periglomerular interneurons comprise at least three classes based on their neurochemical content: TH^+, CB^+, and CR^+ cells.

(B) Grouping of the main classes of cortical interneurons according to their developmental origins. ONL, olfactory nerve layer; GL, glomerular layer: EPL, external plexiform layer; MCL, mitral cell layer; GCL, granule cell layer; LGE, lateral ganglionic eminence.

KCC2 expression during their radial sorting in the cortex (Miyoshi and Fishell, 2011); however, it is presently unclear how this process is integrated with the laminar allocation of interneurons. One possibility is that interneurons get preferentially immobilized in layers with increased network activity, in which modification of calcium dynamics might be more prominent (de Lima et al., 2009). Alternatively, the layer-specific cues that are thought to control the final distribution of interneurons might also regulate the expression of KCC2 in these cells. In agreement with this hypothesis, factors released by cortical cells decrease the mobility of embryonic interneurons in culture (Inamura et al., 2012). In any case, early patterns of activity seem to play a clear role in the final settlement of interneurons, independently of their origin (Bortone and Polleux, 2009; De Marco García et al., 2011).

Integration of GABAergic Interneurons in the Adult Olfactory Bulb

The adult olfactory bulb represents a good model to study the ability of newly generated GABAergic interneurons to integrate into mature networks. Similar to the cerebral cortex, the olfactory bulb is organized as an assembly of excitatory and inhibitory neurons distributed through layers (Zou et al., 2009). However, olfactory interneurons outnumber excitatory neurons in an ~100:1 proportion, perhaps because the primary function of the olfactory bulb is to discriminate sensory information. In addition, neural circuits in the olfactory bulb are continuously remodeled by the addition of new GABAergic interneurons, generated through the process of adult neurogenesis. This circumstance makes the adult olfactory bulb an ideal model for studying how GABAergic interneurons integrate into mature neuronal circuits. Transplantation experiments have shown that embryonic cortical interneurons also have the ability to migrate and functionally integrate in the adult cortex (Alvarez-Dolado et al., 2006; Wichterle et al., 1999), which suggests that this might be a rather general characteristic of GABAergic interneurons.

Two classes of excitatory neurons are present in the olfactory bulb, mitral cells and tufted cells, which are confined to a single layer that lies between the external plexiform and granule cell layers (Figure 5). Both classes of neurons are glutamatergic, but they comprise several different populations that diverge in the spatial organization of their connections and molecular markers (Mizuguchi et al., 2012; Mori and Sakano, 2011). Mitral cells and tufted cells send their primary dendrites into single glomeruli, where they receive inputs from olfactory sensory neurons. In turn, they convey this information to other brain centers in the telencephalon through the lateral olfactory tract (Igarashi et al., 2012). Hence, as in the cortex, excitatory neurons are the main projection neurons in the olfactory bulb.

The olfactory bulb contains several classes of GABAergic interneurons, grouped in three main populations: granule cells, external plexiform layer interneurons, and periglomerular cells (Figure 5) (Batista-Brito et al., 2008). It is worth noting that olfactory bulb interneurons have not been as extensively characterized as cortical interneurons, and so their classification largely relies on marker analyses at this point. Granule cells are the most abundant GABAergic neurons in the olfactory bulb. They have a small soma and make dendrodendritic connections with excitatory neurons (Price and Powell, 1970). Several classes of neurons have been identified within the granule cell layer, including external granule cells, whose soma is located within the mitral cell layer and expresses the glycoprotein 5T4, CR^+ granule cells located in the external aspect of the granule cell layer, and Blanes cells (Imamura et al., 2006; Pressler and Strowbridge, 2006). This later population of interneurons is specialized in inhibiting granule cells, thereby controlling the strength of inhibition on the excitatory neurons (Pressler and Strowbridge, 2006). Many granule cells do not express any known markers,

which suggests an even larger diversity within this population. The most common population of interneurons in the external plexiform layer contains PV (Kosaka and Kosaka, 2008), but several other classes of interneurons seem to exist in this layer (Huang et al., 2013; Krosnowski et al., 2012; Liberia et al., 2012). Interneurons in this layer are thought to provide inhibition to mitral and tufted cells (Huang et al., 2013), probably by targeting their apical dendrites. Finally, three distinct subtypes of interneurons have been identified in the glomerular layer of the mouse, based on the expression of tyrosine hydroxylase (TH), calbindin (CB), and CR, respectively (Kohwi et al., 2007; Kosaka and Kosaka, 2005). These interneurons receive direct input from olfactory receptor neuron axons and synapse with the dendrites of mitral and tufted cells (Kosaka and Kosaka, 2005).

The organization of olfactory bulb interneurons into distinct layers is directly related to their function in the neural circuit, processing olfactory information (Zou et al., 2009). Interneurons in the glomerular layer receive synapses from olfactory receptor neuron axons and, in turn, synapse with the dendrites of mitral cells and tufted cells. In turn, granule cells established dendrodendritic synapses with excitatory neurons in the external plexiform layer. Consequently, the laminar allocation of interneurons largely determines their function within the neural circuits that underlie the processing of sensory information in the olfactory bulb.

Sources of Adult-Born Olfactory Bulb Interneurons

Olfactory interneurons are born remotely in the subpallium and reach their final destination through tangential migration (Altman, 1969; Belvindrah et al., 2009; Luskin, 1993). During embryonic stages, the olfactory bulb emerges as a protrusion of the rostral tip of the telencephalon that is continuous with the region of the subpallium that gives rise to its interneurons (Gong and Shipley, 1995). As development proceeds, however, interneurons must migrate increasing distances to reach their destination. Importantly, many interneurons continue to be generated through adulthood (Lois and Alvarez-Buylla, 1994), which poses a notable challenge for the transit of new inhibitory neurons to the olfactory bulb.

The origin of olfactory interneurons has been classically associated with the LGE, a region that was shown to contribute to the SVZ of the lateral ventricles in the postnatal telencephalon (Stenman et al., 2003; Wichterle et al., 2001). However, recent evidence indicates that the diversity of OB interneurons derives from a more extensive and heterogeneous germinal region than previously thought (Lledo et al., 2008). Genetic fate-mapping analyses have confirmed that the LGE is the main contributor to the adult SVZ. Thus, the majority of dividing cells in the SVZ derive from lineages expressing the subpallial marker Gsh2, and nearly 70% of the olfactory bulb interneurons emerge from these progenitors (Young et al., 2007). The remaining interneurons derive from a lineage of progenitor cells that express the transcription factor Emx1 and are therefore classically considered pallial derivatives (Young et al., 2007). However, this should be interpreted with caution because LGE progenitors may also contain low levels of Emx1 (Waclaw et al., 2009). Independently of their origin, $Emx1^+$ progenitors in the adult are located in the regions of the lateral ventricular wall facing the corpus callosum, from where neurosphere-forming stem cells have been obtained (Ventura and Goldman, 2007; Willaime-Morawek et al., 2006). Finally, a very small fraction of olfactory bulb interneurons (~1%) seem to derive from a lineage of SVZ progenitor cells that express the transcription factor Nkx2-1 (Young et al., 2007), a marker of the MGE.

LGE and pallial progenitors contribute differently to the diversity of olfactory bulb interneurons (Figure 5). For instance, periglomerular cells are produced by both sets of progenitors, although in different proportions. LGE-derived progenitors contribute many TH^+ interneurons and the large majority of CB^+ cells, whereas pallium-derived progenitors produce most CR^+ neurons (Kohwi et al., 2007; Stenman et al., 2003; Young et al., 2007). PV^+ interneurons in the external plexiform layer are also generated from both classes of progenitors, although most seem to derive from the LGE (Li et al., 2011). In the granular cell layer, most CR^+ interneurons develop from pallial progenitors, while the remaining cells are likely derived from the LGE (Kohwi et al., 2007; Merkle et al., 2007; Young et al., 2007).

Each population of olfactory bulb interneurons is produced in a unique temporal pattern and turnover rate (Lledo et al., 2008). This suggests that the neurogenic processes occurring during development and in the adult are not directly equivalent (De Marchis et al., 2007; Lemasson et al., 2005). Interestingly, bromodeoxyuridine (BrdU) labeling experiments revealed that the relative ratio of the different subtypes of olfactory bulb interneurons remains relatively constant from birth to adulthood, although they seem to be produced at different rates. For instance, CR^+ cells make up the largest proportion of newborn neurons in adult mice (Batista-Brito et al., 2008), while TH^+ and CB^+ periglomerular interneurons are produced to a lesser extent, and PV^+ interneurons are not significantly turned over in the adult (Kohwi et al., 2007; Li et al., 2011). It is presently unclear what physiological circumstances determine the precise turnover of the different classes of olfactory bulb interneurons in the adult.

Regional and Laminar Distribution of Adult-Born Olfactory Bulb Interneurons

The mechanisms controlling the migration of embryonic interneurons to the olfactory bulb resemble in many aspects that of cortical interneurons (Long et al., 2007) and will not be considered here in detail. However, the migration of interneurons to the olfactory bulb changes dramatically as the brain matures, because the brain parenchyma becomes progressively less permissive for migration. Adult-born interneurons migrate to the olfactory bulb through the rostral migratory stream (RMS), a highly specialized structure in which chains of migrating neuroblasts are ensheathed by astrocytes (Doetsch and Alvarez-Buylla, 1996; Jankovski and Sotelo, 1996; Lois et al., 1996; Thomas et al., 1996) (Figure 6). Interneurons migrate, crawling into each other in a process that is known as chain migration (Wichterle et al., 1997). Many factors have been shown to influence the tangential migration of olfactory neuroblasts through the RMS (reviewed in Belvindrah et al., 2009), but very little is known on the mechanisms that control the final distribution of newborn interneurons in the olfactory bulb.

Newborn interneurons seem to distribute uniformly throughout the rostrocaudal extent of the olfactory bulb (Lemasson et al., 2005). In contrast, interneurons target a specific layer within the olfactory bulb, according to their fate, in a process that is likely determined at the time of their specification. In agreement

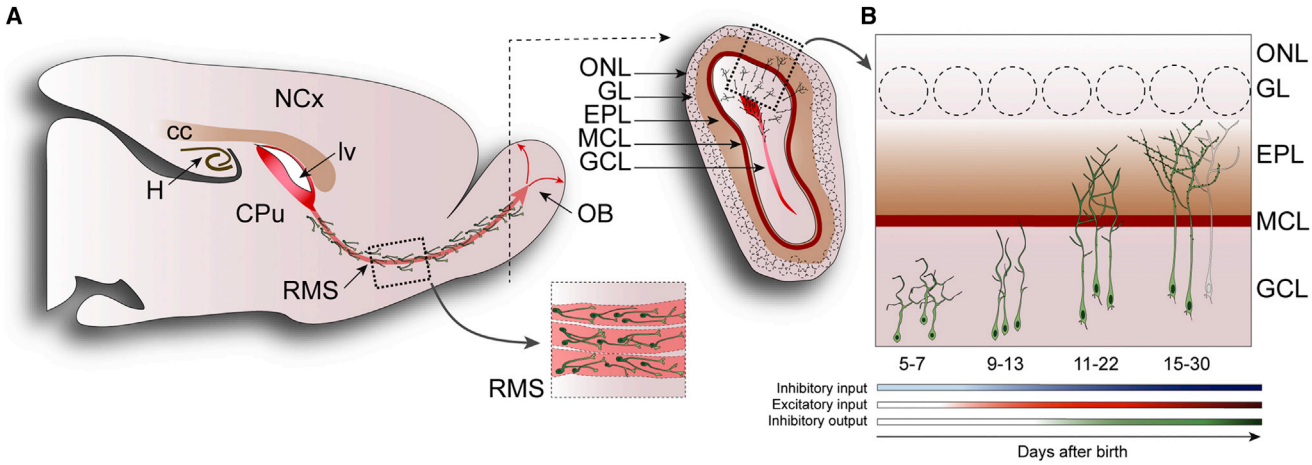

Figure 6. Integration of Adult-Born Interneurons into the Olfactory Bulb

(A) Schematic of sagittal section through the mouse brain illustrating the migration and integration of adult-born GABAergic interneurons into the olfactory bulb. Olfactory bulb interneurons are produced in the SVZ and reach the olfactory bulb though the rostral migratory stream (RMS).

(B) Schematic of a coronal section depicting the laminar organization of the adult olfactory bulb. The inset illustrates different stages in the maturation of granule cells, from their arrival to the olfactory bulb to their integration into functional circuits. The numbers refer to their approximate age in days. ONL, olfactory nerve fiber layer; GL, glomerular layer: EPL, external plexiform layer; MCL, mitral cell layer; GCL, granule cell layer; cc, corpus callosum; CPu, caudoputamen nucleus; H, hippocampus; lv, lateral ventricle; NCx, neocortex.

with this notion, overexpression of the transcription factor Pax6 in migrating neuroblasts promotes their differentiation to periglomerular TH^+ cells at the expense of other interneuron classes (Hack et al., 2005). These results reinforce the view that the laminar allocation is largely linked to the fate of cells originating from different progenitor cells. Since granular and periglomerular interneurons play very distinct roles in the processing of olfactory information (Chen and Shepherd, 2005; Shepherd et al., 2007), the precise targeting of these cells to their appropriate layer seems critical for the function of the olfactory bulb.

Important differences seem to exist in the mechanisms underlying the laminar distribution of cortical and olfactory bulb interneurons. First, olfactory bulb interneurons reside in layers that lack projection neurons, which is in sharp contrast to most of their neocortical counterparts (with the exception of cortical layer I). This suggests that the hypothetical mechanism proposed to regulate the allocation of most neocortical interneurons is unlikely to apply in the olfactory bulb. Second, adult-born interneurons reach their final position by traversing a territory that is largely populated by fully mature, differentiated neurons. This indicates that the mechanisms regulating the integration of interneurons into their appropriate target layer in the olfactory bulb are maintained through adulthood, at least for periglomerular and granule cells.

Reelin is the only factor identified to date that seems to influence the laminar positioning of olfactory bulb interneurons. In contrast to the cerebral cortex, where Reelin regulates the distribution of pyramidal cells and only affects the location of GABAergic interneurons in a non-cell-autonomous manner (Pla et al., 2006), this glycoprotein seems to directly control the migration of olfactory bulb interneurons. Indeed, mitral and tufted cells adopt their final position independently of this signaling system (Devor et al., 1975). Conversely, Reelin produced by these cells is required for interneurons to detach from the RMS and adopt their normal laminar position (Hack et al., 2002; Hellwig et al., 2012). In *reeler* mutants, for example, some TH^+ and CB^+ interneurons fail to reach the glomerular layer and instead reside in the external plexiform layer; some defects have also been reported in the distribution of CR^+ interneurons in the granular layer (Hellwig et al., 2012). Nevertheless, the position of PV^+ interneurons in the external plexiform layer, and most periglomerular interneurons, is unaffected by the loss of Reelin signaling, which suggests that the correct laminar distribution of olfactory bulb interneurons depends on additional factors. Consistent with this idea, a population of glial cells located in the olfactory nerve layer, the olfactory ensheathing cells, releases a chemoattractive activity that attracts migrating neuroblasts in vitro (Zhu et al., 2010). This suggests that olfactory ensheathing cells may contribute to regulate the radial distribution of interneurons in the surface of the olfactory bulb.

Functional Integration of Adult-Born Interneurons

As in the developing cortex, the integration of interneurons in the olfactory bulb also seems under the influence of activity-dependent mechanisms. Migrating neuroblasts are sensitive to the action of neurotransmitters, although they seem to exert different effects than in the cortex. There are no specific studies on the expression of chloride transporters in adult-born interneurons, but analysis of their expression in early postnatal stages suggests that interneurons lack KCC2 when they arrive to the olfactory bulb (Mejia-Gervacio et al., 2011). Consequently, interneurons terminate their migration in the olfactory bulb in an environment with a high concentration of ambient GABA and under depolarizing conditions. Intriguingly, neuroblast migration is reduced by the tonic depolarizing action of GABA acting on $GABA_A$ receptors (Bolteus and Bordey, 2004; Mejia-Gervacio et al., 2011). These results, which contrast the proposed role for hyperpolarizing GABA as a stop signal for cortical interneurons, reveal that the function of ambient neurotransmitters in

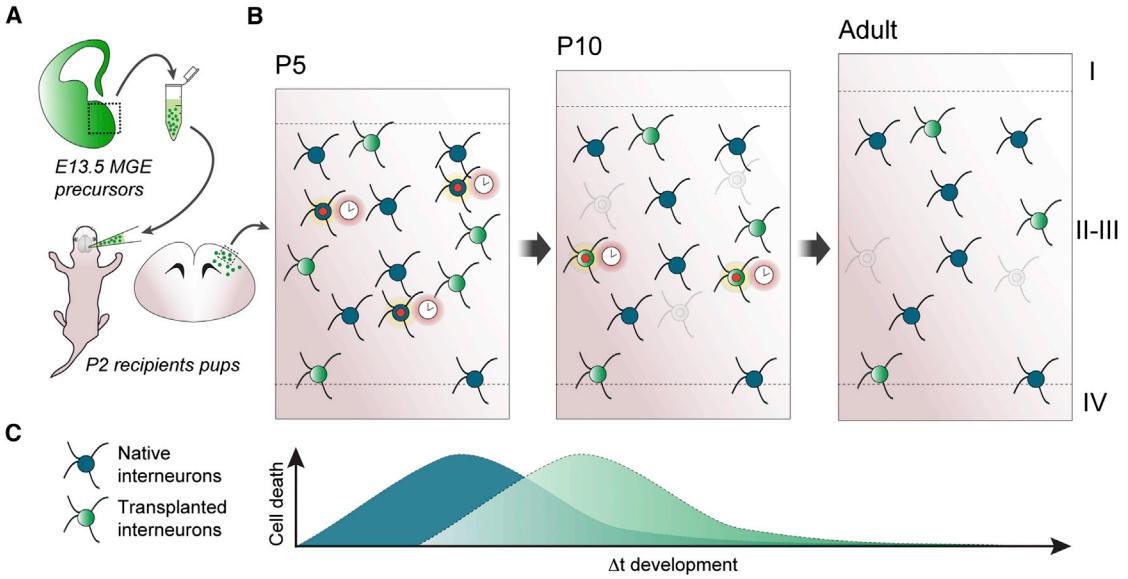

Figure 7. Intrinsic Developmental Cell Death of Cortical GABAergic Interneurons

(A) Schematic diagrams of the experimental paradigm used to study the programmed cell death of cortical interneurons (Southwell et al., 2012). MGE donor cells from GFP-expressing embryos were transplanted into the neocortex of early postnatal recipient mice, and their number and distribution were analyzed several days later, together with the native interneuron population.

(B) Schematic diagrams of coronal sections through the neocortex of transplanted mice at three different time points during postnatal development. Approximately 40% of interneurons (native and transplanted) undergo programmed cell death during early postnatal development. However, each population of interneurons undergoes cell death (red nucleus indicates active caspase-3) according to an internal clock that depends on the actual age of the interneurons, rather than according to environmental influence. Since transplanted interneurons (dark green) were moved forward in development, they undergo programmed cell death several days later than the native population (light green). The time window of cell death largely overlaps with the period of intense synaptogenesis, suggesting that the survival of interneurons might be linked to their recruitment into circuits.

(C) The temporal windows of neuronal cell death for the native (blue) and transplanted (green) interneurons are out of phase due to heterochronic transplantation. MGE, medial ganglionic eminence; I–IV, cortical layers I to IV.

the functional integration of GABAergic interneurons is more complex than previously thought.

Several studies have analyzed in detail the maturation and integration of adult-born interneurons into the olfactory bulb (Figure 6). The synaptic integration of newborn interneurons occurs over a period of approximately 3 weeks (Petreanu and Alvarez-Buylla, 2002), although newborn neurons already receive glutamatergic and GABAergic synapses within 24 hr after leaving the RMS (Katagiri et al., 2011; Panzanelli et al., 2009). As interneurons progressively settle into their final position, they acquire functional properties that make them indistinguishable from preexisting neurons (Belluzzi et al., 2003; Carleton et al., 2003). Interestingly, the majority of functional outputs from newborn interneurons at the end of their integration period and their characteristics do not seem to change over time (Bardy et al., 2010). In contrast, glutamatergic inputs onto newborn interneurons display enhanced plasticity during this period of maturation (Nissant et al., 2009), which may provide a basis for adult neurogenesis-dependent olfactory learning.

General Principles in the Integration of Embryonic and Adult GABAergic Interneurons

There are a number of emerging concepts that can be extracted from our current understanding of the mechanisms controlling the integration of GABAergic interneurons into the developing neocortex and in the mature olfactory bulb. In particular, it seems clear that many of the features that distinguish the different classes of GABAergic interneurons, such as their intrinsic properties and perhaps even their final allocation, are intrinsically determined.

Intrinsic Developmental Programs

Several stages in the development of GABAergic interneurons, both in the cerebral cortex and the olfactory bulb, seem to be regulated by the execution of a maturational program intrinsic to inhibitory neurons. In other words, the behavior of interneurons at any given time in development is better predicted by their cellular age than by changes in the local environment. Since interneurons are born asynchronously, this implies that the developing cerebral cortex contains a mixture of interneurons at diverse stages of maturation. These differences are obviously exaggerated in the olfactory bulb, where adult-born interneurons coexist with interneurons that were generated in the embryo.

The existence of an intrinsic maturational program in GABAergic interneurons predicts that interneurons born at different times would behave differently within the same environment. This has been observed, for example, in relation to the settlement of interneurons in the cortical plate. Birthdating analyses have shown that not all interneurons switch from tangential to radial migration simultaneously in response to a common trigger. Instead, interneurons invade the cortical plate when they are between 6 and 8 days old; therefore, early-born interneurons enter the cortical plate before late-born interneurons (López-Bendito

et al., 2008) (Figure 2). This indicates that the switch from tangential to radial migration is largely determined by the age of interneurons. Consistent with this idea, many late-born (embryonic day 15.5, E15.5) interneurons transplanted into E12.5 embryos settle in deep layers of the cortex instead of their normal superficial location (Pla et al., 2006), probably because under these circumstances they stop responding to the cues that support their tangential migration at the same time as early-born (12.5) interneurons, which settle in deep layers of the cortex. The intrinsic developmental program may therefore influence the settlement of interneurons in the cortex by regulating the responsiveness of each cohort of interneurons to cues present in the cortex.

Transplantation experiments have also revealed that the death of cortical interneurons in the early postnatal cortex might also be under intrinsic control (Figure 7). Southwell and colleagues (2012) observed that many cortical interneurons undergo programmed cell death in vivo between postnatal day 7 (P7) and P11 in vivo, when interneurons are between 11 and 18 days old. When transplanted into older cortices (P3), interneurons undergo programmed cell death later than normal (~P15), which demonstrates that this process is intrinsically linked to the cellular age of interneurons. Consistently, cortical interneurons undergo programmed cell death in vitro with the same temporal dynamics as in vivo (Southwell et al., 2012). In the adult olfactory bulb, interneurons also die within a well-defined temporal window, approximately 15–30 days after birth (Petreanu and Alvarez-Buylla, 2002).

Further evidence supporting the existence of an intrinsic clock that controls the maturation of these cells comes from the analysis of their modulation of ocular dominance plasticity. During a critical period in the postnatal development of the visual cortex, visual experience influences the organization of thalamocortical axon terminals to produce alternating ocular dominance domains (Hensch, 2005). Occlusion of one eye during this period triggers a rapid reorganization of thalamic terminals in the cortex, a process that is regulated by inhibitory neurotransmission. In mice, ocular dominance plasticity peaks between P26 and P28, when interneurons are roughly between 33 and 35 days of age. Transplantation of interneuron precursors into the postnatal cortex reopens the critical period of ocular dominance plasticity when transplanted interneurons reach a cellular age equivalent to that of endogenous inhibitory neurons during the normal critical period (Southwell et al., 2010).

Recent efforts to derive cortical interneurons from human pluripotent stem cells (hPSCs) or human-induced pluripotent stem cells (hiPSCs) have also emphasized the ability of these cells to differentiation according to an intrinsic program of maturation. Both in vitro and after transplantation into the rodent cortex, human GABAergic interneurons derived from hPSCs or hiPSCs mature following a protracted timeline of several months, thereby mimicking the endogenous human neural development (Maroof et al., 2013; Nicholas et al., 2013). Altogether, these findings suggest that multiple aspects of the integration of interneurons in cortical networks are regulated by the execution of a maturational program intrinsic to inhibitory neurons.

Adjusting Inhibition

Several mechanisms dynamically adjust the balance between excitation and inhibition in the adult brain (Haider et al., 2006; Turrigiano, 2011). However, it is likely that developmental programs are also coordinated to play an important role in this process. Indeed, the relative density of pyramidal cells and interneurons remains relatively constant from early stages of corticogenesis, when both classes of neurons are still migrating to their final destination (Sahara et al., 2012). One possibility is that the generation of both classes of neurons is coordinated through some kind of feedback mechanism that balances proliferation in the pallium and subpallium. Alternatively, the production of factors controlling the migration of GABAergic interneurons to the cortex might be proportional to the number of pyramidal cells generated. For example, it has been shown that cortical intermediate progenitor cells (IPCs) produce molecules that are required for the normal migration of interneurons (Tiveron et al., 2006), and mutants with reduced numbers of IPCs have a deficit in cortical interneurons (Sessa et al., 2010).

Cell death is another prominent factor regulating neuronal incorporation during development (Katz and Shatz, 1996; Voyvodic, 1996). It has long been appreciated that a sizable proportion of inhibitory neurons is eliminated from the cerebral cortex through apoptosis during the period of synaptogenesis (Miller, 1995), and recent work estimated that approximately 40% of the interneurons in the cortex perish around this time (Southwell et al., 2012). Similarly, only about half of the adult-born granule cells survive more than a few days after reaching the olfactory bulb (Petreanu and Alvarez-Buylla, 2002).

The mechanisms controlling the death of newborn olfactory bulb interneurons have been studied with some detail. There seems to exist a critical period during which sensory activity influences the survival of newborn interneurons (Kelsch et al., 2009; Yamaguchi and Mori, 2005), which largely overlaps with the period when interneurons become synaptically integrated into the olfactory bulb (15–30 days after birth). During this period, interneurons arriving to the olfactory bulb (i.e., roughly born at the same time) compete for survival, probably because newborn interneurons are more sensitive to the overall activity of nearby circuits than mature olfactory interneurons. In agreement with this idea, interneurons that survived this period tend to persist for life (Winner et al., 2002). Thus, both the synaptic integration and the survival of newborn interneurons seem to depend on sensory activity mechanisms, which are intrinsically linked to the cell excitability. Consistent with this, synaptic development and survival of newly generated neurons are dramatically impaired in anosmic mice (Corotto et al., 1994; Petreanu and Alvarez-Buylla, 2002), while sensory enrichment promotes the survival of newborn olfactory interneurons (Bovetti et al., 2009; Rochefort et al., 2002). Moreover, increasing cell-intrinsic excitability in maturing granule cells enhances their synaptic integration and partially rescues neuronal survival in a sensory-deprived olfactory bulb (Kelsch et al., 2009; Lin et al., 2010), while forced hyperpolarization decreases survival (Lin et al., 2010). Since most interneurons have already matured and received connections by the time they die, it has been hypothesized that only interneurons connected to active circuits would ultimately survive (Petreanu and Alvarez-Buylla, 2002), an idea that has

obtained experimental support in the adult dentate gyrus (Kee et al., 2007). Thus, the death of adult-born interneurons seems to be intimately linked to mechanisms of structural plasticity in the olfactory bulb.

It is presently unclear whether programmed cell death in developing cortical interneurons depends on similar mechanisms than in the olfactory bulb, but recent experiments pointed out an interesting parallel between both structures. Southwell and colleagues (2012) found that heterochronically transplanted interneurons do not influence cell death dynamics in the endogenous population (Figure 7). This seems to suggest that the competition for survival is normally restricted to cortical interneurons born roughly at the same time, as in the olfactory bulb. Thus, it is conceivable that cell death selectively eliminate inappropriately integrated cortical interneurons within specific lineages, although this hypothesis remains to be experimentally tested. In any case, these results reinforce the view that the integration of interneurons into cortical networks critically depends on a maturational program linked to their cellular age.

A Look Ahead

Much progress has been made over the past years regarding our understanding of the mechanisms regulating the migration of embryonic and adult-born GABAergic interneurons. However, our understanding of the integration of these cells into functional circuits in the cerebral cortex and olfactory bulb, respectively, is very limited. We know basically nothing about the mechanisms through which interneurons adopt their precise laminar distributions and how this process influences functional connectivity patterns between interneurons and pyramidal cells. Recent work has led to the suggestion that SST^+ and PV^+ interneurons connect promiscuously to nearby pyramidal cells (Fino and Yuste, 2011; Packer and Yuste, 2011); therefore, the connectivity maps of interneurons could simply result from the overlap of axonal and dendritic arborizations between both cell types (Packer et al., 2012). According to this principle, the laminar allocation of interneurons might be irrelevant for their functional integration into cortical networks, i.e., similar interneurons located in different layers might be interchangeable. On the other hand, it is well established that different classes of interneurons receive distinct excitatory and inhibitory laminar input patterns (Xu and Callaway, 2009; Yoshimura and Callaway, 2005). In agreement with this notion, a remarkable degree of specificity in the cellular selection of postsynaptic targets for at least some classes of interneurons seems to exist. For example, layer IV neurogliaform and SST^+ interneurons selectively target local PV^+ basket cells while largely avoiding pyramidal cells in this layer (Chittajallu et al., 2013; Xu et al., 2013). In contrast to the promiscuous view of cellular targeting by cortical interneurons (Packer et al., 2012), these observations suggest that the fine-scale connectivity of cortical networks might be directly influenced by the appropriate laminar allocation of interneurons. Future experiments should contribute to solve this apparent paradox.

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