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Adult Neurogenesis and the Olfactory System

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Abstract

Though initially described in the early 1960s, it is only within the past decade that the concept of continuing adult neurogenesis has gained widespread acceptance. Neuroblasts from the subventricular zone (SVZ) migrate along the rostral migratory stream (RMS) into the olfactory bulb, where they differentiate into interneurons. Neuroblasts from the subgranular zone (SGZ) of the hippocampal formation show relatively little migratory behavior, and differentiate into dentate gyrus granule cells. In sharp contrast to embryonic and perinatal development, these newly differentiated neurons must integrate into a fully functional circuit, without disrupting ongoing performance. Here, after a brief historical overview and introduction to olfactory circuitry, we review recent advances in the biology of neural stem cells, mechanisms of migration in the RMS and olfactory bulb, differentiation and survival of new neurons, and finally mechanisms of synaptic integration. Our primary focus is on the olfactory system, but we also contrast the events occurring there with those in the hippocampal formation. Although both SVZ and SGZ neurogenesis are involved in some types of learning, their full functional significance remains unclear. Since both systems offer models of integration of new neuroblasts, there is immense interest in using neural stem cells to replace neurons lost in injury or disease. Though many questions remain unanswered, new insights appear daily about adult neurogenesis, regulatory mechanisms, and the fates of the progeny. We discuss here some of the central features of these advances, as well as speculate on future research directions.

1. Preface

Throughout most of the 20th century, a “central dogma of neurobiology” held that neurogenesis occurred only during embryonic development and that the adult central nervous system was static, lacking any capacity for regeneration (see Colucci-D’Amato et al., 2006 for historical overview). This doctrine was exemplified by Ramón y Cajal who stated, “Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated” (Ramon y Cajal, 1913-14). This notion was first challenged in the 1960s, when Altman, using tritiated thymidine, which is taken up by dividing cells and can be detected using autoradiography, showed new neurons in the hippocampus, olfactory bulb, and elsewhere in the brain following injury (Altman, 1962; Altman and Das, 1965; Altman, 1969). Of interest, the studies of Altman and colleagues were influenced, in part, by Allen (1912) who made the following observation: “*The well developed and persistent mantle zone lying along the ectal wall of the lateral ventricle is of particular interest, for in it occur dividing cells found in the oldest specimens which show mitoses, and*

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this layer, unlike the external granule layer of the cerebellum, never entirely disappears in animals examined up to two years of age, the oldest which I have examined." Allen did go on to note that he could not determine if the sustained mitotic activity in older animals generated glia or neurons, a question that remained unanswered until the work of Altman cited above. Subsequently, Kaplan and Hinds (1977) used electron microscopy to confirm the neuronal phenotype of adult generated cells in the olfactory bulb and hippocampus. These results, however, received relatively little attention and were largely dismissed.

In the 1980s, studies from Fernando Nottebohm's group showed neurogenesis in the vocal control centers of adult songbirds. Songbird neurogenesis is seasonal, functional, and related to song learning (Goldman and Nottebohm, 1983; Paton and Nottebohm, 1984; Alvarez-Buylla and Nottebohm, 1988; Alvarez-Buylla et al., 1988), but it was initially dismissed as occurring only in birds. It wasn't until the 1990s, with the isolation of multi-potential neural stem cells from adult brain (Reynolds and Weiss, 1992), and the demonstration that dividing cells in the subventricular zone (SVZ) could migrate and become neurons (Lois and Alvarez-Buylla, 1993; Luskin, 1993; Rousselot et al., 1995), that adult neurogenesis in mammals became widely accepted. It is now established that neurogenesis continues throughout adulthood in two areas of mammalian brain, the dentate gyrus of the hippocampal formation, which generates new granule cells, and the SVZ which gives rise to new olfactory bulb interneurons. The occurrence of adult neurogenesis in other brain regions remains controversial (Gould, 2007).

The idea that the adult brain was static made intuitive sense, because it was believed that the connections in the central nervous system were so complex that new neurons could not possibly be added and make proper connections in a functioning circuit. This remains a challenge in understanding adult neurogenesis—how do new cells integrate into functional synaptic circuits without disrupting ongoing function?

2. Olfactory System – Cellular and Synaptic Organization

The mammalian olfactory system is an excellent model for studying the development of neuronal circuitry. Odor processing begins in the olfactory epithelium, where the sensory neurons are located, and then proceeds into the olfactory bulb, followed by primary olfactory (piriform) cortex (Figure 1). Olfactory cortical areas project widely throughout the neuroaxis, including back into the olfactory bulb. Olfactory cues guide many behaviors, most importantly feeding, social and reproductive behaviors. Additionally, there is continuous remodeling of olfactory circuitry throughout life as neurons are added and replaced (Lledo et al., 2006). The fundamental principles of organization and information flow in the olfactory system, including the continual addition of new neurons, are broadly conserved across species as well as phyla.

Molecular odorants in inhaled air interact with odorant receptors expressed on the cilia of olfactory sensory neurons in the nasal epithelium. Each OSN expresses only one of the large family of odorant receptors (~1200 in mouse) (Buck and Axel, 1991; Chess et al., 1994; Serizawa et al., 2003; Zhang et al., 2007). OSN axons travel in the olfactory nerve through the cribriform plate and into the glomerular layer of the olfactory bulb surrounded by a specialized type of glial cell, the olfactory ensheathing cell (Doucette, 1984; Au et al., 2002). In the olfactory bulb, axons of OSNs expressing the same odorant receptor converge into one or two glomeruli (typically one lateral and one medial glomerulus) (Mombaerts et al., 1996; Feinstein and Mombaerts, 2004). All axons converging in a given glomerulus express the same odorant receptor (Treloar et al., 2002). In the glomeruli, OSN axons synapse with the dendrites of the mitral and tufted cells, the main projection neurons of the olfactory bulb, and populations of interneurons, periglomerular cells (Kasowski et al., 1999).

Mitral cells, whose cell bodies reside in the mitral cell layer (MCL), extend one apical dendrite which arborizes extensively within one glomerulus, and several lateral or secondary dendrites into the external plexiform layer (EPL) (Figure 1). Their axons project via the lateral olfactory tract to piriform cortex (Price and Powell, 1970a; Walz et al., 2006). The molecular specificity established in the epithelium, with only 1 odorant receptor expressed in each OSN, is maintained because each mitral cell receives afferent input in only one glomerulus, where all the incoming axons express the same odorant receptor. Mitral cells are modulated, however, by two classes of interneurons, the periglomerular (PG) cells and the granule cells. In both cases, they employ a unique connection, the reciprocal dendrodendritic synapse. The dendrodendritic synapse typically occurs with the apposition of a specialized dendritic spine (gemmule) on the interneuron with the dendritic shaft of the projection neuron. The synaptic specializations include an inhibitory interneuron-to-mitral cell synapse, and an adjacent excitatory mitral-to-interneuron synapse (Hirata, 1964; Andres, 1965; Rall et al., 1966; Hinds and Hinds, 1976; Jackowski et al., 1978; Greer and Halasz, 1987).

Tufted cells, the second population of projection neurons in the olfactory bulb, are located both proximal to the mitral cell layer (deep tufted cells) and midway in the EPL (middle tufted cells). There is also a population of external tufted cells located just deep to the glomeruli, but these appear to have their axons restricted to intrabulbar circuits (Liu and Shipley, 1994; Belluscio et al., 2002; Wachowiak and Shipley, 2006 for review). The apical dendrites of the middle and deep tufted cells behave similarly to those of mitral cells—extensive arborization within a single glomerulus. The secondary dendrites, however, differ in that they remain restricted to the most superficial portion of the EPL, proximal to the glomerular layer. The secondary dendrites of mitral cells are usually in the deeper portions of the EPL (Macrides and Schneider, 1982; Mori et al., 1983; Orona et al., 1984). Given their differences in laminar organization, and perhaps cortical projections, mitral and tufted cells have been suggested to form parallel pathways for processing odor information (Shepherd et al., 2004; Greer et al., 2007).

The PG cells are a heterogeneous population of interneurons surrounding the glomeruli. They can be classified into many subtypes based on molecular phenotype, morphological characteristics, and synaptic connections. The majority of the PG cells are GABAergic. A significant number of PG cells are also dopaminergic, but only a subpopulation of the dopaminergic cells co-express GABA. Subpopulations express different calcium binding proteins, such as calretinin and calbindin. Some receive input directly from the OSNs in addition to forming dendrodendritic synapses with mitral and tufted cell apical dendrites, while others form only dendrodendritic synapses (Kosaka et al., 1998; Kosaka and Kosaka, 2005; Whitman and Greer, 2007b). PGs modulate synaptic signaling within the glomerulus as well as between glomeruli. They may contribute to lateral inhibitory/excitatory circuits that regulate the specificity of functional activity within small populations of glomeruli, but their function in odor processing has yet to be fully elucidated (cf. Wachowiak and Shipley, 2006, for further discussion and review).

Granule cells are the largest population of interneurons in the bulb, out-numbering mitral cells by approximately 100:1 (Shepherd et al., 2004). Their cell bodies reside in the granule cell layer (GCL) in the center of the bulb, and they extend one long apical dendrite into the EPL, where it branches extensively. There are at least three subpopulations of granule cells. Granule cells located deep in the GCL usually have dendrites that arborize within the deeper portion of the EPL, where they interact with the lateral dendrites of mitral cells. Granule cells in more superficial positions in the GCL have dendritic arbors in the superficial portion of the EPL, where the lateral dendrites of tufted cells predominate. A third population has extensive dendritic arborization throughout the EPL (Mori et al., 1983; Orona et al., 1984; Greer, 1987; Imamura et al., 2006). Within the EPL, granule cell dendrites form dendrodendritic synapses with the lateral dendrites of 100-150 mitral or tufted cells and modulate projection

neuron output. Granule cells are unique because they are anaxonic; their only mode of output is through the reciprocal dendrodendritic synapses established by their spiny processes in the EPL (Price and Powell, 1970b). They do receive additional input, however, at their cell bodies and basal dendrites within the GCL. These axodendritic synapses are from centrifugal fibers from a variety of other brain regions, as well as axon collaterals from mitral and tufted cells. Many centrifugal fibers enter the olfactory bulb through the anterior commissure from areas including the anterior olfactory nucleus (AON), piriform, periamygdaloid, and lateral entorhinal cortex. These excitatory projections are usually bilateral (reviewed in (Shipley and Ennis, 1996). Additional modulatory inputs include cholinergic and GABAergic fibers from the nucleus of the diagonal band (Carson, 1984; Shipley and Adamek, 1984), serotonergic fibers from the dorsal and median raphe nuclei (McLean and Shipley, 1987), and noradrenergic fibers from the locus coeruleus (McLean et al., 1989; McLean and Shipley, 1991).

Neuronal circuitry in the olfactory bulb is not static; it is highly dynamic throughout the life of the individual. Of the main cell types in the olfactory bulb, only the projection neurons are stable (Mizrahi and Katz, 2003). OSNs are continuously replaced in the olfactory epithelium and new axons must find the proper glomerulus and synaptic targets (Beites et al., 2005). Of particular interest, both types of interneurons in the olfactory bulb, PG cells and granule cells, continue to be generated throughout life, and must integrate into the existing neuronal circuitry, without disrupting ongoing function (Lledo et al., 2006). This occurs in all species studied, including humans (Bedard and Parent, 2004; Curtis et al., 2007; Maresh et al., 2008).

3. Adult Neurogenesis

The olfactory system is one of only two areas of the mammalian brain to exhibit continuing neurogenesis in the adult (Figure 2). The other, the dentate gyrus (DG) of the hippocampal formation, is important for learning, memory, and mood regulation. In the DG, stem cells reside in the subgranular zone (SGZ) and give rise to neuroblasts which become granule cells in the overlying granule cell layer (GCL) (Ming and Song, 2005). In the olfactory system, however, cells are born in the SVZ lining the lateral ventricles and then migrate up to 5mm (in mice) along a well-delineated pathway, the rostral migratory stream (RMS) into the olfactory bulb, where they differentiate into granule cells or PG cells (Alvarez-Buylla and Garcia-Verdugo, 2002; Lledo et al., 2006). The vast majority, about 95%, of the new neurons in the olfactory bulb differentiate into granule cells (Lledo and Saghatelian, 2005). The minority that differentiate into PG cells, however, form all of the molecular and morphological subtypes of PG cells identified (Bagley et al., 2007; Whitman and Greer, 2007b; Batista-Brito et al., 2008; Brill et al., 2008). In the early postnatal period, there are additional migratory pathways from the SVZ of GABAergic cells into other forebrain regions, including cortex, striatum and nucleus accumbens (Inta et al., 2008).

3.2 Adult Neurogenesis in Primates

The prevalence of adult neurogenesis in the subventricular zone of macaque monkeys, and the migration of neuroblasts into the olfactory bulb, was shown clearly by Kornack and Rakic (2001). Because of the extended length of the lateral olfactory tract, peduncle, in primates, neuroblasts migrated for distances of up to 2cm. BrdU labeled cells did not appear in the olfactory bulb until at least 75 days post-injection, consistent with the long migratory path from the subventricular zone to the olfactory bulb via the rostral migratory stream. A proliferative population of cells is found in the subventricular zone of the human (Sanai et al., 2004; Quinones-Hinojosa et al., 2006). While cells with a migratory phenotype were found, evidence for the presence of a rostral migratory stream was lacking. Curtis et al. (2007) also reported on the organization of ongoing neuroblast generation in the subventricular zone of humans, and moreover that a rostral extension of the lateral ventricle through the lateral olfactory tract/peduncle was accompanied by a rostral migratory stream. The presence of a rostral migratory

stream in the human was contested by Sanai et al. (2007) who argued that migratory neuroblasts within a well defined migratory stream were not apparent in the data from Curtis et al. (2007). More recently, Kam et al. (2009) sought to refute the concerns raised by Sanai et al. (2007) with a more detailed analysis of the cellular organization in the human migratory stream. In several respects, the organization appears comparable to that of the subventricular zone leading to the notion that this may be more a rostral extension of the primary proliferative zone rather than the well defined migratory pathway described in other species. In the more widely studied rodent migratory stream chains of double-cortin labeled neuroblasts are evident (e.g. Whitman et al., 2009). A comparable organization of neuroblast chains was seen in the macaque rostral migratory stream (Kornack and Rakic, 2001), but clear evidence in the human is lacking.

While the status of an intact rostral migratory stream in the human olfactory system may continue to be debated (Gould, 2007), there appears a wider consensus that newly differentiated neurons are found in the adult human olfactory bulb, even among the elderly. Doublecortin positive cells with both migratory and immature granule cell morphological features are evident throughout the human olfactory bulb (i.e., Maresh et al., 2008). Similarly, indices of cell division, including Ki67 and PCNA, are found in the glomerular and granule cell layers of the adult human olfactory bulb and colocalize with neuronal markers (Bedard and Parent, 2004).

4. Stem Cells

Within the SVZ, GFAP (glial fibrillary acidic protein)-expressing astrocyte-like cells function as neural stem cells (Doetsch et al., 1999; Garcia et al., 2004). These adult stem cells are derived from radial glia (Merkle et al., 2004; Merkle et al., 2007), which function as neural stem cells during embryonic development (Anthony et al., 2004). GFAP-expressing stem cells are termed “astrocyte-like” because they display many typical glial properties, but they also have unique functional characteristics between those of astrocytes and radial glia, particularly with regard to potassium channels (Liu et al., 2006). Stem cells, also known as B-type cells, divide slowly to give rise to transit-amplifying cells, the C cells, which then divide rapidly and give rise to neuroblasts, the A cells (Lois and Alvarez-Buylla, 1994), which express the migratory markers doublecortin (DCX) and PSA-NCAM. Stem cells exist not only in the SVZ, but also in the RMS, although in smaller numbers (Gritti et al., 2002; Hack et al., 2005; Alonso et al., 2008; Mendoza-Torresblanca et al., 2008).

Increasing evidence has shown that the SVZ is not a homogeneous region, but rather that precursors in different areas of the SVZ or RMS give rise to different subtypes of neurons in the olfactory bulb. Genetic fate-mapping with markers of different embryonic areas has shown that adult SVZ stem cells are derived from both the medial ganglionic eminence and the lateral ganglionic eminence (Young et al., 2007). Furthermore, stem cells derived from different embryonic populations reside in different portions of the SVZ and give rise to different types of interneurons in the adult olfactory bulb (Young et al., 2007). Using a virally-mediated method of marking specific radial glia and their progeny, Merkle and colleagues have shown which areas of SVZ produce each type of olfactory interneuron (Merkle et al., 2007). PG cells are generated predominately from stem cells in the RMS and anterior-medial areas of the SVZ, with TH cells arising from dorsal SVZ areas adjacent to cortex, calbindin cells from ventral areas, and calretinin cells from RMS and anterior medial SVZ. Superficial granule cells are derived primarily from dorsal regions of the SVZ, whereas deep granule cells are derived from ventral SVZ areas. Interestingly, calretinin granule cells come from the same regions as calretinin PG cells. Regardless of the age of the animal, the types of cells derived from each SVZ area remain the same, indicating that stem cells do not migrate and that they retain their inherent potential.

Consistent with the observation of the stability of stem cell subpopulations within the SVZ, when stem cells are transplanted to different regions within the SVZ, they retain the potential of their region of origin (Merkle et al., 2007). In non-SVZ environments, however, SVZ cells can have more diverse fates. When stem cells or committed neural progenitors are transplanted from SVZ to ectopic brain locations, they form two glial cell populations, with astrocytic or oligodendritic characteristics, rather than forming neurons (Seidenfaden et al., 2006). Transplanting cells from early postnatal SVZ into postnatal cerebellum (which is a neurogenic and gliogenic environment) leads to the formation of multiple glial cell types as well as cerebellar interneurons (Milosevic et al., 2008). Interestingly, when progenitors from the hippocampal subgranular zone are transplanted to SVZ, they migrate along the RMS and differentiate into olfactory interneurons, including TH-positive dopaminergic interneurons, a fate never seen in the hippocampus (Suhonen et al., 1996).

4.2 Proliferation

A number of factors have been implicated in the control of proliferation in the SVZ and RMS. Many of these factors also have important roles in embryonic development, such as sonic hedgehog (Shh), which is expressed in the SVZ and regulates cell proliferation by acting on both GFAP-expressing stem cells, and transit-amplifying cells (Palma et al., 2005). Other signaling pathways shown to affect proliferation include Eph/ephrin (Conover et al., 2000; Holmberg et al., 2005), Galectin-1, a carbohydrate binding protein (Sakaguchi et al., 2006), querkopf, a transcriptional co-activator necessary for self-renewal properties (Merson et al., 2006), beta-catenin, which functions to keep cells in a proliferative state (Adachi et al., 2007), p27KIP1, an inhibitor of cyclin-dependent kinase 2, and thus regulator of cell-cycle length (Doetsch et al., 2002; Li et al., 2009) and BM88/Cend1, a neuronal lineage marker implicated in control of cell-cycle exit (Katsimpardi et al., 2008). Pregnancy causes a transient increase in proliferation and neurogenesis, an effect mediated through increased levels of prolactin (Shingo et al., 2003). Through an unknown mechanism, prolonged seizures increase proliferation in the SVZ, cause an increase in the area of the RMS, and cause some cells to exit the RMS prematurely (Parent et al., 2002). GABA mediates a feedback mechanism between neuroblasts and stem cells. Neuroblasts release GABA non-synaptically, which activates GABA_A receptors on GFAP-expressing stem cells. This activation prevents progression through the cell cycle, limiting proliferation (Wang et al., 2003; Liu et al., 2005). There may be a further feedback loop involving glutamate signaling from astrocytes to neuroblasts (Platel et al., 2007; Platel et al., 2008).

4.3 The Neurovascular Niche

Endothelial cells are an important part of the stem cell niche, leading to the term neurovascular niche (Tavazoie et al., 2008). Throughout development, neurogenesis and angiogenesis are often stimulated by the same growth factors (Ward and Lamanna, 2004). When neural stem cells (NSCs) are co-cultured with endothelial cells, the endothelial cells secrete soluble factors which stimulate self-renewal of NSCs and inhibit differentiation. Subsequent removal of the endothelial cells results in an increase in the number of neurons produced, compared to cells that had not been cultured with endothelial cells (Shen et al., 2004). The influences between NSCs and endothelial cells are bidirectional, with co-culture stimulating vascular-endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) production and tube formation among endothelial cells (Li et al., 2006). Both *in vitro* and *in vivo*, VEGF increases proliferation in both the SVZ and SGZ. DCX-expressing neuroblasts express the receptor VEGFR2/Flk-1 (Jin et al., 2002). Pigment epithelium-derived factor (PEDF) is expressed by endothelial and ependymal cells in the SVZ and stimulates NSC self-renewal (Ramirez-Castillejo et al., 2006). *In vivo*, stem cells and their progeny in the SVZ are often in contact with blood vessels, frequently in areas that lack astrocyte and pericyte coverage, allowing small molecules from the blood to enter the SVZ (Tavazoie et al., 2008). In stroke models, neuroblasts

migrate to the area of infarct in close association with angiogenic blood vessels in the area (Ohab et al., 2006; Yamashita et al., 2006; Thored et al., 2007). They may be attracted by vascular production of Ang1 and SDF1 (Ohab et al., 2006).

5. Migration

After birth in the SVZ, neuroblasts organize themselves into chains as they join the RMS (Figure 3). Neuroblast migration in the SVZ occurs in various directions, but within the RMS they migrate in chains and 80% move rostrally, towards the olfactory bulb (Bolteus and Bordey, 2004). In adults, neuroblasts migrate tangentially through the RMS in chains of cells, associated closely with astrocytes (Lois and Alvarez-Buylla, 1994). When they reach the olfactory bulb, migrating neuroblasts detach from the chains and migrate radially to their final positions in the GCL or glomerular layer. Migration in the RMS is not uniformly in the rostral direction; cells can stop or even reverse direction. Migratory speeds are variable, but are on the order of 70-80 $\mu\text{m/hr}$ in slices (Nam et al., 2007). Unlike neuronal migration during embryonic development, RMS neuroblasts do not have a scaffolding of radial glia that mediates migration, either during tangential or radial migration. Recent evidence shows the migratory chains of neuroblasts are closely associated with blood vessels and suggests that the blood vessels may form a scaffold for migration in the RMS (Snapyan et al., 2009; Whitman et al., 2009) and within the olfactory bulb for radial migration into the laminae (Bovetti et al., 2007).

Within the SVZ, the flow of cerebral spinal fluid (CSF) may influence neuroblast migration. Ciliated cells within the lateral ventricle create a flow of CSF from caudal to rostral that allows for the development of a gradient of molecules secreted by the choroid plexus, in the caudal portion of the ventricle. In mice with defective cilia (Tg737^{orp} mutants), neuroblasts fail to migrate properly from the SVZ into the RMS, indicating that normal CSF flow is necessary for properly oriented neuronal migration (Sawamoto et al., 2006).

Many factors have been shown to influence migration in the RMS, but long-distance cues from the olfactory bulb are not necessary. Even after removal of the olfactory bulb, precursors continue to divide in the SVZ and migrate through the RMS. Without their target, however, neuroblasts accumulate in the RMS, and after several months cell death increases (Kirschenbaum et al., 1999). Similarly, in mice with lesions disconnecting the RMS from the olfactory bulb, neuroblasts continue to migrate from the SVZ to the point of the lesion, where they accumulate (Jankovski et al., 1998; Alonso et al., 1999). Activity from the olfactory bulb, however, can influence proliferation and survival along the pathway. When afferent activity to the olfactory bulb is removed via unilateral olfactory axotomy, there is an increase in cell death at all levels of the SVZ-RMS pathway, as well as an enhancement of proliferation, even on the contralateral intact side (Mandairon et al., 2003). Ablation of the main olfactory epithelium leads to an increase in proliferation of stem cells residing in the RMS, whereas olfactory enrichment causes increases in proliferation of putative stem cells in both SVZ and RMS (Alonso et al., 2008).

5.2 Migratory Environment

Local interactions between migrating cells and their environment are important in the development and control of the migratory pathway. Astrocytes in the RMS can modulate the speed of migrating neuroblasts. They express the GABA transporter GAT4, and can therefore regulate extracellular GABA concentration. Increasing extracellular concentrations of GABA reduce migratory speed (Bolteus and Bordey, 2004; Platel et al., 2008). Deletion of the *Vax1* homeobox gene leads to a severe disruption of the SVZ-RMS-OB pathway, with an expanded SVZ, no clear RMS, small olfactory bulb and disrupted populations of interneurons. This is likely the result of anatomical disruption of the pathway, since ependymal cells and astrocytes do not differentiate properly and *Vax1*-deficient cells can migrate normally when transplanted

into a wild-type environment. Thus, it is likely not a cell-intrinsic defect, but a defect of the migratory environment (Soria et al., 2004). Mice lacking inhibitor of DNA binding 2 (*Id2*) show normal proliferation in the SVZ, but neuroblasts in the RMS do not develop typical migratory morphology, and the entire RMS appears disorganized. Many of these neuroblasts then seem to prematurely differentiate into astroglia, rather than neurons (Havrda et al., 2008).

A number of cell surface receptors are important in proper chain migration and, interestingly, also in proper formation of the surrounding glial tubes. Integrin receptors on migrating neuroblasts interact with laminin in the extracellular matrix to guide migration (Emsley and Hagg, 2003). In the perinatal period, as the pathway matures, there is a switch in the subunits of integrin and laminin expressed. Blocking integrins inhibits cellular protrusions and translocation of migrating cells (Murase and Horwitz, 2002). Mice lacking $\beta 1$ integrin in the CNS have defects in chain migration. Neuroblasts do not form proper chains, the astrocytic tubes are disrupted, and migration is slowed (Belvindrah et al., 2007). A similar phenotype is seen in mice with a conditional deletion of the receptor tyrosine kinase ErbB4, which interacts with its ligands, the neuregulins. Both chain migration and glial tube organization are disrupted. Additionally in these mice, however, cells accumulate in the RMS within the olfactory bulb, indicating that they fail to switch from tangential to radial migration (Anton et al., 2004). Loss of NCAM also causes both migratory defects, leading to a small olfactory bulb, and disrupted organization of the astrocytes. Neuroblasts in the RMS express the polysialylated-form of NCAM (PSA-NCAM). *In vitro*, removing the PSA from NCAM causes chains to become less tightly packed (Chazal et al., 2000; Hu, 2000). In PSA-NCAM KO mice, migrating neuroblasts accumulate at the caudal pole of the RMS and fail to properly migrate into the olfactory bulb, particularly during early developmental periods, supporting the hypothesis that cell surface adhesion molecules are an important constituent of the migratory process (Cremer et al., 1994; Ono et al., 1994; Hu et al., 1996; Gheusi et al., 2000).

The formation of glial tubes is also disrupted in Bax knock-out mice, which have decreased programmed cell death. Although these mice have normal-sized olfactory bulbs, display normal olfactory behavior, and have no proliferation deficits, the architecture of the RMS is abnormal, with improper formation of glial tubes and premature exit and differentiation of neuroblasts (Kim et al., 2007). Because these mice lack the normal cell death in the olfactory bulb, new granule cells are not needed to replace dying ones. Therefore, some signal from the olfactory bulb may be missing, contributing to the disruption of the migratory pathway.

5.3 Guidance Cues

Many soluble molecules and their receptors, first discovered for their importance in axon guidance, also attract or repel migrating neuroblasts in the RMS. GDNF (glial derived neurotrophic factor) is an attractive guidance cue for cells from SVZ and RMS, although this effect requires NCAM expression (Paratcha et al., 2006). Netrin is expressed by mitral cells, and its receptors DCC and neogenin are expressed in or around the RMS. Blocking DCC alters the direction of protrusions on migrating cells (Murase and Horwitz, 2002). The repulsive cue Slit and its receptors Robo1-3 are also involved in RMS migration. Slit1 and Slit2 are expressed in the SVZ and RMS, as are their receptors Robo1 and Robo3/Rig1. Slit1-deficient mice have normal proliferation in the SVZ, but some cells migrate abnormally into the corpus callosum (Nguyen-Ba-Charvet et al., 2004). Slit is also a candidate molecule for the repulsive cue secreted by the choroid plexus, forming a gradient from caudal to rostral in the CSF (Sawamoto et al., 2006). Prokineticin 2 (PK2) is another potential secreted attractive cue. PK2 is expressed in the olfactory bulb and its receptors PKR1 and PKR2 are expressed on migrating neuroblasts and transit-amplifying cells in the SVZ and RMS (Ng et al., 2005; Puverel et al., 2009). PK2 knock-out mice have severely disrupted olfactory bulb architecture (Ng et al., 2005), although

it is not clear that this is solely an effect of disrupted RMS migration. Sonic hedgehog is also chemoattractive to neuroblasts from the SVZ, and may function to regulate the rate new neurons leave the SVZ (Angot et al., 2008).

5.4 Radial Migration

Little is known about the mechanisms that regulate the switch between tangential migration in the RMS and radial migration into the olfactory bulb layers. In the olfactory bulb, cellular chains dissociate as they exit the RMS and cells migrate individually into and through the GCL. Two extracellular matrix molecules, reelin (Hack et al., 2002) and tenascin-R, have been implicated as guidance cues and potential regulators of the migratory switch, and tenascin-R expression has been shown to be regulated by activity (Saghatelyan et al., 2004). Slit signaling may also play a role. *In vitro*, the absence of slit1 leads to a decrease in chain migration, in favor of dispersed migration, and Slit expression decreases as cells change from tangential to radial migration (Nguyen-Ba-Charvet et al., 2004). As noted above, in ErbB4 knock-out mice, neuroblasts accumulate in the RMS within the olfactory bulb, presumably because they cannot successfully switch to radial migration (Anton et al., 2004). These molecules are expressed uniformly along the rostral-caudal axis of the olfactory bulb, leaving open the question of why some neuroblasts exit the RMS in the caudal olfactory bulb, while others continue more rostrally. Neuroblasts within the olfactory bulb may use blood vessels as a scaffold during radial migration in the olfactory bulb, through interaction with the extracellular matrix and astrocytic endfeet (Bovetti et al., 2007).

6. Differentiation

Petreanu and Alvarez-Buylla (2002) defined five stages in the differentiation of adult-born granule cells. Stage 1 cells are migrating tangentially through the RMS, and have a very simple morphology with a prominent leading process and a small trailing process. These cells are present 2-7 days after retroviral infection in the SVZ. Stage 2 cells (days 5-7) are migrating radially through the GCL, also with a simple morphology. Stage 3 cells (days 9-13) appear to have stopped migrating and reached their final position in the GCL. They have a simple dendrite extending toward, but not past, the mitral cell layer. Stage 4 cells (days 11-22) have an extensive dendritic arbor, but no spines, and at stage 5 (days 15-30) cells have a mature granule cell morphology, with spiny dendrites. Using *in vivo* imaging of virus-labeled newborn neurons, Mizrahi (2007) has shown the dynamic nature of dendritic formation and development and the high levels of structural plasticity in new neurons.

Adult-born granule cells have a unique sequence of electrophysiological maturation, and do not appear to simply recapitulate embryonic developmental patterns of neuronal maturation. Stage 1 and 2 migratory cells have membrane properties similar to immature neuronal precursors, and do not show spontaneous postsynaptic currents. Cells at stages 3-5 show spontaneous inhibitory and excitatory postsynaptic currents, but only the most mature cells are able to fire action potentials. By stage 5 cells are electrophysiologically indistinguishable from mature granule cells. During development, granule cells can fire action potentials by postnatal day 2-4, even if they do not display synaptic currents. The delay in spiking ability relative to synaptic inputs is unique to the development of adult-born cells in olfactory bulb (Carleton et al., 2003). Adult-born PG cells with mature morphology also show membrane properties and currents similar to known types of mature PG cells (Belluzzi et al., 2003).

Environmental signals influence morphological development. In addition to its roles in proliferation and migration discussed above, GABA is also an important regulator of early dendritic growth in new olfactory bulb neurons. GABA stabilizes lamellipodia in dendritic growth cones and new dendritic segments (Gascon et al., 2006). Blocking GABA_A receptors destabilized the lamellipodia and led to shorter dendritic segments. These effects are mediated

by GABA-induced depolarization and Ca²⁺ influx. Although the signals mediating it are unknown, the phosphorylation of CREB appears to be important in the maturation of new neurons (Giachino et al., 2005). CREB phosphorylation increases in cells entering the olfactory bulb, then decreases after dendrite elongation and spine formation. *In vitro*, inhibiting CREB blocks morphological development of SVZ-derived neuroblasts.

Although it is now clear that different types of interneurons arise from progenitors in specific areas of the SVZ (Merkle et al., 2007; Young et al., 2007), the molecules specifying progenitor fate have only begun to be recognized. The transcription factor Pax6 is expressed by a subset of precursors in the SVZ and RMS, and is necessary for the formation of dopaminergic PG cells, but not granule cells or other types of PG cells (Hack et al., 2005; Kohwi et al., 2005). Er81, another transcription factor, may also be involved in specifying a dopaminergic phenotype (Saino-Saito et al., 2007). BMP4 may promote neuronal fate in the olfactory bulb (Liu et al., 2004). The zinc-finger transcription factor Sp8 is important in the generation of some of the GABAergic and calretinin-expressing subtypes of interneurons in the olfactory bulb (Waclaw et al., 2006).

6.2 Cell Death and Survival

Between 15 and 45 days after generation, approximately 50% of the newly generated granule cells die; the remaining cells can survive for periods up to a year (Petreanu and Alvarez-Buylla, 2002; Winner et al., 2002). The processes regulating death and survival are poorly understood, but activity plays an important role. In the adult, enriched odor exposure increases survival (Rochefort et al., 2002), presumably by increasing activity, whereas naris occlusion decreases survival of new granule cells (Mandairon et al., 2006), particularly between days 14-28 after birth when new neurons are differentiating and integrating into the circuit (Yamaguchi and Mori, 2005). Naris occlusion in the perinatal period also decreases the number of newborn granule cells, as well as their dendritic length and spine density, without affecting the pre-existing granule cells (Saghatelian et al., 2005). Similarly, destruction of the OE leads to decreased survival of neuroblasts, possibly through down-regulation of CREB phosphorylation. Transgenic mice lacking CREB also show reduced survival of new neurons (Giachino et al., 2005). While activity has been implicated in the survival of new neurons, it is not known if new neurons are specifically recruited to active areas, or if they are randomly distributed and then those not synaptically integrated and functionally active die.

Cholinergic inputs have been shown to affect survival of new cells in the olfactory bulb, but results are somewhat conflicting. Lesions of the cholinergic forebrain decrease the number of new neurons in the GCL and increase the number of apoptotic cells (Cooper-Kuhn et al., 2004). Systemic administration of an acetylcholinesterase inhibitor increases survival of new cells in the olfactory bulb four weeks after BrdU administration, with no effect on proliferation in the SVZ (Kaneko et al., 2006). Chronic nicotine exposure, however, decreases the number of newborn granule cells, and mice lacking the $\beta 2$ nicotinic receptor subunit have an increased number of new neurons (Mechawar et al., 2004). There is thus an overall pro-survival effect of cholinergic signaling, but an anti-survival effect of $\beta 2$ signalling. Newborn neurons in the GCL express a variety of acetylcholine receptors, including the $\alpha 7$, $\beta 2$, m1, and m4 subunits (Kaneko et al., 2006). Noradrenergic signaling has also been implicated in survival of new cells in the olfactory bulb (Bauer et al., 2003; Veyrac et al., 2005) and noradrenergic fibers have been shown to remodel in response to sensory deprivation (Gomez et al., 2006), suggesting a possible mechanism for involvement in the sensory dependent survival of new cells.

Olfactory learning influences both survival and placement of new neurons. Mice required to learn an olfactory discrimination task during the usual time of peak cell death (15-30 days after BrdU injection) show an increase in survival of new granule cells. Interestingly, the increases

in survival are concentrated in the area of the olfactory bulb responsive to the non-reinforced odor. Mere exposure to the odorants, without the learning paradigm, had no effect on granule-cell survival (Alonso et al., 2006). Increased survival of new granule cells is also seen with a go-no go discrimination task, and the effects vary based on the timing of the learning. The effects of learning on survival are most pronounced among cells in the deep GCL (Mouret et al., 2008).

7. Synaptic Integration

A leading question in the adult neurogenesis field has always been: how do new neurons synaptically integrate into the circuit without disrupting ongoing function? There is a variety of evidence that new neurons are synaptically integrated. Transynaptic transport from a mitral cell into a BrdU labeled PG cell has been demonstrated (Carlen et al., 2002). New granule cells with mature morphologies display spontaneous synaptic potentials, including two distinct glutamatergic inputs with different kinetics (Carleton et al., 2003). Among new PG cells, a small proportion display spontaneous excitatory synaptic currents, and a larger proportion respond to stimulation of the olfactory nerve (Belluzzi et al., 2003; Grubb et al., 2008). Neuroblasts at all stages of maturation, including migratory cells, express functional GABA receptors (Belluzzi et al., 2003; Carleton et al., 2003; Wang et al., 2003; Bolteus and Bordey, 2004), but these likely respond to extrasynaptic GABA. In PG cells, despite functional GABA receptors at all ages, no responses to glutamate were evident until 4 weeks after generation in the SVZ (Belluzzi et al., 2003).

Using synaptic markers and electron microscopy, we recently showed that synaptic integration of granule cells occurs in two stages. New granule cells first receive axodendritic synapses from centrifugal fibers and/or axon collaterals of mitral and tufted cells on their soma and basal dendrites in the GCL. These connections are formed as early as 10 days after birth in the SVZ, before dendritic elaboration in the EPL. Later, beginning at 21 days, reciprocal dendrodendritic synapses form in the EPL (Whitman and Greer, 2007a). Since the only output of granule cells is through inhibitory dendrodendritic synapses in the EPL, the initial formation of basal synapses provides a mechanism for new neurons to receive information about the network before contributing to it. It also allows higher brain regions to influence maturation and survival. Similar results were recently reported by Kelsch et al. (2008). New neurons integrating into a functioning circuit thus “listen before they talk” (Whitman and Greer, 2007a; Kelsch et al., 2008).

Additional evidence for synaptic integration comes from the observation that adult-born neurons express immediate-early genes in response to novel odors (Carlen et al., 2002; Magavi et al., 2005). The response of the population of adult-born granule cells is greater than that of the mature granule cells. Moreover, familiarizing mice with the test odors increases the response of adult-born cells, while the response of the preexisting cells decreases. Exposure to or familiarization with odors does not effect survival of new granule cells, so the increased responsiveness is not due to increased survival (Magavi et al., 2005). Immediate early gene expression in granule cells is heavily influenced by centrifugal input (Sallaz and Jourdan, 1996), so may therefore not reflect dendrodendritic circuits with mitral cells, but instead earlier inputs from centrifugal fibers.

Recent work using a PSD-95 viral vector has shown that new PG cells form dendrodendritic synapses with mitral and tufted cell dendrites, and that they continue to modify their synaptic connections after reaching morphological maturity. Additionally, olfactory input accelerated development of new PG cells and increased synaptogenesis (Livneh et al., 2009).

8. Adult versus Developmental Neurogenesis

Is adult neurogenesis simply a continuation of the embryonic developmental process? Adult and neonatal neurogenesis contributes different populations of granule cells, suggesting that adult neurogenesis may be functionally distinct from embryonic and perinatal development. Cells born in the early postnatal phase are born in both the SVZ and within the olfactory bulb, and are found primarily in the outer parts of the GCL. Adult-born cells are more likely to be deeper in the GCL (Lemasson et al., 2005). As discussed above, deep granule cells interact primarily with the lateral dendrites of mitral cells, whereas superficial granule cells preferentially interact with the lateral dendrites of tufted cells. The differing positions of the developmentally-generated and adult-generated granule cells lead to the intriguing hypothesis that they may be involved in different circuits. Furthermore, although half of adult-born granule cells die within six weeks of their birth, granule cells born in the postnatal period almost all survive into adulthood. Early olfactory experience increases the number of granule cells born in the neonatal period, but has no effect on adult neurogenesis (Lemasson et al., 2005). Additionally, during the first three postnatal weeks there is significant development of the migratory pathway between the SVZ and olfactory bulb, from a diffuse collection of migrating cells to the well-defined pathway of neuroblast chains associated with glial tubes (Pencea and Luskin, 2003; Peretto et al., 2005; Law et al., 1999).

Approximately 10,000 cells per day are estimated to migrate to the olfactory bulb via the RMS (Lledo and Saghatelian, 2005), but the contribution of adult-born cells to the total population of interneurons remains controversial. In vivo imaging gives an estimate of a turn-over rate of ~3% per month for PG cells in the adult (Mizrahi et al., 2006). This is lower than other estimates, and may be due to methodological reasons involving the transgene used to identify the cells. Recently, using a genetic fate-mapping technique that labels all adult-born neurons, Ninkovic et al. (2007) suggested that the proportion of adult-born granule cells reaches a plateau, whereas there is continuous addition of PG neurons. The results for PG cells are difficult to interpret, however, since they only looked at NeuN-expressing PG neurons, and NeuN is expressed only in a subpopulation of PG cells, not in all PG cells. Using a similar technique, but with a nestin promoter instead of a GLAST promoter, Lagace et al. (2007) showed continuous addition of both granule and PG cells. Genetic ablation of the majority of adult-born neurons leads to severe decreases in granule cell number, particularly in the deep granule cell layer, suggesting that nearly all deep granule cells, and approximately half of superficial granule cells, are replaced during the life of the animal (Imayoshi et al., 2008).

9. Functional Significance

The functional significance of adult neurogenesis in the olfactory bulb is unclear. Genetic ablation of adult-born cells, with a resulting decrease in granule cell number, does not cause any deficits in olfactory discrimination or acquisition of olfactory associated memories, at least in the tested paradigms (Imayoshi et al., 2008). Olfactory enrichment increases neuronal survival and improves odor memory (Rocheffort et al., 2002). NCAM-deficient mice, which have a migratory defect in the RMS leading to a significant reduction in number of granule cells, are impaired in olfactory discrimination, but show no deficits in olfactory detection or short-term olfactory memory (Gheusi et al., 2000). These animals are, however, able to learn an olfactory discrimination task when one of the odors is paired with a positive stimulus (Schellinck et al., 2004).

The increase in neurogenesis during pregnancy (Shingo et al., 2003) indicates that neurogenesis might be involved in maternal behavior. Mice heterozygous for the prolactin receptor have defects in maternal behavior (Lucas et al., 1998), and show a smaller increase in neurogenesis during pregnancy than wild-type mice (Shingo et al., 2003). Infusing a prolactin receptor

antagonist into the lateral ventricle of rats, where it could affect progenitors in the SVZ, also disrupts maternal behavior (Bridges et al., 2001). Female mice exposed to pheromones of dominant males show an increase in neurogenesis in both the SVZ and hippocampus, mediated by the prolactin receptor and LH receptor, respectively. Neurogenesis is necessary for female mate preference (Mak et al., 2007). Based on this evidence it is tempting to speculate that ongoing adult neurogenesis is important for not only the acquisition or discrimination of new odors important in survival, but also odor cues affecting species-specific behaviors, though further work is necessary to more fully develop these ideas.

10. Adult Neurogenesis in the Dentate Gyrus

In the dentate gyrus (DG) of the hippocampal formation, the other area of continuing adult neurogenesis in mammals, basic principles of maturation and synaptic integration are similar to those described above for the olfactory system, but there are important differences. New dentate granule cells (DGCs) born in the SGZ migrate only a short distance into the overlying granule cell layer (GCL), which they do within three days (Figure 4). They next extend dendrites and axons, with the axon reaching area CA3 of the hippocampus by 10 days. Dendritic spines are first formed at 16 days, and there is an increase in spine density until 56 days, when it plateaus (Zhao et al., 2006).

Morphologically mature adult generated DGCs are integrated into the hippocampal synaptic circuit. Staining for synapsin, a marker of presynaptic specializations, and electron microscopy show axosomatic (van Praag et al., 2002), axodendritic, and axospinous synapses (Toni et al., 2007). New DGCs display electrophysiological properties that are similar to those of mature neurons, fire action potentials, have spontaneous postsynaptic potentials, and respond following stimulation of the perforant pathway (van Praag et al., 2002). New dendritic spines often synapse on multi-synapse axonal boutons, indicating they may preferentially contact boutons already involved in a synapse (Toni et al., 2007).

Unlike in the olfactory bulb, the maturation of synaptic inputs onto new dentate granule cells follows the same pattern seen in development. At 3 days, new neurons are initially silent, but by 7 days begin to show slow GABAergic inputs, before the dendrites have developed spines. Fast glutamatergic transmission develops next, when cells have mature morphology and are electrically excitable, followed finally by fast GABAergic transmission (Esposito et al., 2005; Ge et al., 2006). There is a critical period, between 1 and 1.5 months after generation, when new neurons display enhanced LTP (Schmidt-Hieber et al., 2004; Ge et al., 2007), a time course similar to that seen during the perinatal developmental critical period. Induction of LTP increases proliferation of DG progenitors, and enhances survival of 1-2 week old DG neurons, but has no effect on neuronal differentiation (Bruehl-Jungerman et al., 2006). Recently, disrupted-in-schizophrenia 1 (DISC1), a schizophrenia susceptibility gene, has been implicated in migration, dendritic development, and synaptic integration of new DGCs. Surprisingly, disruption of DISC1 increases dendritic arborization and speeds maturation and synaptic integration (Duan et al., 2007).

Like in the olfactory system, GABA signaling in the DG plays an important role in neuronal development. Transit-amplifying cells in the DG receive GABAergic inputs, which cause depolarization and an increase in intracellular Ca^{2+} , and promote neuronal differentiation (Tozuka et al., 2005). When the depolarizing effects of GABA on young cells are blocked, newborn cells in the DG show no synaptic currents at 7 days, and reduced frequency and amplitude of synaptic currents at later stages. They also show decreases in dendritic length, branching and complexity, indicating that dendritic development and synaptogenesis are coupled. The depolarizing effect of GABA is required for synaptic integration in the DG (Ge et al., 2006).

Learning is important in survival of new dentate granule cells, but only learning tasks that require the hippocampus affect survival (Gould et al., 1999). The increases in survival only occur when learning happens at a specific “critical period” approximately one week after cell division (Epp et al., 2007). Individual differences in ability to learn a task correlate with survival of DGCs (Dalla et al., 2007). Ablating neurogenesis impairs spatial memory and contextual fear conditioning (Saxe et al., 2006; Imayoshi et al., 2008), but actually improved performance on some working memory tasks (Saxe et al., 2007). Reduced neurogenesis also impaired long-term retention of spatial memory as well as object recognition tasks (Jessberger et al., 2009).

In addition to effects on learning and memory, hippocampal neurogenesis is important in mood regulation. Chronic stress leads to decreases in hippocampal neurogenesis, an effect that can be reversed by antidepressant treatment (Duman, 2004). In fact, a variety of antidepressant treatments, including multiple classes of medications and electroconvulsive therapy, increase hippocampal neurogenesis, leading to the hypothesis that clinical depression may be a disorder of neurogenesis (Malberg et al., 2000; Duman, 2004; Dranovsky and Hen, 2006). Antidepressants have no effect on neurogenesis in the SVZ (Kodama et al., 2004). Neurogenesis in the SGZ is also enhanced by free access to a running wheel, which increases proliferation, or an enriched environment, which increases survival (van Praag et al., 1999b; van Praag et al., 1999a). Of interest, none of these interventions have an effect on olfactory neurogenesis (Brown et al., 2003).

Neurotrophic factors, particularly BDNF and VEGF, are important for the neurogenic mechanisms of antidepressants and environment (Rossi et al., 2006; Castren et al., 2007; Warner-Schmidt and Duman, 2007). VEGF signaling through the Flk1 receptor is necessary and sufficient for both the increased cell proliferation caused by antidepressants, and for their behavioral effects (Warner-Schmidt and Duman, 2007). As noted above, precursors in the SVZ also express the VEGF receptor Flk1 and proliferate in response to VEGF (Jin et al., 2002), yet they show no response to antidepressant administration. The mechanisms by which antidepressants lead to increases in neurotrophic factors are unknown, and may be localized. There are clearly important differences in the control of proliferation and survival between the two neurogenic regions, as might be expected given their differing functions.

11. Conclusions and Future Directions

There is a great deal of interest in harnessing the power of adult neurogenesis to replace neurons lost to injury or neurodegenerative disease. In stroke models, progenitors from the SVZ can migrate to areas of injury and differentiate into neurons (Yamashita et al., 2006). The interaction with blood vessels seems especially important in guiding neuroblasts to ischemic areas (Ohab et al., 2006; Yamashita et al., 2006; Thored et al., 2007). VEGF-overexpressing mice show greater functional recovery, and increased neurogenesis in the SVZ and at the ischemic border after infarct (Wang et al., 2007). As a consequence, there is a developing literature on the potential of neurogenesis in stroke recovery (reviewed in Chopp et al., 2007).

Since the recognition of continuing adult neurogenesis, much progress has been made in understanding its control and function, but many important questions remain. We still do not understand the functional significance and evolutionary advantages of adult neurogenesis, in either olfactory bulb or hippocampus. Nor do we understand why progenitors in the SVZ and SGZ continue to proliferate and produce new neurons for the olfactory bulb and hippocampal formation, to the exclusion of other brain regions. While there is evidence to suggest that in the olfactory bulb ongoing neurogenesis may provide for the replacement of interneurons lost through programmed cell death, the signaling mechanisms underlying this process are only a matter of speculation. The role of aging, both of the organism and the progenitor/stem cell,

has not been fully examined, but seems likely to provide new clues about age-related declines in both olfactory ability and hippocampal mediated behaviours. Finally, while all will agree that therapeutic strategies built upon stem cells offer great hope, we do not know if these unique populations within the SVZ and SGZ can be rerouted and reprogrammed to functionally replace neurons lost to injury or disease.

Thus, while much remains to be done, and surely the horizon will continue to recede, work of the past several decades has now shown clearly that developmentally finite capacity for plasticity set down by Ramon y' Cajal was in error. The CNS is capable of profound ongoing structural and functional plasticity; we need only to ask the right questions in order to recognize it when it occurs.

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Glossary

Abbreviation List

SVZ

subventricular zone

RMS

Rostral Migratory Stream

OB

olfactory bulb

SGZ

subgranular zone

OR

	odorant receptor
OSN	olfactory sensory neuron
MCL	mitral cell layer
EPL	external plexiform layer
PG	periglomerular
GCL	granule cell layer
AON	anterior olfactory nucleus
DG	dentate gyrus
GFAP	glial fibrillary acidic protein
DCX	doublecortin
NCAM	neural cell adhesion molecule
NSC	neural stem cell
VEGF	vascular-endothelial growth factor
BDNF	brain-derived neurotrophic factor
CSF	cerebral spinal fluid
PK2	Prokineticin 2
DGC	dentate granule cell
DISC1	Disrupted-In-Schizophrenia 1

Figure 1. Cellular Organization of the Olfactory Bulb

Schematic of the primary cellular organization of the olfactory bulb. Subpopulations of olfactory sensory neuron axons, shown in red, blue, and purple, innervate specific glomeruli based on odor receptor expression. The projection neurons, mitral and tufted cells, extend a single apical dendrite which arborizes within one glomerulus, and several lateral dendrites in the external plexiform layer. In the glomerulus, OSN axons make excitatory synapses onto the apical dendrites of mitral/tufted cells, as well as onto the periglomerular cell dendrites. Intraglomerular circuits also include reciprocal dendrodendritic synapses between the mitral/tufted cell dendrites and the periglomerular cell dendrites. The other primary population of interneurons, granule cells, have their somata located in the granule cell layer and an apical spiny dendrite that arborizes in the external plexiform layer, where they establish reciprocal dendrodendritic synapses with the secondary or lateral dendrites of mitral/tufted cells. Centrifugal axons distribute across the olfactory bulb laminae. The rostral migratory stream provides a continuous addition of new neuroblasts, which differentiate into granule and periglomerular cells. ONL, olfactory nerve layer; GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; IPL, internal plexiform layer; GCL, granule cell layer; RMS, rostral migratory stream; OSN, olfactory sensory neuron; PG, periglomerular cell, M, mitral cell; Gr, granule cell MNB, migrating neuroblast.

Figure 2. Adult Neurogenesis

Schematic of neurogenic regions of the mouse brain and developmental stages of new interneurons in the olfactory bulb. In the dentate gyrus, neuroblasts are born in the subgranular zone and migrate into the overlying granule cell layer, where they differentiate into dentate granule cells. Neuroblasts born in the SVZ migrate through the RMS using a unique form of migration, tangential chain migration. In the olfactory bulb, neuroblasts migrate radially into the granule cell layer and glomerular layer and differentiate into granule cells and periglomerular cells. Granule cells first receive synapses on their basal dendrites, as their apical dendrites grow into the external plexiform layer. They then elaborate an extensive apical dendritic arbor and form spines and reciprocal synapses with the dendrites of mitral and tufted cells. DG, dentate gyrus; CC, corpus callosum; Ctx, cortex; SVZ, subventricular zone; RMS, rostral migratory stream; OB, olfactory bulb.

Figure 3.

Stem cells in different areas of SVZ give rise to specific types of neurons. Stem cells within the RMS and in anterior medial areas of SVZ form most new PG cells and calretinin-expressing PG and granule cells. Dorsal regions adjacent to cortex give rise to TH+ (dopaminergic) PG cells and superficial granule cells. Deep granule cells and calbindin-expressing PG cells come from ventral SVZ. CC, corpus callosum; Ctx, cortex; SVZ, subventricular zone; RMS, rostral migratory stream; OB, olfactory bulb; TH, tyrosine-hydroxylase; CR, calretinin; CB, calbindin.

Figure 4. Migration in the RMS

A: Overview of the path of the RMS from the lateral ventricle to the olfactory bulb. DCX⁺ neuroblasts are labeled. B: Magnification of the RMS, showing the chains of DCX⁺ neuroblasts (green), GFAP⁺ astrocytes (red), and nuclei (stained with DRAQ5, a nuclear marker) (blue). Scale bar in A equals 1mm and in B equals 50 μ m. LV: lateral ventricle; Ctx: Cortex; RMS: rostral migratory stream; OB: olfactory bulb; D: dorsal; V: ventral; C: caudal; R: rostral.

Figure 5. Hippocampal Neurogenesis
Schematic diagram of dentate granule cell maturation. Cells proliferate in the subgranular zone (SGZ) and migrate into the overlying granule cell layer within 3 days. By 10 days they extend dendrites into the molecular layer and an axon to CA3. Dendritic spine formation begins at 16 days, and increases in density to 56 days, when it plateaus. ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone. Modeled after: (Schmidt and Duman, 2007).