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Brain Size and Limits to Adult Neurogenesis

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Abstract

The walls of the cerebral ventricles in the developing embryo harbor the primary neural stem cells from which most neurons and glia derive. In many vertebrates, neurogenesis continues postnatally and into adulthood in this region. Adult neurogenesis at the ventricle has been most extensively studied in organisms with small brains, such as reptiles, birds, and rodents. In reptiles and birds, these progenitor cells give rise to young neurons that migrate into many regions of the forebrain. Neurogenesis in adult rodents is also relatively widespread along the lateral ventricles but migration is largely restricted to the rostral migratory stream into the olfactory bulb. Recent work indicates that the wall of the lateral ventricle is highly regionalized with progenitor cells giving rise to different types of neurons depending on their location. In species with larger brains, young neurons born in these spatially specified domains become dramatically separated from potential final destinations. Here we hypothesize that the increase in size and topographical complexity (e.g. intervening white matter tracts) in larger brains may severely limit the long-term contribution of new neurons born close to, or in, the ventricular wall. We compare the process of adult neuronal birth, migration, and integration across different species with different brain sizes, and discuss how early regional specification of progenitor cells may interact with brain size and affect where and when new neurons are added.

GRAPHICAL ABSTRACT

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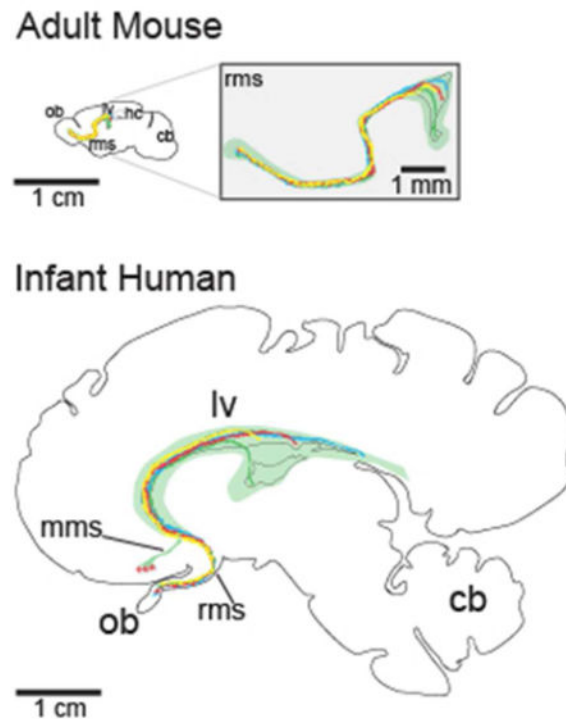
CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

The authors take responsibility for the accuracy of how the data presented and discussed. MFP, SFS, and AAB wrote the original article and JV, MFP, AAB contributed to edits and graphics, prepared by SFS. MFP and SFS contributed equally to this manuscript.

We discuss current work on adult neurogenesis across several species and propose that the tremendous increase in brain size between these species has significantly influenced the manner in which newly born neurons are able to contribute to adult brain circuits. This graphic illustrates the dramatic increase in distances that young neurons must migrate within the rostral migratory stream (RMS) in the human brain compared to the mouse brain; such changes may limit the circuits able to receive new neurons and the duration of neurogenesis through life.



Historical Perspective

In his book *Degeneration and Regeneration of the Nervous System*, Ramon y Cajal wrote that: “*In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated*” (Ramon y Cajal, 1928). Following Cajal’s identification of nerve cells as independent units of brain circuits, it became deeply established in the neurosciences, as well as in the general public, that no new neurons are added to the brain once fetal development is complete. This dogma persisted for most of the 20th century until [^3H]-thymidine became available for cellular birth dating. The incorporation [^3H]-thymidine into dividing cells was used in conjunction with Nissl staining to identify newly born cells with neuronal morphology. Work using this approach suggested that new neurons are born in multiple brain regions in adulthood. The regions where labeled cells were found included the cortex of the rat, the granule cell layer of the hippocampal dentate gyrus in the rat and the cat (Altman, 1963), and the rat olfactory bulb (OB) (Altman, 1967; Bayer and Altman, 1975). Subsequent ultrastructural studies supported the idea that the adult rat dentate gyrus and OB contain young neurons (Kaplan and Hinds, 1977). The interpretation of these results was questioned for several reasons: (i) the possibility that

[³H]-thymidine labelling was not in new neurons but in closely-adjoint proliferative glial cells, (ii) whether the radioactive-labeling (relatively few grains per cell) was sufficient to reflect true cell division, and (iii) that the putative labeled cells could have incorporated [³H]-thymidine due to DNA repair (Rakic, 1985, 2002a). While controversial, this initial work was the first evidence for adult incorporation of new neurons in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and the OB, sites which have been confirmed in subsequent studies (reviewed in Fuentealba et al., 2012; Yu et al., 2014).

Renewed interest in adult neurogenesis came from independent studies in songbirds, a model organism to study vocal learning (Thorpe, 1954; Nottebohm, 2004). Seasonal changes in the size of a key region of the song control pathway, the high vocal center (HVC), were found to correlate with changing levels of testosterone (Nottebohm, 1981). Short survivals after [³H]-thymidine exposure revealed the presence of dividing cells within the ventricular zone (VZ) on the walls of the lateral ventricles (Fig. 1). With longer [³H]-thymidine post-labeling intervals, labeled neurons were found in the HVC (Goldman and Nottebohm, 1983). Further work using electrophysiology confirmed the neuronal identity of the labeled cells (Paton and Nottebohm, 1984). New neurons were found to synaptically integrate within the HVC (Paton and Nottebohm, 1984; Burd and Nottebohm, 1985) and send projections to the distant nucleus robustus archistriatalis (RA) (Alvarez-Buylla and Kirn, 1997). The amount of adult neurogenesis in birds correlates with seasonal and hormonal patterns, and with complex experiences, suggesting a possible functional role in plasticity and/or learning (Barnea and Nottebohm, 1994; Nottebohm et al., 1994; Alvarez-Buylla and Kirn, 1997; Nottebohm, 2004). This work clearly demonstrated that the newly added neurons can become part of functional circuits in the adult brain, and are involved in an ongoing process of neuronal replacement (Nottebohm, 2004). Early investigators assumed that the progenitor cells for adult neurogenesis would be simple and undifferentiated, possibly cells retained from fetal development (Altman, 1969), but work in songbirds demonstrated that this is not the case. Radial glia (RG) cells in the adult songbird VZ (Fig. 2) were found to incorporate [³H]-thymidine and their division correlated with the production of young neurons, providing the first evidence that these cells are the adult neural stem cells (NSCs) (Alvarez-Buylla et al., 1990a). These and other studies using birds provided several levels of evidence for adult neurogenesis including the identification of proliferating neuronal progenitors, electrophysiological and ultrastructural identification of the new neurons, and a possible functional importance for their integration into established adult circuits.

The challenge of adding new neurons

The addition of new neurons into an adult network requires the coordination of cell division, migration, maturation, and integration into existing circuits. To begin, progenitor cells must be maintained for extended periods of time past embryogenesis into adulthood to generate new neurons. This continued proliferation in the adult brain must be regulated, as the presence of dividing NSCs into adulthood has been proposed as a possible source for brain tumors (Jacques et al., 2010; Alcantara Llaguno et al., 2011; Cuddapah et al., 2014). Next, young neuroblasts need to migrate varying distances based on their birthplace using cues to guide them to their final destination (Rousselot et al., 1995; Lim et al., 1997; Wu et al., 1999; Hack et al., 2002; Bolteus and Bordey, 2004). The distances that separate sites of

origin from destinations in the juvenile and adult brain result in migratory routes that (i) are orders of magnitude longer than in the embryo, when the brain is relatively small, (Figs. 3, 4), and (ii) contain more complexities, such as extensive vascularization, increasing regions of white matter, and a very dense network of mature dendrites, axons and synapses. Once the young neurons complete this journey, they must begin the process of integration into fully functional networks, without deleterious effects on the working of these circuits (Nottebohm, 2004; Song et al., 2005; Lazarini and Lledo, 2011). We suggest that amidst these challenges, one of the most important restrictions to widespread adult neurogenesis is brain size. Given the early regional specification of NSCs in development, the increased migration requirements on young neurons and the changes in the architecture of neurogenic zones in a larger brain may impose strict limitations for the delivery of neurons to many brain regions. These structural constraints may also lead to variability in adult neurogenesis between species.

Adult neurogenesis in species with different brain sizes

Adult neurogenesis in the V-SVZ has been described in greatest detail in species with small brains like rodents, birds, and reptiles, making it difficult to evaluate the influence of brain size on this process. Species with larger brains (especially humans) are more technically challenging to study, which greatly limits our ability to accurately ascertain the presence of adult neurogenesis. In this section we will evaluate the evidence for adult neurogenesis and its unique features in several species with brains of different sizes (Figs 1, 2). We will consider humans and primates alongside other mammals where more experimental data are available.

Reptiles—In the adult reptile brain, many new neurons are born and migrate to brain regions throughout the telencephalon; however, most reptiles where this process has been identified have very small brains (Gonzalez-Granero, et al., 2011). In the adult lizard VZ, proliferating RG cells persist, suggesting that these cells function as progenitors (Yanes et al., 1990; Font et al., 2001). The generation of neurons from dividing RG has not been directly demonstrated by lineage tracing, but young migratory neurons can be found nearby, and the vast majority of [³H]-thymidine labeled cells in the VZ have characteristics of RG (Garcia-Verdugo, et al., 2002). Most young neurons migrate either a short distance along RG into regions near the VZ like the medial, dorsal, and lateral cortices, and the striatum, but some make the relatively long journey to the OB (Fig. 1) (Pérez-Cañellas and García-Verdugo, 1996; Font et al., 2001). Adult-born cells in lizards apparently differentiate into various types of mature neurons including cortical projection neurons (Peñafiel et al., 1996; Lopez-Garcia et al., 2002). The medial cortex is the reptile homologue to the mammalian dentate gyrus (Rodríguez et al., 2002; Kaslin et al., 2008; Kempermann, 2012). This region, which likely has a role in spatial navigation, receives many new neurons in adulthood from the VZ and may take as long as 2 weeks to migrate (Lopez-Garcia et al., 1988; Day et al., 2001; Rodríguez et al., 2002). Interestingly, VZ-derived neurons can also replace damaged neurons in the lizard medial cortex following chemical (Font et al., 1991, 1997; Ramirez-Castillejo 2002) or physical injury (Romero-Alemán et al., 2004). Newly born neurons in the lizard brain contribute greatly to the pallium; in the turtle brain, however, neuroblasts target

the OB and striatum in greater proportion (Pérez-Cañellas et al., 1997). It remains unclear to what extent adult neurogenesis in reptiles is part of a process of continuous brain growth, neuronal replacement or both. The above studies suggest that in reptiles, cells born in the walls of the lateral ventricles can reach many telencephalic structures. It will be interesting to determine to what extent, and in what brain regions, neurogenesis continues in reptiles with larger brains (e.g. in large species of Crocodilia) where target regions are further from the VZ.

Birds—As described by the early studies in songbirds, new neurons are born in the VZ in the walls of the lateral ventricles where proliferating RG persist. From this germinal zone, young neurons migrate widely into many structures of the telencephalon (Fig. 1). Neuronal dispersal has been best studied in canaries (Alvarez-Buylla and Nottebohm, 1988), where many of the cells are destined for the nearby avian striatum (previously known as the lobus parolfactorius). Pallial regions, including the HVC, also receive many new neurons. Interestingly, proliferation is most abundant in hot spots on the ventral VZ (Alvarez-Buylla, et al., 1988), facing the avian striatum and the border between hyperpallium and mesopallium (previously termed hyperstriatum and hyperstriatum ventralis, respectively). Adult neurogenesis has been found in several bird species, but as with reptiles, most of the brains are relatively small and there is variability between species. Canaries and other songbirds have large brains in relation to their body mass, but their absolute brain size is still small. In most birds, neurons need to migrate no more than a centimeter, at most, from their site of birth in the VZ to their final destination anywhere in the telencephalon. The amount of time it takes for this process to occur in canaries is approximately 2–3 weeks after the cells are born, based on [³H]-thymidine labeling (Alvarez-Buylla and Nottebohm, 1988). Although adult neurogenesis has been found in the forebrain of small parrots like budgerigars (Nottebohm, 1987), larger parrots have not been studied. Other birds where adult neurogenesis has been found include adult doves (Ling et al., 1997), chickadees (Barnea and Nottebohm, 1994), and chickens and quails (Nottebohm, 1985; Nottebohm and Alvarez-Buylla, 1993). During embryonic development, the zebra finch forebrain has a second layer of proliferating cells separated from the VZ, in what appears to be an avian version of a developmental sub-ventricular zone (SVZ) (Charvet and Streidter, 2009). Interestingly, this layer of proliferating cells is diminished, or possibly absent, in the adult (DeWulf and Bottjer, 2002). As we will discuss next, an expanded ventricular-subventricular zone (V-SVZ) for adult neurogenesis is a prominent feature in the developing mammalian brain and may have emerged as a place to generate the larger numbers of new neurons required to build larger brains. We next turn to mammals where, although adult neurogenesis is less widespread, we have an opportunity to compare adult neurogenesis at the V-SVZ between species with much greater brain size variability.

Mammals

Adult mammals also have neurogenesis along the walls of the lateral ventricle, similar to lizards and birds; however, the migratory routes of these young neurons are mostly restricted to a rostral migratory stream (RMS) that is directed to the OB. These restrictions in mammals may not only be a consequence of which adult circuits continue to receive new neurons, but may be influenced by the more complex brain structure. Mammals also have a

second primary site of adult neurogenesis away from the wall of the lateral ventricle in the dentate gyrus of the hippocampus. Unlike birds and reptiles, where new neurons in the medial cortex (the DG homolog) are born in the VZ, in mammals the progenitor cells for this region are away from the ventricle, in the SGZ. As we will discuss below, the presence of progenitors in the SGZ places them closer to the circuits that receive the new neurons. These new neurons migrate a much shorter distance than those born in the mammalian V-SVZ, and are therefore perhaps less affected by changes in brain size.

Mice—We will begin our survey of the unique features of mammalian V-SVZ adult neurogenesis in the relatively small brains of rodents, where recent advances have progressed most rapidly due to the availability of genetic tools. In the adult mouse, the primary precursors, also known as B1 cells, have many characteristics of astrocytes (Doetsch et al., 1999; Kriegstein and Alvarez-Buylla, 2009) and maintain epithelial properties of their predecessors which are RG (Merkle et al., 2004; Mercier et al., 2002; Mirzadeh et al., 2008). RG in the developing mammalian brain function as primary progenitors for neurons (Miyata et al., 2001; Noctor et al., 2001; Campbell and Götz, 2002; Weissman et al., 2003; Anthony et al., 2004). In adult mammals, most RG cells transform into parenchymal astrocytes perinatally. B1 cells retain an apical contact with the ventricular lumen like RG cells, but do not have contact with the pial surface, as many RG cells do (Fig. 2). Instead, most B1 cells have their cell body in the SVZ with end-feet on blood vessels, similar to that of many astrocytes. Therefore, the adult mammalian periventricular germinal zone includes ventricular and subventricular domains and this has led to the more recent denomination V-SVZ (Fuentelba et al., 2012). The apical-ventricular contact of B1 cells is surrounded by ependymal cells (E cells). E cells are multi-ciliated, epithelial cells that play a key role in CSF homeostasis and circulation, but also contribute to the regulation of B1 cell proliferation (Lim and Alvarez-Buylla, 1999; Gajera et al., 2010; Khatri et al., 2014). It has been suggested that B1 cells can divide to either self-renew or generate C cells (the transit amplifying, or intermediate progenitor cell), but the actual mode of B1 cell division in vivo remains unknown. C cells, in turn, give rise to A cells, the young migratory neurons, some of which continue to divide as they migrate away from the V-SVZ. (Lois and Alvarez-Buylla, 1994; Menezes and Luskin, 1994; García-Verdugo et al., 1998; Doetsch et al., 1999). A cells express doublecortin (DCX), a cytoskeletal-associated protein required for proper neuronal migration, as well as a polysialylated version of the neuronal adhesion molecule NCAM (PSA-NCAM). These neuroblasts move along each other using chain migration through the V-SVZ and then anteriorly along a structure called the rostral migratory stream (RMS) (Altman, 1969; Lois and Alvarez-Buylla, 1994). Neuroblasts in the RMS travel to the OB, where they mature primarily into granule cells (GCs) and some peri-glomerular (PGCs) interneurons. This journey ranges in distance from 3 to 8 mm depending on their site of birth (Doetsch and Alvarez-Buylla, 1996) and takes cells between 3–7 days (Lois and Alvarez-Buylla, 1994; Petreanu and Alvarez-Buylla 2002).

Other mammals—Despite broad similarities in sites of neuronal birth and migration in mammals, the architecture of the V-SVZ can vary considerably between species. Unlike in rodents, in many mammals including rabbits (Ponti et al., 2006), sheep (Brus et al., 2013b), and cows (Rodriguez-Perez et al., 2003), the adult V-SVZ contains regions with a hypo-

cellular gap layer that is largely devoid of cell bodies separating the ependymal cells from astrocytes. This hypo-cellular gap is a prominent feature of the adult human V-SVZ (Sanai et al., 2004) as we will discuss in further detail below; however, in most other mammals the V-SVZ also contains many chains of young neurons migrating to the OB. Whereas in rodents and humans the olfactory ventricle closes during development, the RMS of many adult mammals (e.g. rabbit, cat, sheep, and cow) contains an open olfactory ventricle with a prominent V-SVZ along it. In the young postnatal rabbit (Ponti et al., 2006), chains of migrating neurons extending into the neighboring parenchyma are present in a dorsolateral expansion of the V-SVZ (called the abventricular SVZ). While the rabbit V-SVZ has a GFAP+ glial meshwork, this is less prominent within the abventricular SVZ: in this region, neuroblasts are tightly associated with blood vessels and axonal processes. These parenchymal chains appear directed to cortex, though no specific target has been established, and suggest the possibility of additional migratory routes during the early postnatal period. The architecture of the RMS also varies considerably, even within species. In domesticated cats, when brain size is held constant, the RMS length and width are also consistent, whereas in different dog breeds where brain size is more variable, the length and width of the RMS are also more varied (Malik et al., 2012). In this study, the RMS was measured to be between 10–15 mm in cats and 20–30 mm in dogs, however migration rates and lineage tracing were not evaluated.

The migration and maturation rates of young neurons appear greatly protracted in species with larger brains. In the adult sheep, migration from the SVZ to the OB may take as long as one month (Brus, et al., 2013a, 2013b). This is compared to 3–7 days in mice that it takes for young neurons to make the journey from the V-SVZ to the OB (Rousselot, et al., 1995; Petreanu and Alvarez-Buylla 2002). Compared to mice, where the RMS is approximately 4 mm long, in the sheep it is ~20 mm long. If the cells migrate at a similar speed between the two species, it would take about 5 times longer for cells to make the journey from the proximal V-SVZ to the OB in the sheep compared to mice. Migrations are likely even longer in larger species taking into consideration that many cells originate from caudal the walls of the lateral ventricles in the caudal telencephalon. These studies suggest that despite the similarities of many key features of adult neurogenesis, the requirement for longer and more tortuous migration routes in larger brains may lead to dramatic differences in the kinetics of this process. The maturation of new neurons in the sheep brain also appears longer compared to mice. Mature BrdU+/NeuN+ cells are scarce in the adult sheep OB 3 months after BrdU injections and their total number keeps increasing up to 8 months post-BrdU (Brus et al., 2013b). This is compared to 2–3 weeks that it takes for new neurons to mature in mice (Petreanu and Alvarez-Buylla 2002). Therefore, both migration and maturation of new neurons destined for the OB take much longer in the larger brain of sheep compared to mice.

Humans and non-human primates—In primates the cortex has dramatically expanded (Fig. 1), in many cases accompanied by cortical tissue folding (gyrification) and higher cognitive function (Ghosh and Jessberger, 2013). Even in species with brains that have undergone this growth there is variability in brain size that is associated with differences in the anatomy of neurogenic sites and the perdurance of these proliferative regions. Interest in

studying adult human neurogenesis was stimulated by an early study using rare BrdU-treated adult brain samples (Eriksson 1998), where a few cells were identified in the V-SVZ that had incorporated BrdU. We next review the limited evidence for human V-SVZ neurogenesis, and then compare this with evidence from smaller non-human primate brains.

In the adult human brain, proliferation in the V-SVZ is scarce. Nonetheless, small numbers of cells cultured from intraoperative samples of the adult human V-SVZ can proliferate and generate immature neurons in vitro (Sanai et al., 2004). This study also found rare TUJ1, PSA-NCAM+ cells in the V-SVZ. More recent studies showed that DCX+ neuroblasts in the V-SVZ and the RMS of the adult human are extremely rare and only a small portion express proliferative markers (Wang et al., 2011). The numbers of DCX+ cells found in adults in this study were much lower compared to those observed at the fetal ages tested, in agreement with work from other groups (Bédard and Parent, 2004; Sanai et al., 2004). These studies also found only a few DCX+ neuroblasts in the olfactory tract and none in the OB. The inability to regularly birthdate human specimens has stimulated the development of new strategies, such as the use of carbon 14 (^{14}C) (Spalding et al., 2005). This approach takes advantage of the increased atmospheric levels of ^{14}C during the height of atomic bomb testing between the 1940s and the mid-1960s. Cells that were dividing during these years would be expected to have elevated levels of ^{14}C in their DNA. Work using ^{14}C birthdating also concluded that there is little to no postnatal neurogenesis in the adult human OB (Bergmann et al., 2012).

A study of the postnatal development of the human V-SVZ revealed many young neuroblasts immediately adjacent to the ependyma; these cells are mostly gone by two years of age (Sanai et al., 2011). This same layer adjacent to the ependyma in older humans is largely devoid of cell bodies and is referred to as the “hypocellular gap”. The decrease in migrating neurons in this region coincides with a reduction in proliferation. Similar to humans, adult macaques and marmosets also have a hypocellular gap layer next to the wall of the lateral ventricle (Sanai et al., 2004; Quiñones-Hinojosa et al., 2006; Gil-Perotin et al., 2009; Sawamoto et al., 2011) (Fig. 2). The emergence of this hypocellular gap in the V-SVZ could correlate with the disappearance of cells migrating to the OB in adulthood. However, this relationship has not been investigated, and we know that in humans there are other potential targets, in addition to the OB, for periventricular migrating young neurons present in infants.

In the infant human, a medial migratory stream (MMS) was identified containing many neuroblasts migrating in the medial prefrontal cortex. This collection of young neurons, not found in the mouse brain, or yet in other primates, appears to be destined for the ventral medial prefrontal cortex, an area important for social decision-making and risk processing (van den Bos and Güroglu, 2009; Schonberg et al., 2012). Novel migratory pathways may be more prevalent in brains with a protracted development or during the early postnatal period (as described above in rabbits).

The extent of continued neurogenesis in the adult non-human primate V-SVZ also remains in question. There is evidence for the adult production of new neurons in the V-SVZ of some non-human primates, and the V-SVZ in these species has unique features. In the adult marmoset brain the RMS does not appear as a continuous path with chains of migrating

neuroblasts, particularly within the olfactory tract (Sawamoto et al., 2011), though it was present in neonatal samples. In rhesus monkeys, a cell-dense region is present at the ventral anterior V-SVZ, termed the vfSVZ (Pencea et al., 2001; Rakic, 2002b), which is equivalent to the anterior V-SVZ in the mouse brain but is more expanded ventrally. An elaboration of the V-SVZ was observed in adult squirrel monkeys where it gives rise to two ventral extensions, a rostral and caudal expansion populated by PSA-NCAM+ Tuj1+ cells. They converge to form a unified RMS that is anteriorly directed to the OB (Bedard et al., 2002a). It would be interesting to test whether this caudal ventral extension serves as a shortcut to the longer dorsal route along the lateral ventricle.

Primate brains, including humans, provide a dramatic example of how brain size could influence the presence of neurogenesis in the adult. Migratory paths of young neurons to the OB greatly increase from infancy into adulthood (Fig 3). The minimum distance from the ventral anterior V-SVZ to the olfactory tract (OT) in the human brain at birth is about 12–15 mm, but cells must travel nearly the same distance again once they enter the tract to reach destinations in the main olfactory bulb. So the putative RMS in the human newborn is about 30 mm. Furthermore, cells could be born more caudally in the LV, which would easily double or triple the length of their total migration (Fig. 3). In the adult human brain all of these sizes are further increased, with the distance from the ventral anterior V-SVZ to the entrance of the OT measuring closer to 25–30 mm (Mikula et al., 2007). Once entering the OB, cells must migrate nearly the same distance again to reach most distal portions of the OB. The RMS in adult humans would therefore be 50–60 mm long if this migratory path was retained in the adult. In line with our hypothesis, these long distances imposed by bigger brains might create unique challenges to young neurons and ultimately limit their presence with age. As indicated above, rare, individual cells expressing markers of young migrating neurons and a clear leading process have been detected along this path (Nader et al. 2004; Wang et al., 2011). This raises the question of whether the rare lone-ranger neurons still make this very long journey in the adult human brain.

Fundamental questions remain regarding the duration and locations where adult neurogenesis persists in the human brain. While most studies support the presence of V-SVZ neurogenesis in the infant primate brain, there is little evidence for the presence of a significant number of new neurons in the V-SVZ of adolescent and adult human brains. However, significant growth of the brain occurs after infancy, exemplified in humans (Figs. 1, 3), and this could limit the contribution of neurons born in the V-SVZ to targets that become too distant. These conclusions must be tempered by the current limitations of our tools. Sample variability, particularly in adult ages, may be partially responsible for generating data that are difficult to compare directly. Advances in approaches and techniques will hopefully provide novel ways to study adult neurogenesis more consistently in humans.

Widening the search for adult neurogenesis

Different sites in mammals

Immunostaining for progenitor cell markers, and the expression of DCX and PSA-NCAM in young migrating neuroblasts (Brown et al., 2003; Couillard-Despres et al., 2005) have suggested that there may be additional brain regions where adult neurogenesis occurs.

Adult-born BrdU+ cells expressing markers of young neurons (such as DCX and TUJ1) have been reported in the adult rat neocortex and striatum (Dayer et al., 2005) and the adult rabbit striatum (Luzzati et al., 2006). BrdU+ cells have also been observed in the hypothalamus of adult mice, sheep, and voles (Fowler et al., 2002; Kokoeva et al., 2005, 2007; Migaud et al., 2010) and the amygdala of adult voles (Fowler et al., 2002, 2005). In the adult rodent neurogenic niche, the process of neuronal birth, migration, and maturation has been documented using not just marker expression and BrdU incorporation, but also genetic lineage tracing, retroviral labeling, ultrastructural characterization, and co-labeling with other cell-type markers. As these tools are not always available in all species, the expression of markers of young neurons is also used to explore new species in addition to new brain regions (Chawana et al., 2013; Patzke et al., 2013, 2014). However, it is important to keep in mind that each of these tools on their own has significant limitations. Some of the original criticisms of adult neurogenesis still apply: thymidine analogue-labeling can also be found in non-dividing cells and the timing and dosing directly affect the extent of labeling and the health of labeled cells. Furthermore, thymidine analogues can be incorporated into cells during DNA repair or DNA replication that does not accompany cell division (Rakic, 2002a, 2002b; Gould, 2007). In addition, the dosing and detection of BrdU are frequently variable between studies. The neuroblast marker, DCX, has been used as a proxy for evidence of active neurogenesis; however, both DCX and PSA-NCAM expression can persist in mature neurons (Knoth et al., 2010; Klempin et al., 2011; Kohler et al., 2011) and this expression is associated with features of plasticity and remodeling (Bonfanti, 2006; Bloch et al., 2011; Nacher et al., 2002, 2004, Vellema, et al., 2014). Work on novel adult neurogenic sites must be supported by fate mapping and lineage tracing studies to identify progenitors and mature, integrated adult-born neurons, as has been performed for the forebrain in songbirds and the V-SVZ-OB, and SGZ-DG in rodents.

Different sites in monkey

As in other species, alternative sites for adult neurogenesis have been suggested in primates, including the cortex (Gould et al., 1999; Cai et al., 2009; Fung et al., 2011), striatum (Bédard et al., 2002b), and the amygdala (Bernier et al., 2002; Zhang et al., 2009). Rare BrdU+ NeuN+ cells were found in the striatum of adult squirrel monkeys three weeks post-injection (Bédard et al., 2002b); however, a different study used expression profiling to demonstrate that most if not all striatal interneurons in macaque monkeys are made during gestation and found no evidence for BrdU-labeling in neurons in this region (Wang et al., 2014). Conflicting observations have also been made in the neocortex. In early adult macaque studies, BrdU labeling of NeuN+ cells was found in the prefrontal cortex, the inferior temporal lobe, and the striatum (Gould et al., 1999). These results contradicted studies in macaques that showed no [³H]-thymidine labeling (Rakic, 1985) or little to no BrdU incorporation (Kornack and Rakic, 2001; Koketsu et al., 2003) in neurons of the adult cortex, despite evidence of proliferation in the dentate gyrus. Koketsu, et al. did find rare BrdU+/NeuN+ cells (<0.01% of NeuN+ cells) and BrdU+/DCX+ cells in the frontal cortex, but the morphology and level of staining in these cells was different from those observed in the OB of juvenile monkeys. Thus the incorporation of new neurons in the primate cortex still remains uncertain; if present, the available evidence suggests that this is a rare phenomenon.

Different sites in humans

^{14}C labeling has been used to ask whether other human brain regions have adult-born neurons. A recent study found evidence for adult neurogenesis in the striatum (Ernst et al., 2014). Retrospective birth-dating was performed using tissue from patients who had received the thymidine analogue, IdU, for radiosensitization. IdU+/NeuN+ cells were found in the striatum of patients exposed to higher doses of this thymidine analog, contradicting other work suggesting that striatal interneurons are generated embryonically (Wang et al., 2014). In another use of ^{14}C birth-dating, glial and vascular cells, but not neurons, were shown to have significant turnover in brain tissue of patients who had ischemic stroke (Huttner et al., 2014). This study's finding of no neurogenesis in response to cortical injury in humans did not agree with other human studies (Jin et al., 2006; Martí-Fàbregas et al., 2010) or the finding of post-injury neurogenesis in rodents (Parent et al., 2002; Parent, 2003; Kaneko and Sawamoto, 2009; Magnusson et al., 2014). Although the use of ^{14}C birthdating is an innovative way to use existing brain bank material, additional validation of this approach as a method to evaluate the age of individual cells is necessary. Other processes, such as DNA damage or methylation could affect the extent of ^{14}C incorporation; DNA methylation levels, for example, are variable even within a sorted population of neuronal nuclei (Iwamoto et al., 2011). Despite how little is currently known about the accuracy of this approach, it represents a novel way to evaluate cellular age in postmitotic cells.

The study of human brain tissue is singularly challenging. The protocols used to prepare human samples can have high variability, and fixation methods are not standardized between brain banks or institutions. Issues also arise when considering the genetic and environmental individuality, lifestyle characteristics, and the clinical history (eg. epilepsy, tumor) of the tissue. Some of these experimental uncertainties could explain the difficulty in reaching a consensus over whether and to what extent adult human neurogenesis persists.

We next consider the growing data on the early regionalization of NSCs in germinal regions, and how this particular feature of development might interact with increasing brain size to limit adult neurogenesis.

Embryonic regional specification: possible limits on adult neurogenesis

The work we have reviewed suggests that adult V-SVZ neurogenesis may be less prevalent in larger brains. One possible explanation is that brain growth anatomically limits the ability of young neurons to move from different progenitor regions to their final destination. Neuronal diversity arises from differences in progenitor cell specification that is highly linked to the location within the developing and adult V-SVZ. Neural circuits, which require multiple neuronal types, recruit them from different pools of progenitors within these highly regionalized germinal niches. Building the brain, therefore, requires the eventual relocation of young neurons from their sites of production to their final destination.

Progenitor heterogeneity is established very early during the development of the neural tube (Puelles et al., 2000). Both spatial (dorsal-ventral and rostro-caudal) gradients of morphogens (secreted signaling molecules) and temporal patterning determine the types of neurons produced in specific locations. These signals are integrated for a given position and

transduced into differential expression of transcription factors that will direct the production of specific neuronal subtypes. The combinatorial expression of *Hox* genes divides the caudal neural tube along the A-P axis into the hindbrain segments called rhombomeres, and segments of the spinal cord (Keynes and Lumsden, 1990; Gavalas et al., 1998). In the spinal cord, progenitors have differential exposure to Shh based on their dorsal-ventral position, resulting in a variety of spinal cord neurons (Jessell, 2000). Establishment of these gradients of morphogens must happen when the CNS is very small. As the CNS grows, positional segmentation becomes fixed, however progenitor areas continue to expand as they pattern the development of the neuroaxis into the major CNS subdivisions. In the forebrain, this gene expression topography dictates not only the large pallial/subpallial division between the progenitor zones that will produce projection neurons and interneurons, respectively, but also more specific boundaries of structures that will emerge in the adult brain. These mechanisms of regional specification appear to be highly conserved in vertebrates (Macdonald et al., 1994; Bachy et al., 2001; Marshall and Goldman, 2002; Marín and Rubenstein, 2003; Puelles and Rubenstein, 2003; Kessaris et al., 2006).

In mice, the spatial organization established in the embryo appears to be preserved in the adult V-SVZ (Fig. 4). Regional specification during early development leads to a graded expression of transcription factors in B1 cells (Kohwi et al., 2005; Young et al., 2007; Sequerra, 2014). These cues segregate the V-SVZ into regions that produce different subtypes of OB interneurons depending on whether the progenitor cells are located on the septal, lateral, or dorsal wall of the lateral ventricle (Merkle et al., 2007). For example, superficial GCs and GABAergic tyrosine hydroxylase (TH)+ PGCs come from progenitors in the dorsal and cortical V-SVZ, while deep GC and GABAergic calbindin (CB)+ PGCs arise from the ventral V-SVZ. These regions can be further subdivided. In the anterior ventral V-SVZ alone, there are microdomains of B1 cells that produce four previously undescribed OB neuron subtypes (Merkle et al., 2014). Recent work indicates that regional B1 cell specification occurs during very early stages of forebrain development (Fuentelba et al., 2015). Therefore, progenitor cell parcellation, essential for creating diversity in the neuronal progeny, is established early in development and continues into the adult neurogenic niche. Although it has not been studied as extensively, regional restrictions likely also exist in the avian brain (Scott and Lois, 2007). Whether such spatial organization exists in the dentate SGZ of the rodent brain is under investigation (Li, et al.2013; Sugiyama et al., 2013; Bekiari et al., 2014).

How much of the spatial patterning of adult NSCs observed in rodents is conserved in larger and more complex primate brains? During embryonic development, many of the same transcriptional domains are present in primate brains as in mouse brains; however the exact territories of these domains and the subtypes of cells they produce are expanded (Reinchisi et al., 2012; Hansen et al., 2013; Ma et al., 2013) (Fig. 4). This creates a topographical challenge in linking germinal zones to the destinations where neurons might be needed as the brain grows during normal development (Fig. 3).

Shortening the migratory requirements through displaced progenitors

One method for dealing with the increase in size during development is to have adult germinal zones closer to the sites where the new neurons are required. A striking example of displaced progenitor cells is a greatly expanded fetal progenitor zone in primates called the outer V-SVZ. This region contains RG-like progenitor cells unanchored in the VZ, called outer RG cells (Hansen et al., 2010). The outer RG cells generate a large population of projection neurons and in humans this region may have grown in size to facilitate cortical expansion (Lui et al., 2011). To produce this additional layer of progenitors during development, human RG at the ventricle divide horizontally via a mechanism called mitotic somatic translocation (MST) (LaMonica et al., 2013; Ostrem et al., 2014). This is a process where the soma of the progenitor quickly jumps in the direction of the developing cortical plate, away from the ventricle, before dividing. This mode of cell division moves the progenitors closer to the target areas of cortex decreasing the migratory distances for young neurons.

Another example of progenitors that reside near where the neurons are required is the SGZ of the hippocampus. SGZ progenitors are developmentally derived from the ventricular wall, and eventually move closer to their target regions. The primary progenitors in the SGZ have astroglial characteristics and are known as radial astrocytes (Seri et al., 2001, 2004; Kriegstein and Alvarez-Buylla, 2009) based on their prominent radial process that traverses the granule cell layer, or Type I cells (Gage, et al., 1998; Kronenberg, et al., 2003). In the SGZ, radial astrocytes give rise to intermediate progenitors known as D cells, or type II progenitors (Seri et al., 2001, 2004; Filippov et al., 2003; Hodge et al., 2008). The type II progenitors in turn give rise to type III cells, young neurons that express DCX, prior to their final maturation in the granule cell layer of the DG. These processes occur within the SGZ, requiring only a short migration of the newly produced neurons from their site of birth into the granule cell layer of the DG.

For many neuronal cell types, radial displacement of progenitor cells alone is not sufficient to reduce the distance from sites of birth to final destination. Some neuronal precursors, such as those that generate cortical interneurons, are not radially linked to target areas; their progeny require long tangential migrations. In rodents, young migrating interneurons use fast migration speeds and long tangential migratory routes to go from the subpallium, the ventral source of most interneurons in the mouse brain, to their dorsal cortical destinations (Anderson et al., 1999, 2001; Wichterle et al., 2001; Marín et al., 2010). How large can the brain grow while maintaining a productive tangential migration mechanism to feed areas like the cortex with sufficient interneurons? The primate and human subpallium contains the ventral progenitor areas for these cells, but its organization is more complex with an outer layer of progenitor cells not observed in the mouse (Hansen et al., 2013). Some groups have even proposed that larger non-human primate and human brains may generate more interneurons by the addition of a neurogenic zone in the dorsal ventricular wall (Zecevic et al., 2005; Jakovcevski et al., 2011; Radonji et al., 2014); this idea is still under debate (Molnár and Butt, 2013). There is also recent data that in both rabbit and human brains, the birth of new neurons persists late into gestation (Malik et al., 2013; Arshad et al., 2015); such protracted neurogenesis could provide an extended source of neurons for larger brains.

The regionalization of early progenitor zones and their preservation in the adult niche is not completely understood, particularly in humans. Regional specification happens early in development and appears to be conserved among vertebrates, underscoring the importance of preserved genetic mechanisms in establishing the V-SVZ germinal micro domains. Progenitor zones and their potential target areas become greatly separated in bigger brains (see Fig. 3). The resulting distances and possible increase in complexity (e.g. white matter expansion) may severely limit or even impede neuronal navigation in larger brains. This hypothesis could explain the growing evidence that migration from the walls of the lateral ventricles to the OB is rare, or non-existent, in the adult human brain.

A functional role for new neurons in small brains

What is the function of adult-born neurons, and can larger brains do without them? Thus far we have focused on how increasing brain size might limit the presence of adult neurogenesis. However, there might be examples where the functional benefit of newborn neurons for certain regions may outweigh the challenges of maintaining neurogenesis and neuronal migration in a larger brain. Unfortunately, the purpose of adult neurogenesis remains unknown, and studies focusing on possible functions are generally performed in animals with small brains like birds and rodents. (For reviews see: Nottebohm, 2004; Zhao et al., 2008; Lazarini and Lledo, 2011; Aimone et al., 2014). The findings from these studies suggest that adult-born neurons contribute to neural circuit plasticity.

In songbirds, correlations between neuronal replacement and environmental complexity, or with the changing environment at different times of the year, suggest that adult neurogenesis may be linked to circuit plasticity possibly associated with learning and memory (Nottebohm, 1981, 2004). Consistently, higher levels of adult neurogenesis are observed in open-ended learners like canaries compared to zebra finches, which are closed-ended learners (Alvarez-Buylla et al., 1990b). Targeted deletion of HVC projection neurons, that are normally replaced in adult male zebra finches, results in a severe deterioration of song (Scharff et al., 2000). Interestingly, with time these cells were replaced via adult neurogenesis, and the birds' original song was restored to varying degrees. These data suggest that the newly formed neurons participate in song production and are integral part of the circuits required for this behavior, but likely are not the only substrate for memory. Song learning in birds clearly provides a powerful system to further investigate the function of new neurons, but future experiments may require better tools to directly manipulate the different components of neuronal addition (birth, migration and integration), cell replacement (cell death) or the functioning of newly incorporated nerve cells. Methods for the genetic modification of songbirds have been developed (Agate et al., 2009; Scott et al., 2010) and these techniques could allow for more direct testing of the function of the new neurons in the avian brain.

Studies in the rodent olfactory system, which can take advantage of current genetic tools, suggest that adult neurogenesis may also be related to plasticity, but the precise function of new neurons in the OB remains unclear. Granule cells are the most commonly recruited neuronal type in the adult OB. Their survival appears to be closely tied to their level of activity. While proliferation, migration, and integration were not affected by decreased

activity (i.e. loss of olfaction), olfactory deprivation has been shown to increase cell death (Petreanu and Alvarez-Buylla, 2002) and decrease the total number of newborn cells in the OB (Alonso et al., 2006; Bastien-Dionne et al., 2010). Conversely, an odor-enriched environment is associated with increased numbers of newly born cells (Bovetti et al., 2009). Genetic modification of the electrical properties of adult-generated neurons, via viral-induced expression of K⁺ or Na⁺ channels, showed that their intrinsic activity level, but not their overall firing patterns, affects their survival (Lin et al., 2010). This mechanism of linking neuronal activity with survival could allow for precise modification of the OB circuit in relation to sensory experience, but how the new neurons enhance olfactory function is not known. Other studies have attempted to correlate V-SVZ proliferation to olfactory behavioral changes. Use of irradiation to reduce proliferation at the V-SVZ did not alter olfactory detection or short-term olfactory memory, but decreased long-term olfactory memory (Lazarini et al., 2009). Other groups have also linked changes in proliferation at the V-SVZ to changes in olfactory memory (Rocheffort et al., 2002; Sultan et al., 2010) as well as other odor-dependent tasks, such as olfactory fear-conditioning (Valley et al., 2009).

Direct ablation of newly born OB cells, via cre-induced diphtheria toxin (DTA) expression, does not appear to have dramatic effects on spontaneous or innate odor discrimination (Imayoshi et al., 2008). However, in aged mice where V-SVZ neurogenesis is lower, fine odor discrimination (but not discrete odor discrimination) was impaired relative to young mice, and this impairment was partially reproduced by decreasing EGFR signaling in young mice (Enwere et al., 2004). Thus, depending on the specific odor task, the effect of adult neurogenesis on olfactory function can vary. Mathematical modeling of the OB circuit also suggests that neurogenesis could permit maximal discrimination of odors in an unsupervised manner and maintain this task in changing environments (Cecchi, et al., 2001). Such a function for OB neurons is reminiscent of pattern separation, a term borrowed from computational neuroscience modeling.

Pattern separation is also one of the main roles postulated for continued neuronal production in the adult SGZ. This process describes the task of making similar neural patterns of activity more distinct, which could be key for learning and memory. A role for adult-born neurons in the SGZ has been found in contextual fear-conditioned learning, recall in a radial arm maze task (Clelland et al., 2009; Creer et al., 2010; Sahay et al., 2011), memory consolidation (Kitamura and Inokuchi, 2014) and forgetting (Akers et al., 2014). Thus, in two different circuits, there appears to be a similar role and possible adaptive benefit from the continual addition of young neurons. The modulation of neurogenesis in the SGZ is also influenced by extrinsic factors such as an enriched environment (Kempermann et al., 1997), exercise (van Praag et al., 1999), and stress (Duman et al., 2001; Veenema et al., 2007). Aging can also decrease SGZ proliferation (Kuhn et al., 1996) as was observed in the V-SVZ (Enwere et al., 2004). Tools to more precisely alter neurogenesis or neuronal recruitment will be required to ascertain the function(s) of adult born neurons in these circuits and how this dynamic process is regulated.

While the specific role of adult neuronal addition and replacement remains unclear, available evidence suggests that it is a mechanism of plasticity. The potential constraints associated with larger brains (as discussed above) and the requirement for longer neuronal migrations,

need to be balanced with the potential functional benefits of having new neurons in particular brain circuits. Birds, for example, may have adapted neuronal replacement as a method to increase synaptic space for learning while still maintaining a small brain to facilitate flight (Fernando Nottebohm, personal communication). Humans, on the other hand, do not rely on olfaction as much as other species, such as dogs and mice, which might explain the lack of a prominent RMS in the adult human brain. If plasticity is the main function of new neurons, larger brains may have less of a need for the continued production of new neurons into adulthood because they already have enough neurons as a substrate for new learning and memory.

Conclusion

Cajal's proclamation *that in the adult "....Everything may die, nothing may be regenerated"* was followed by the careful statement: *"It is for the scientists of the future to change, if possible, this harsh decree"* (Ramon y Cajal, 1928). A century has passed, and technological advances and new experimental data have shown that adult neurogenesis does in fact occur in reptiles, birds and mammals. However, the location and magnitude varies in different species and there is little evidence that this process contributes to normal regeneration or repair in mammals. Comparative studies thus far suggest that the continued production of young neurons in the V-SVZ and migration into the OB is reduced in species with larger brains. Early regional specification of NSCs during fetal development establishes the sites where specific neuronal types are generated, and these proliferative regions become increasingly separated as the brain grows. In species with larger brains, such as humans, the dramatic brain growth between the late fetal period and infancy may subsequently result in a severe limitation for adult neurogenesis to continue from increasingly distant V-SVZ sources. The extensive expansion of the human forebrain could also impose migratory distances and obstacles that are unsurpassable for young migrating neurons. However, other factors, such as a functional benefit from adding new neurons to specific circuits, could work in conjunction with or in opposition to brain size. There may be examples of large brains that have devised developmental mechanisms to bypass limitations of neuronal migration. Additional comparative studies between diverse species (Patzke et al., 2013) could help fill these gaps in the field.

Even if it is rare, the process of adult neurogenesis has taught us much about how new neurons can be produced, migrate, and integrate into existing circuits in an adult brain. These processes could underlie new approaches to brain repair. It will be important to understand which brain circuits can incorporate new neurons and how to enhance delivery of new neurons to these regions. These are key challenges for future work in adult neurogenesis and neuronal replacement.

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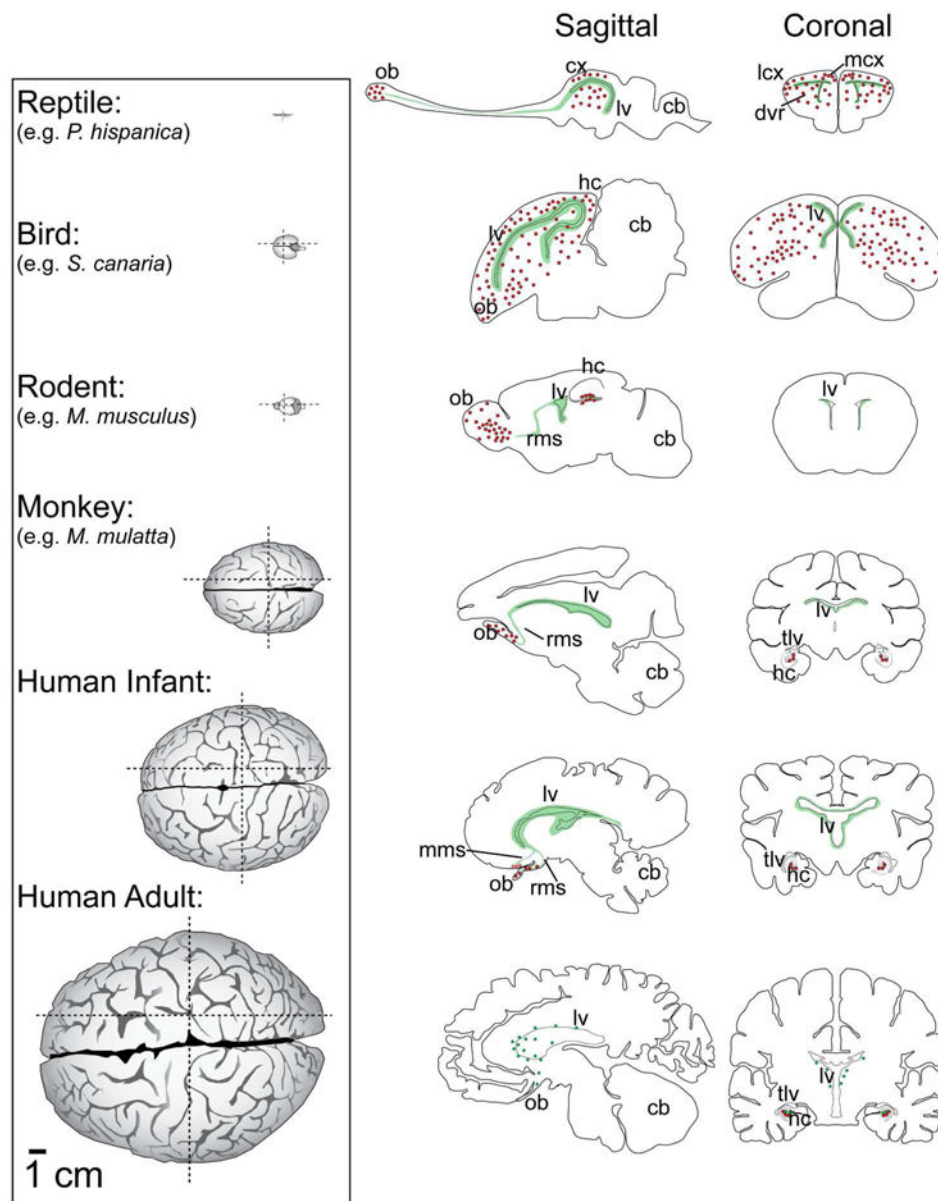


Figure 1. Neurogenic zones and migration destinations across several species and their relationship to brain size. (Left column) Dorsal view of the brains of several species all scaled according to the 1 cm scale bar at the bottom left. (Middle column) Sagittal view of each brain at the parasagittal plane of the RMS and olfactory bulb in each species. Green regions indicate germinal zones. Red dots indicate destinations of the migratory young neurons. Bottom row is scaled according to the lower left 1 cm scale bar, other sections are not to scale. (Right column) Coronal view of each brain. (Reptile): The lizard *P. hispanica* is shown as an example of adult neurogenesis in the reptile. (Bird): The canary is shown, highlighting the extensive ventricular germinal zone and regions that continue to receive adult born neurons. (Rodent): The adult mouse has a pronounced rostral migratory stream from the ventricles as well as abundant hippocampal neurogenesis. (Monkey): The macaque is one of the original

non-human primates where adult neurogenesis was studied. Progenitor cells are abundant along the SVZ, cells proliferate and migrate along the RMS to the OB, and the SGZ in the hippocampus contains proliferating progenitor cells that produce adult-born granule cells. (Human infant:) During early postnatal life there are still many dividing cells and clusters of DCX+ cells along the LV walls. The rostral migratory and medial migratory streams are present after birth until approximately 18 months of age, however the medial stream is directed out of the plane of the section towards the reader, so its destination is represented by red dots with dashed lines. (Human adult:) Potential neurogenic sites in the adult human brain are shown, however the extent of these processes are still controversial. Progenitor cell proliferation has been detected in the SVZ, but most samples do not contain evidence of an RMS. cb, cerebellum; cx, cortex; dvr, dorsal ventricular ridge; hc, hippocampus; lcx, lateral cortex; lv, lateral ventricle; mcx, medial cortex; mms, medial migratory stream; ob, olfactory bulb; rms, rostral migratory stream; tlv, temporal lobe of the lateral ventricle. References: Reptile: (Font et al., 2001; Luzzati et al., 2009; Gonzalez-Granero, S.; Lezameta, M; Garcia-Verdugo, 2011) Bird: (Alvarez-Buylla et al., 1988; Vellema et al., 2011) Mouse: (Lein et al., 2007) Monkey: (Mikula et al., 2007) Human infant: (Sanai et al., 2004, 2011; Quiñones-Hinojosa et al., 2006; Bayer and Altman, 2007; Wang et al., 2011) Human Adult: ((Mikula et al., 2007; Woolsey and Gado, 2007).

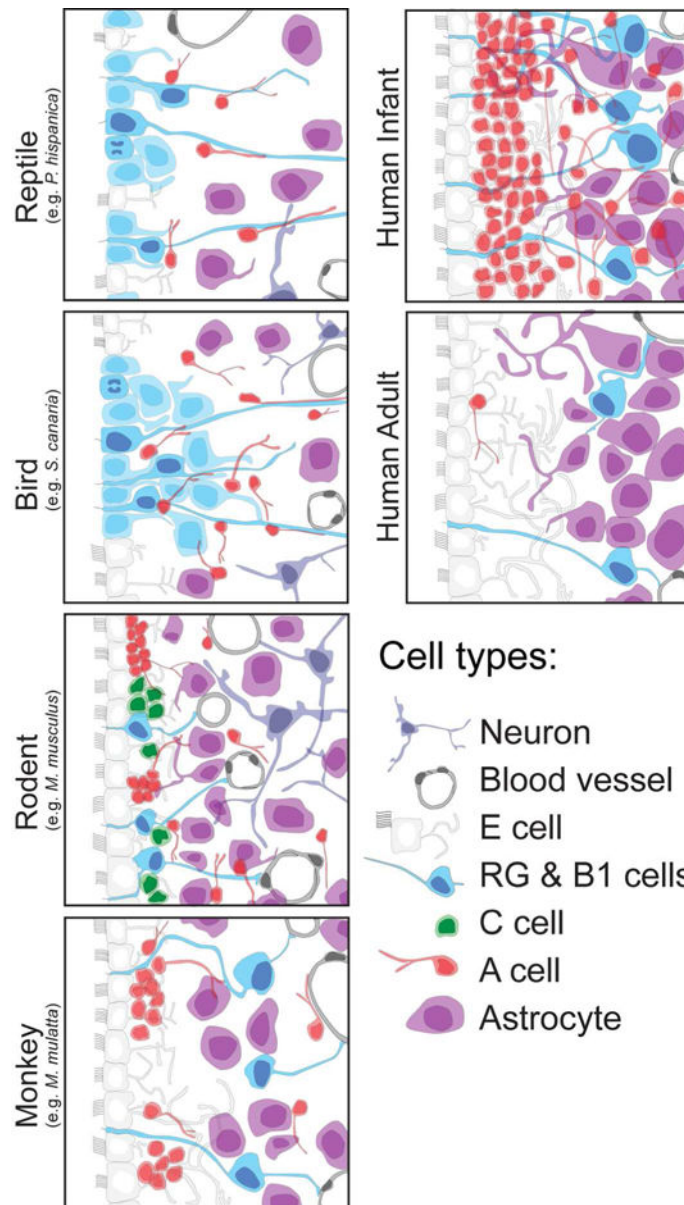


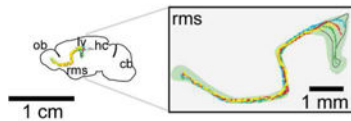
Figure 2.

Schematic of the different neuronal precursor cells within the SVZ across several species.

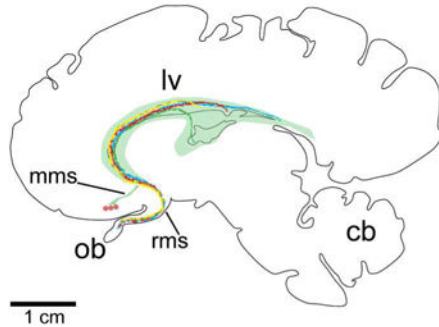
The adult SVZ consists of many of the same cell types across different species.

Multiciliated E cells (white) line the walls of the lateral ventricles and are separated from a layer of glial cells (purple) and proliferating neuronal progenitors (blue) by migrating type A neuroblasts (red). In the adult human, the SVZ contains a hypocellular gap layer between the ependymal cells (white), astrocytes (purple) and rare progenitor cells (blue).

Adult Mouse



Infant Human



Adult Human

**Figure 3.**

Sagittal representation of the spatial separation of neurogenic niches through development in the mouse and human brain. Sagittal sections at the parasagittal plane of the RMS and olfactory bulb in the mouse (top), human infant (middle), and adult human (bottom). With increased size, the progenitor domains (the migratory routes are represented by different colored lines) of the adult human V-SVZ are likely to have expanded and be further separated to cover equivalent areas. Additionally, potential brain targets are further away from the adult V-SVZ in the human than in the mouse resulting in longer and more variable neuronal migratory routes. All sections are scaled to the same 1 cm scale bar, except for the magnified view of the mouse RMS. cb, cerebellum; hc, hippocampus; lv, lateral ventricle; mms, medial migratory stream; ob, olfactory bulb; rms, rostral migratory stream.

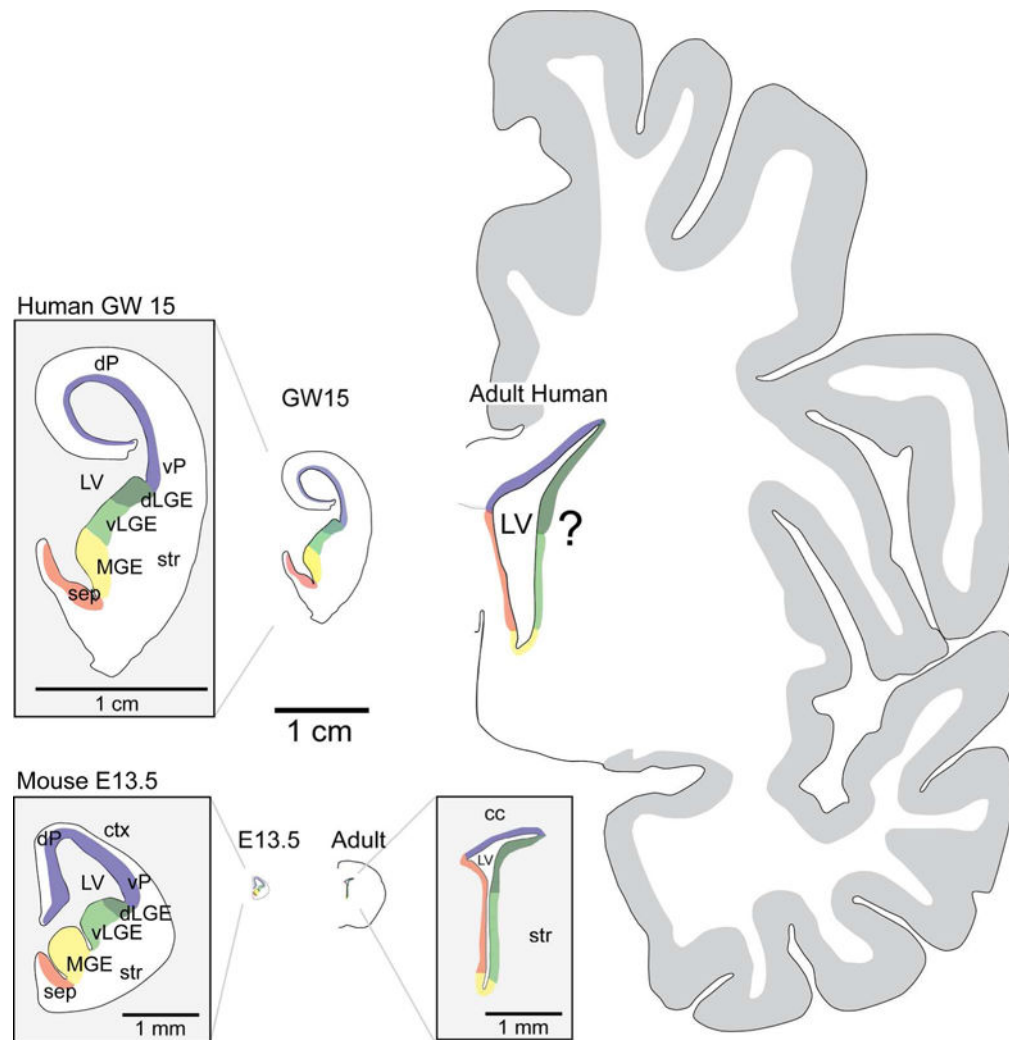


Figure 4.

Coronal representation of the neurogenic niches through development in the mouse and human brain. Coronal sections of the human (top row) and mouse (bottom row) brain at embryonic (GW 15, E 13.5) and adult ages showing divisions of the ventricular wall into neurogenic microdomains (represented by different colors). These domains become more clearly established as development progresses and are detailed in the embryonic mouse and human (magnified views of GW 15 human and E 13.5 mouse). Adult NSCs retain this positional information in the mouse V-SVZ, however whether similar preservation occurs in the adult human is unknown. All unmagnified views are scaled relative to the 1 cm scale bar in the center. cc, corpus callosum; ctx, cortex; dLGE, dorsal lateral ganglionic eminence; dP, dorsal pallium; GW, gestational weeks; LV, lateral ventricle; MGE, medial ganglionic eminence; sep, septum; str, striatum; vLGE, ventral lateral ganglionic eminence; vP, ventral pallium.