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Progress in Neurobiology 80 (2006) 281–307

progress in Neurobiology

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A comparative framework for understanding the biological principles of adult neurogenesis

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Received 20 June 2006; received in revised form 3 November 2006; accepted 9 November 2006

Abstract

Adult neurogenesis has been identified in all vertebrate species examined thus far. However, an evolutionary trend towards a reduction in both the number of proliferation zones and the overall number of newborn cells has been revealed in more recent lineages of vertebrates, such as mammals. Adult neurogenesis, and in particular the characterization of adult neural stem cells in mammals has been the focus of intense research with the goal of developing new cell-based regenerative treatments for neurodegenerative diseases, spinal cord injury, and acute damage due to stroke. Conversely, most other vertebrate classes, which display widespread production of adult neurons, are not typically used as model systems in this context. A more profound understanding of the structural composition and the mechanisms that support proliferation zones in the mature brain have become critical for revealing how adult neural stem cells are maintained in these regions and how they regulate neurogenesis. In this review we argue that comprehensive analyses of adult neurogenesis in various vertebrate and invertebrate species will lead to a more complete understanding of the fundamental biology and evolution of adult neurogenesis and provide a better framework for testing hypotheses regarding the functional significance of this trait.

Keywords: Neurogenesis; Neural stem cell; Proliferation; Brain; Evolution; Vertebrate; Invertebrate; Adult; Larval; Retina

Contents

Abbreviations: BrdU, 5-bromo-2′-deoxyuridine; CNS, central nervous system; dUTP, deoxy-uridine triphosphate; FGF, fibroblast growth factor; GABA, gamma-amino butyric acid; GFAP, glial fibrillary acidic protein; NMDA, *N*-methyl-D-aspartate; CA1, Cornu Ammon-1; PVZ, periventricular zone

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0301-0082/$ – see front matter
doi:10.1016/j.pneurobio.2006.11.007

1. Introduction

Adult neurogenesis appears to be a somewhat extreme and uneconomical form of structural remodeling, compared to the relatively subtle modifications in synaptic morphology that is known to mediate functional plasticity of neural circuitry. Nonetheless, it is precisely this attribute of adult neurogenesis that is beginning to redefine contemporary notions of neural plasticity. Thus, it is no surprise that the field of adult neurogenesis has in the last few decades become one of the most research-intensive fields in the neurosciences. However, despite the impressive progress made on delineating the molecular and cellular properties underlying the process of adult neurogenesis in a few laboratory models, we know very little about the anatomical organization, species diversity, functional significance and evolutionary history of this trait. The importance of understanding the basic cell biology of adult neurogenesis is paramount, but without considering how the natural environment regulates neurogenesis and how this trait has evolved, our understanding remains incomplete. Our current knowledge of adult neurogenesis rests on studies of no more than a few dozen species worldwide, and only a small subset of these species has undergone detailed anatomical mapping for the presence of this trait (Fig. 1). Considering that the animal kingdom consists of approximately 1.5 million known species, this represents a very tiny sampling of the potential diversity of adult neurogenesis.

Adult neurogenesis is broadly defined as the birth and maturation of new neurons that add to, or replace neurons in, existing circuitry under normal physiological or pathological conditions. Research on traditional vertebrate models continues to have a strong presence in the literature, comprised of detailed studies of rodents (Altman and Das, 1965; Altman, 1969; Kaplan and Hinds, 1977; Bayer et al., 1982; Corotto et al., 1993; Seki and Arai, 1995; Kuhn et al., 1996; Rietze et al., 2000; Liu and Martin, 2003; Maslov et al., 2004; Bauer et al., 2005) and songbirds (Goldman and Nottebohm, 1983; Nottebohm, 1985; Alvarez-Buylla and Nottebohm, 1988; Alvarez-Buylla et al., 1990; Nottebohm and Alvarez-Buylla, 1993; Barnea and Nottebohm, 1994; Nottebohm, 2002a,b; Margotta and Caronti, 2005). More recently mammalian research has been extended to the brains of New and Old World primates (McDermott and Lantos, 1990; Gould et al., 1999a,c; Kornack and Rakic, 1999, 2001; Bernier et al., 2002; Koketsu et al., 2003; Ngwenya et al., 2006) and postmortem humans (Eriksson et al., 1998; Kukekov et al., 1999; Bédard and Parent, 2004). In the last 15 years, adult neurogenesis in the reptilian brain of selected species of lizards and turtles has been investigated (García-Verdugo et al., 1989; Perez-Sanchez et al., 1989; Pérez-Cañellas and García-Verdugo, 1996; Pérez-Cañellas et al., 1997; Font et al., 2001; Marchioro et al., 2005). By contrast, despite early experiments on the localization of adult neurogenesis in frogs and salamanders dating back to 1968, there are very few contemporary publications on amphibian adult neurogenesis (Minelli and Quaglia, 1968; Graziadei and Metcalf, 1971; Richter and Kranz, 1981; Mackay-Sim and Patel, 1984; Bernocchi et al., 1990; Polenov and Chetverukhin, 1993; Dawley et al., 2000). In the last decade, teleostean fishes have emerged as a prominent model, renowned for their robust neurogenic capacity throughout the adult CNS (Zupanc and Zupanc, 1992; Zupanc and Horschke, 1995; Zupanc et al., 1996, 2005; Maeyama and Nakayasu, 2000; Zikopoulos et al., 2000; Byrd and Brunjes, 1998, 2001; Ekström et al., 2001; Adolf et al., 2006; Grandel et al., 2006; Zupanc, 2006).

Invertebrates have received little attention with respect to adult neurogenesis in comparison to their vertebrate counterparts. Our understanding of this biological trait stems primarily from two major invertebrate groups: insects and crustaceans. Crickets have long been the leading insect model (Cayre et al., 1994, 1996; Scotto-Lomassese et al., 2000, 2002; Malaterre et al., 2002), although a small number of other insect species have been examined (Norlander and Edwards, 1970; Technau, 1984; Ito and Hotta, 1992; Fahrbach et al., 1995; Booker et al., 1996; Cayre et al., 1996; Dufour and Gadenne, 2006). Laboratory studies of adult neurogenesis in crustaceans have been, for the most part, limited to a variety of species of crab (Harzsch and Dawirs, 1996; Schmidt, 1997; Schmidt and Harzsch, 1999; Hansen and Schmidt, 2001, 2004; Sullivan and Beltz, 2005) and lobster (Harzsch et al., 1999; Schmidt, 2001). In addition to select arthropod species, convincing evidence of continual neurogenesis in adult hydrozoans (Phylum: Cnidaria) has also been presented (Sakaguchi et al., 1996; Miljkovic-Licina et al., 2004), but overall there have been very few studies in this area. To date, we have been unable to identify a single study that has examined adult neurogenesis in some of the most primitive invertebrate groups, namely annelids, nematodes, and flatworms. Nor has there been any investigation of this trait in chelicerates or myriapods, the other major classes of arthropod. Furthermore, there has been a general lack of research in more phylogenetically recent invertebrates, including molluscs, echinoderms, and protochordates. Finally, within the vertebrate and invertebrate

models studied thus far the main, focus has been on the brain as the putative site of adult neurogenesis. Few studies have investigated whether this same trait is present in the spinal cord, sensory systems, autonomic, and peripheral nervous systems of animals. One exception has been the discovery of continual retinal neurogenesis in adult fishes (Johns, 1977; Johns and Easter, 1977; Meyer, 1978; Marcus et al., 1999; Ekström et al., 2001) and amphibians (Straznicky and Gaze, 1971; Dunlop and Beazley, 1981; Reh and Constantine-Paton, 1983; Wetts and Fraser, 1988; Wetts et al., 1989). An earlier account has also shown *de novo* neuronal proliferation in the normal spinal cord of a gymnotiform teleost (Anderson and Waxman, 1985). Moreover, reviews on the common properties of neurogenesis in the adult brain of invertebrates and vertebrates (e.g. Cayre et al., 2002) are rare compared to reviews that focus solely on adult neurogenesis in vertebrates (Alverez-Buylla and Lois, 1995; Scharff, 2000; Doetsch and Scharff, 2001; Zupanc, 2001a; Alvarez-Buylla et al., 2002; García-Verdugo et al., 2002; Lie et al., 2004; Mackowiak et al., 2004; Emsley et al., 2005; Abrous et al., 2005). Thus, the extent of shared and/or divergent characteristics of adult neurogenesis among animals is largely unexplored.

Correlations between adult neurogenesis and learning (Nottebohm, 1985, 2002a,b; Nottebohm and Alvarez-Buylla, 1993; Denisenko-Nehrbass et al., 2000; Snyder et al., 2001; Scotto-Lomassese et al., 2003; Chambers et al., 2004; Enwere et al., 2004; Barker et al., 2005; Magavi et al., 2005; Alonso et al., 2006), seasonality (Alverez-Buylla and Lois, 1995; Clayton, 1998; Dawley et al., 2000; Nottebohm, 2002a,b; Hansen and Schmidt, 2004; Hoshooley and Sherry, 2004), and environmental stimuli (Ramirez et al., 1997; Scotto-Lomassese et al., 2000; Peñafiel et al., 2001) have been observed. While this list is far from comprehensive, these findings begin to unveil the extent to which adult neurogenesis plays a central role in, and is shaped by, the daily lives of adult species. The purpose of this review is to examine the anatomical and functional diversity and evolutionary trends of adult neurogenesis within the animal kingdom by considering the principle biological properties of this trait. We set in motion this review by first considering the definition of an adult species, and the variation in lifespan and growth across animals. Thereafter, this review is divided into five major sections, each discussing the current state of knowledge of the biological question at hand and proposing avenues for future research. Herein, we use the

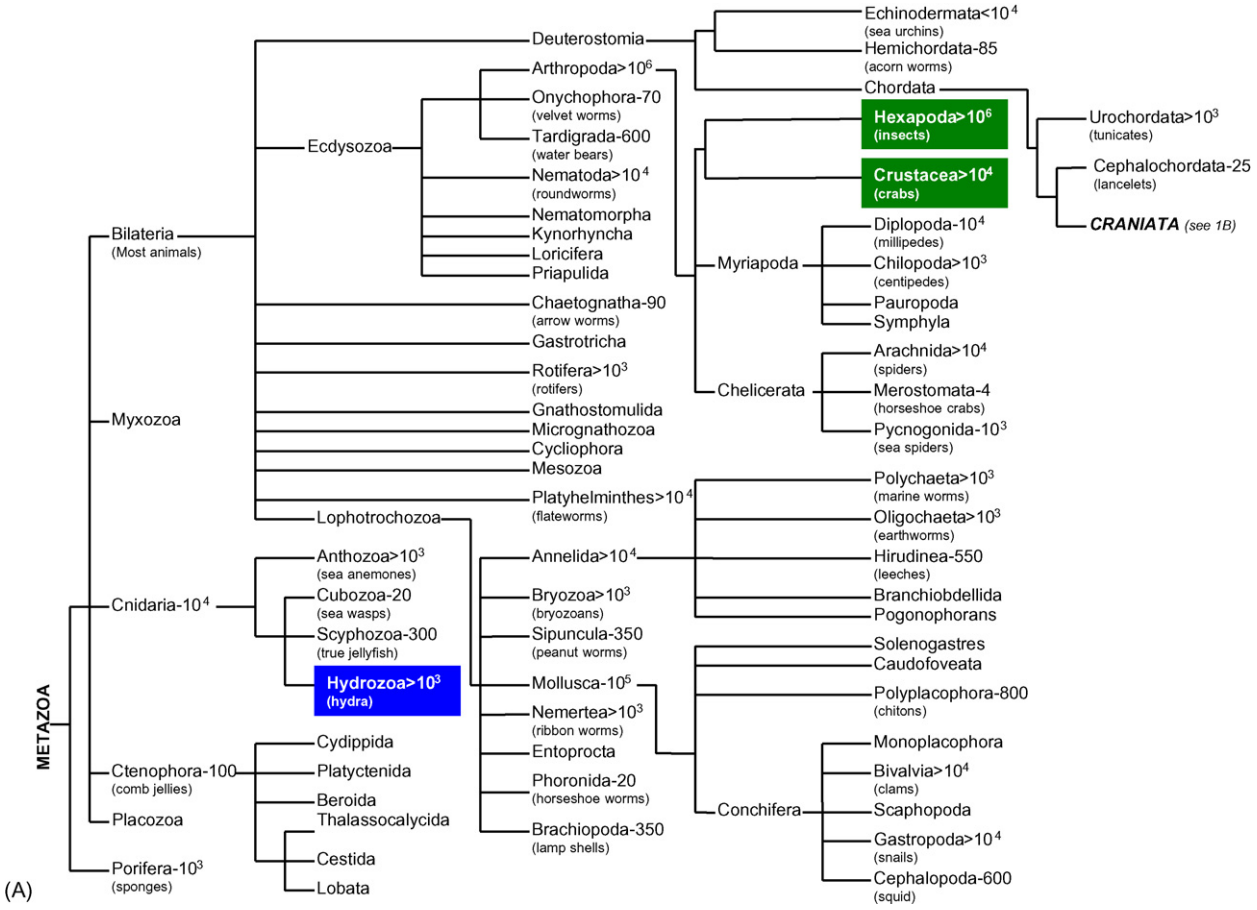

Fig. 1. Cladogram showing the phylogenetic relationship among metazoans (A), craniates (B) and tetrapods (C) along with the taxonomic groups in which adult neurogenesis has been confirmed: blue 1–5 species; green 6–10 species; red >10 species. The approximate number of species and common names are identified for the dominant groups. Note that the majority of investigations examining the presence of adult neurogenesis have taken place in tetrapod vertebrates (C) with the exception of teleost fishes (B), while invertebrates (A) remain largely unexplored. Cladistic lineages were constructed based on information from *The Tree of Life web project* (1995–2004). Species numbers were compiled from Ruppert and Barnes (1996), Burnie and Wilson (2001), Moyle and Cech (2004), and Pechenik (2005) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).

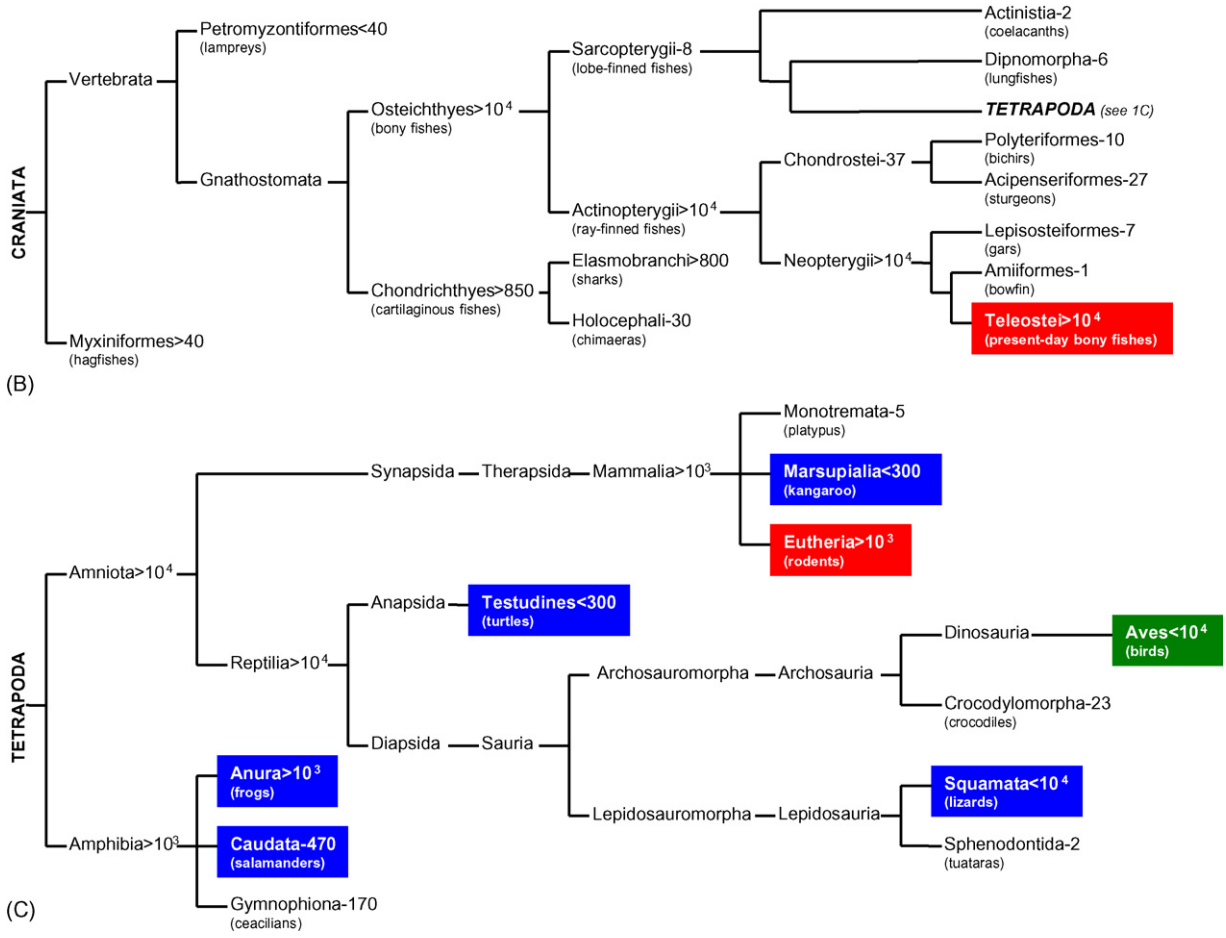

Fig. 1. (*Continued*).

terminology ‘‘neurogenic compartment’’ to refer to the birthplace or proliferation zone of neurons.

2. Defining an adult species: lifespan and growth considerations

Although this may seem intuitive, defining an adult species in the animal kingdom can sometimes be a daunting task, given the variation in aging across organisms. The aging process and time scale of lifespan depend on a suite of factors, including the genetic background, gender, artificial selection on laboratory populations, and the experimental condition to which the animal is exposed (Rakic, 2002; Abrous et al., 2005; Ricklefs, 2006).

Most would agree that the age at sexual maturity is a reasonable biological indicator of the onset of adulthood, however the point at which this occurs during the lifespan of a species is highly variable. A further complication is that not all species become sexually reproductive during their lifetime. For example, many invertebrate species remain asexual throughout ontogeny, while social insect ‘‘workers’’ remain non-reproductive within their colony (Jemielity et al., 2005). However, presuming a species is sexually mature, the notion of adult life stages, often classified as young, middle, and old in the literature, must further be considered. Mammalian studies of adult neurogenesis have already ascertained that different stages of adulthood are paralleled with different levels of cell proliferation and neuronal differentiation across neurogenic compartments (Altman and Das, 1965; Kaplan et al., 1985; Seki and Arai, 1995; Kuhn et al., 1996; Tropepe et al., 1997; Gould et al., 1999c; Jin et al., 2003; Amrein et al., 2004b; Bondolfi et al., 2004; Enwere et al., 2004; Heine et al., 2004; Driscoll et al., 2006; Luo et al., 2006). By contrast, almost no investigations have taken place on other vertebrate or invertebrate species in this context, with the exception of a recent study on the tropical lizard (Marchioro et al., 2005). Given the persistent evidence in mammalian models, there is a strong likelihood that similar adult age-related differences in neurogenesis are present in non-mammalian species. In light of this, caution must be exercised when generalizing the results of adult neurogenesis studies to even closely related species, since adult age differences of only a few months may lead to conspicuous differences in cell proliferation and differentiation.

Individual invertebrates and vertebrates age at different rates, but the biological basis of this variation is poorly understood (Finch, 1990). A prime example is the variation in lifespan among castes of social insects. Here, queens live up to 500 times longer than males and 10 times longer than non-reproductive workers. Social insect queens live for 10.1 years

on average, but in some cases may live for as long as 30 years. By contrast, in solitary insects, the adult stage lasts only for 0.1 years on average (Jemielity et al., 2005). In mammals the midpoint of the average lifespan for mice is approximately 1.5 years of age, while this is 10 years in macaques, and about 30 years in humans (Finch, 1990). However, more ancient vertebrate lineages, such as fish and reptiles, demonstrate three distinct types of senescence. For example, different reptiles can exhibit rapid senescence, gradual senescence (comparable to the majority of vertebrates), or slow/negligible senescence, which can be observed in turtles, tortoises and crocodiles who continue to grow throughout life and may live for more than a century (Patnaik, 1994). In invertebrates, such life-long continuous growth has also been recorded in decapod crustaceans (Schmidt and Harzsch, 1999; Schmidt, 2001). Short-lived species of amphibians show gradual senescence as in laboratory mammals, whereas long-lived species of fishes and reptiles show slow senescence (Kara, 1994). Interestingly, evolutionary studies demonstrate that species with near-centenarian lifespan and a slow rate of aging have evolved repeatedly and independently in bivalves, fish, reptiles, and mammals (Jemielity et al., 2005). However, whether the concept of adult neurogenesis is meaningful, or even applicable in species with so-called ''indeterminate growth'' remains debatable.

It has not been our intention here to define an ''adult species'', but for practical reasons it is judicious to accept the conventional view that sexually mature animals have achieved adulthood. However, in a comparative context there may be as many definitions of adulthood as there are major taxonomic groups, and as a result, studies of adult neurogenesis must be designed accordingly. Considering the variation in modes of senescence, time scales of aging and extrinsic and intrinsic factors across species, it may in fact be impossible to standardize the definition of an adult species. As an alternative, we suggest that future studies take into account these elements on a species to species basis in order to accurately report novel neurogenic findings and allow for proper age-matched comparisons between species.

3. Anatomical loci of adult neurogenic compartments

The goal of this section is to provide a broad overview of all major neurogenic compartments identified to date within various metazoans. Here, we do not restrict ourselves to only the confines of the brain, but further seek to highlight those species that present unique regions of continuous adult neurogenesis. The neurogenic compartments that have been identified in adult invertebrate and vertebrate species are summarized in Tables 1 and 2, respectively, along with the corresponding references.

3.1. Neurogenic loci in adult invertebrates

Cnidarians have commonly gone unnoticed during comparative studies of adult neurogenesis; however, this organism may be among the first to possess this trait as a mechanism for neuronal replacement (Sakaguchi et al., 1996). Considering

Table 1
Localization of *in vivo* adult neurogenic compartments in invertebrates

Division	Species	Site	References
Cnidaria	*Hydra viridissima*	Gastric region	Sakaguchi et al. (1996)
Insecta	*Acheta domesticus*	MB	Cayre et al. (1994, 1996), Scotto-Lomassese et al. (2000, 2002, 2003), and Malaterre et al. (2002)
	Gryllomorpha dalmatina	MB	Cayre et al. (1996)
	Gryllus bimaculatus	MB	Cayre et al. (1996)
	Tenebrio molitor	MB	Cayre et al. (1996)
	Zophobas sp.	MB	Cayre et al. (1996)
	Harmonia axyridis	MB	Cayre et al. (1996)
	Oncopeltus fasciatus	MB	Cayre et al. (1996)
	Aleochara curtula	MB	Bieber and Fuldner (1979)
	Stagmomantis carolina	MB	As reviewed by Cayre et al. (2002)
	Agrotis ipsilon	MB	Dufour and Gadenne (2006)
Crustacea	*Carcinus maenus*	LC, HBC	Schmidt (1997) and Hansen and Schmidt (2001, 2004)
	Libinia emarginata	LC, MC, HBC	Sullivan and Beltz (2005)
	Pagurus bernhardus	LC	Schmidt and Harzsch (1999)
	Cancer pagurus	LC	Schmidt and Harzsch (1999)
	Hyas araneus	LC	Harzsch and Dawirs (1996)
	Panulirus argus	LC, MC	Schmidt and Harzsch (1999) and Schmidt (2001)
	Homarus americanus	LC	Harzsch et al. (1999) and Schmidt and Harzsch (1999)
	Cherax destructor	LC	Schmidt and Harzsch (1999) and Sandeman and Sandeman (2000)
	Sicyonia brevirostris	LC	Schmidt and Harzsch (1999)
Mollusca	*Aplysia californica*[a]	Unknown	Cash and Carew (1989)
Urochordata	*Ciona intestinalis*[a]	Dorsal strand plexus	Mackie (1995)

HBC, hemi-ellipsoid bodies; LC, lateral soma cluster; MB, mushroom bodies; MC, medial soma cluster.
[a] Presence of adult neurogenic compartments in these species remains unclear.

that the phylum Cnidaria is believed to possess the first organized CNS, the identification of neurogenic compartments in such an ancestral system provides an ideal starting point for elucidating the evolutionary origin of this trait (Holland, 2003; Miljkovic-Licina et al., 2004). The gastric region has been reported as the primary neurogenic compartment in the adult hydra (Class: Hydrozoa). Here, large interstitial stem cells become committed to a neuronal fate following cell division (Sakaguchi et al., 1996). Although the size of adult animals remains constant, during adulthood neurons and epithelial cells are lost to the extremities by sloughing off or to developing buds. Therefore, it is crucial that a system of continuous neurogenesis is present in the hydra to replace those neurons lost and to maintain functionality in the gastric region.

More species of insects have been examined to date for the presence of neurogenic compartments than any other group of invertebrates (Fig. 1A; Table 1; Norlander and Edwards, 1970; Technau, 1984; Ito and Hotta, 1992; Cayre et al., 1994, 1996;

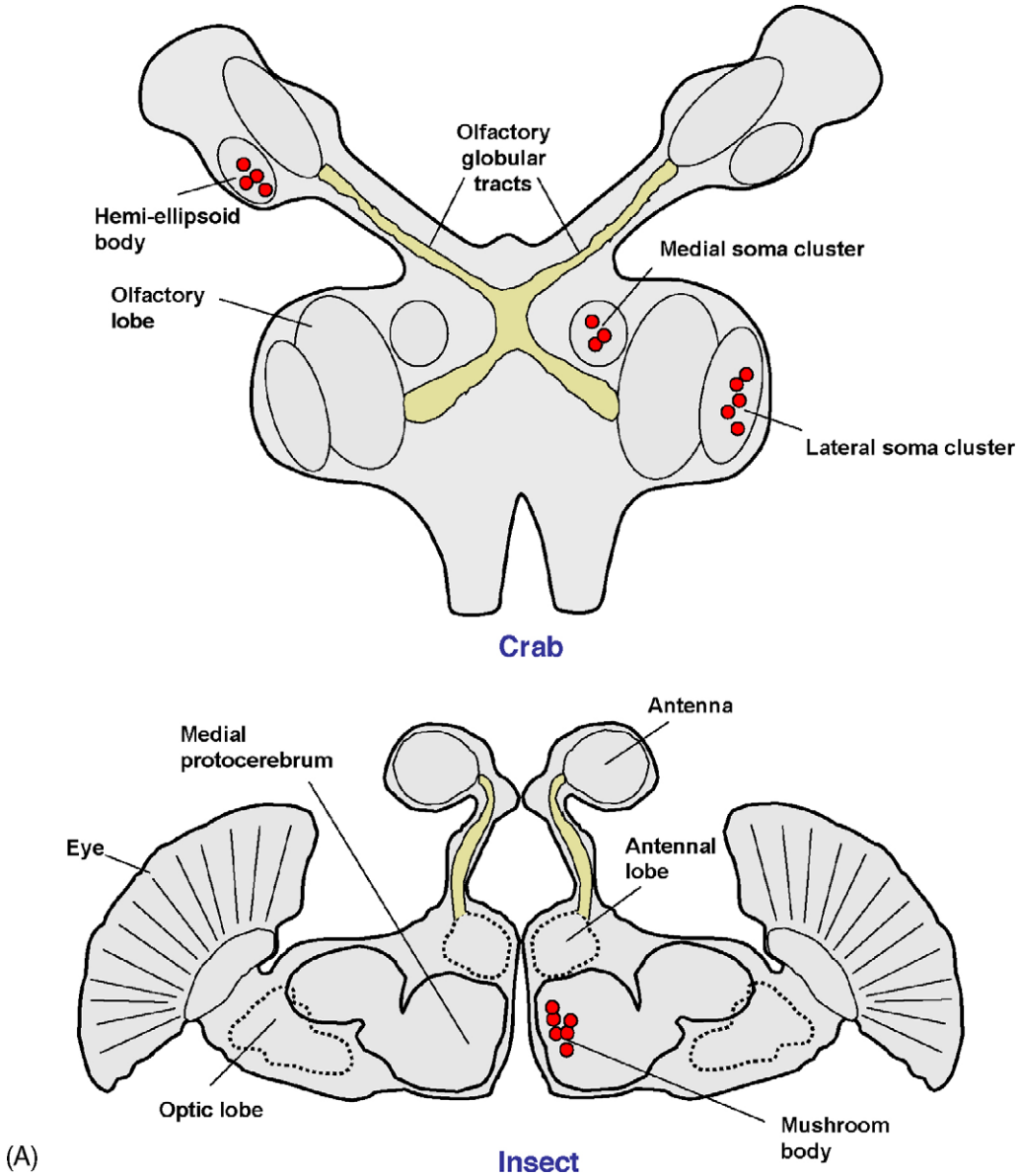

Fig. 2. Schematic representation of brain neurogenic zones in two representative invertebrates (A) and four representative vertebrates (B). Relative positions of neurogenic zones are demarcated by red dots. Overall brain size, size of brain subregions and size of neurogenic zones are not drawn to scale. Schematics are adapted from Sullivan and Beltz (2005), Cayre et al. (2002), Font et al. (2001), Doetsch and Scharff (2001), and Wullimann (1998). Abbreviations—Teleost fish: OB, olfactory bulb; Vp, ventral pallium; Dp, dorsal pallium; PO, preoptic area; Hypo, hypothalamus; PT, posterior tuberculum; Th/pTe, thalamus/pre-tectum; TeO, optic tectum; TL, torus longitudinalis; VCe, valvula cerebelli; CCe, corpus cerebelli; FLo/VLo, facial lobe/vagal lobe; MO, medulla oblongata. Lizard: OB, olfactory bulb; OT, olfactory tract; Ctx, isocortex; MC, medial cortex; Sp, subpallium; ssm, sulcus septomedialis; Sv/t, sulcus ventralis/terminalis; TeO, optic tectum; Ce, cerebellum; MO, medulla oblongata. Bird: OB, olfactory bulb; X, area X; LPO, lobus parolfactorius; LV, lateral ventricle; RA, robust nucleus of the archistriatum; HVC, high vocal center; HP, hippocampal formation; MO, medulla oblongata; Ce, cerebellum. Rodent: OB, olfactory bulb; Ctx, isocortex; RMS, rostral migratory stream; Str, striatum; cc, corpus callosum; Th, thalamus; DG, dentate gyrus; H, hippocampus; MB, midbrain; Ce, cerebellum; MO, medulla oblongata (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).

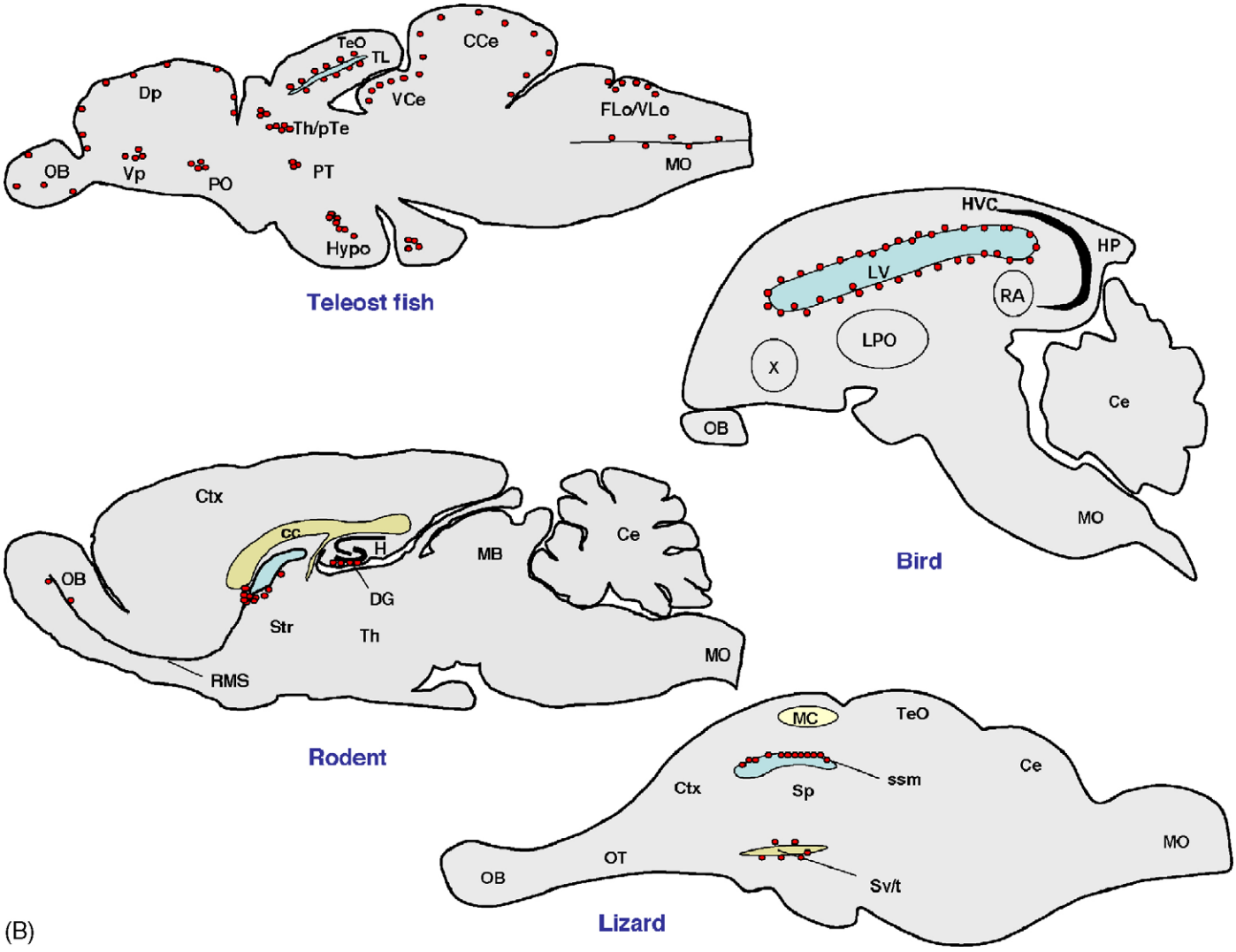

Fig. 2. (*Continued*).

Fahrbach et al., 1995; Booker et al., 1996; Scotto-Lomassese et al., 2000, 2002; Malaterre et al., 2002; Dufour and Gadenne, 2006). It is agreed however, that in most insects, mushroom body neuroblast proliferation does not occur after preimaginal development (Fahrbach et al., 1995; Malaterre et al., 2002). In those exceptions, research has ascertained that the mushroom bodies (corpora pedunculata) are the major neurogenic compartments in adults (Fig. 2A; Cayre et al., 2002). Mushroom bodies are present in the phylum Annelida, and all arthropod groups with the exception of crustaceans (Strausfeld et al., 1998). This raises the intriguing question of whether adult neurogenesis is also occurring in annelids, chelicerates, and myriopods at this site in adulthood. Considering the close evolutionary relationship between annelids and arthropods, it is tempting to speculate that this process could be taking place in these groups, as has been long-established in the mushroom bodies of insect species.

Until now, anatomical investigations of insects have yet to report proliferation outside of the major mushroom body cortices and associated fibres (Bieber and Fuldner, 1979; Technau, 1984; Withers et al., 1993). Mushroom bodies are considered the dominant integrative centre for multimodal inputs from the antennae, the eyes, and the palpae, and are comprised of Kenyon cells and differentiated neuropils (Cayre et al., 1996, 2002; Malaterre et al., 2002). Support for a potential role in learning and memory has also led to the comparison of the mushroom bodies with the hippocampus of mammals (Strausfeld et al., 1998). Conclusive evidence of adult neurogenesis is available for several species from the orders *Orthoptera* (i.e. grasshoppers, crickets) and *Coleoptera* (i.e. beetles), as well as *Oncopeltus fasciatus* (milkweed bug), *Stagmomantis carolina* (praying mantis), and *Agrotis ipsilon* (black cutworm moth) (Bieber and Fuldner, 1979; Cayre et al., 1994, 1996, 2002; Scotto-Lomassese et al., 2000, 2002, 2003; Malaterre et al., 2002; Dufour and Gadenne, 2006). For instance, in the 50-day-old adult cricket (*Acheta domesticus*), 20% of the small Kenyon cells are produced during adult life, significantly contributing to remodeling of the mushroom body cortex (Malaterre et al., 2002). A similar process in the development of newborn Kenyon cells has been demonstrated in species of coleopterans (Cayre et al., 1996).

In adult decapod crustaceans, neurogenesis is a continuous process occurring among the different neuronal cell types of the central olfactory pathway (Schmidt and Harzsch, 1999; Schmidt, 2001). These cell types include progenitors of both projection neurons and interneurons that undergo mitosis and are associated with the olfactory and accessory lobes. Similar to teleost fishes, most decapod crustaceans continue to grow throughout adult life with appendages and antennules growing with each molt (Hansen and Schmidt, 2001). During this process many new aesthetascs (sensilla) containing olfactory receptor neurons are added peripherally to the base of the antennules, whereas old sensilla are shed at the tip (Sandeman and Sandeman, 1996). As a result, an overall net increase in olfactory sensory neurons persists during adult life, which is then paralleled by a life-long addition of neurons in the central olfactory pathway (Schmidt, 1997; Sandeman et al., 1998).

Evidence for adult neurogenesis has been confirmed among a number of crab species (*Carcinus maenas, Pagurus bernhardus, Cancer pegurus, Hyas araneus, Libinia emarginata*), the American (*Homarus americanus*) and spiny (*Panulirus argus*) lobsters, crayfish (*Cherax destructor*) and shrimp (*Sicyonia brevirostris*) (Fig. 1A; Table 1; Harzsch and Dawirs, 1996; Schmidt, 1997, 2001; Harzsch et al., 1999; Schmidt and Harzsch, 1999; Sandeman and Sandeman, 2000; Hansen and Schmidt, 2001, 2004; Sullivan and Beltz, 2005). In all species examined, the lateral soma clusters, consisting of olfactory projection neurons, have been identified as a universal neurogenic compartment (Fig. 2A; Schmidt and Harzsch, 1999; Sandeman and Sandeman, 2000; Hansen and Schmidt, 2001; Sullivan and Beltz, 2005). Additional neurogenic compartments have been observed in the medial soma clusters of the adult spiny lobster, resident to proliferative interneurons, and the soma clusters of the hemi-ellipsoid bodies in the adult shore crab (Hansen and Schmidt, 2001; Schmidt, 2001). The hemi-ellipsoid bodies, in particular, are suggested to be homologous to the insect mushroom bodies, acting as the multimodal integration centre in crustaceans (Strausfeld et al., 1998). However, to date active proliferation in the hemi-ellipsoid bodies has only been observed in the shore crab, indicating both an inter-class difference in the proliferative capacity of this structure.

Several major gaps exist in the literature with regard to invertebrate adult neurogenesis. As a consequence, we are presented with a fragmented picture of the extent of neurogenic compartments across these species. In particular, minimal interest has been directed towards echinoderms, molluscs, and protochordates (see Fig. 1A). These latter two groups are exemplary of more highly evolved nervous systems, with protochordates leading to present-day vertebrates. Given their taxonomic position, the identification of neurogenic compartments in the vertebrate-like nervous system of transitional forms, such as cephalochordates, is imperative to understanding the phylogenetics underlying this trait. Aside from preliminary observations in urochordates and developmental work on gastropod molluscs, the picture is grossly incomplete. In the ascidian (Class: Ascidiacea), *Ciona intestinalis*, observations of neurons at varying stages of differentiation in the dorsal strand plexus of the visceral nervous system of adults, show promise that adult neurogenesis may in fact be occurring in the autonomic nervous system of this species (Mackie, 1995). Conversely, despite the exceptional growth of gastropod molluscs from postembryonic development to sexual maturity by an increase in neuron number and neuron size, in adult gastropods, the consensus remains that additional linear growth is due solely to somatic enlargement of individual neurons; as has been described in the pond snail, *Lymnaea stagnalis* (Croll and Chiasson, 1988). In conflict with this notion, the marine mollusk, *Aplysia californica*, has revealed modest neuronal proliferation from late stage 12 juveniles into early adult stages, though the source of replicating neurons is unknown (Cash and Carew, 1989).

3.2. Neurogenic loci in adult vertebrates

Neurogenesis in the adult mammalian forebrain has been localized to the subependymal zone, which is a layer of cells surrounding the ependymal lining of the lateral ventricles, as well as the subgranular zone in the dentate gyrus of the hippocampus. A common notion is that the embryonic subventricular zone gives rise to the adult subependyma and the embryonic ventricular zone gives rise to the adult ependyma. This is part of the reason why the term ‘‘subventricular zone’’ is used to describe the region of neurogenesis surrounding the adult forebrain lateral ventricles. However, there is no conclusive evidence of such a lineage relationship in mammals and the evidence is even less apparent in other vertebrate species. Moreover, at least a subset of radial glial cells that reside in the embryonic ventricular zone are neural stem cells that ultimately reside within the subependyma in adulthood (Alvarez-Buylla et al., 2001), with little or no evidence for the presence of neural stem cells within the adult ependyma (Chiasson et al., 1999; Doetsch et al., 1999), although this remains controversial (Johansson et al., 1999). Thus, in order to simplify our discussion, we have adopted the term periventricular zone (PVZ) to refer to all cell layers lining the brain ventricles in adult vertebrates, while we continue to use the term subgranular zone to describe the neurogenesis within the dentate gyrus of the adult hippocampus. This same terminology is used in Table 2. There have been extensive analyses of these two neurogenic compartments in the adult mammalian brain, and in particular the adult rodent brain. As a result, we refrain from providing a detailed overview and instead direct the reader to recent review articles for more detailed information (e.g. Ming and Song, 2005; Alvarez-Buylla and Lim, 2004; Doetsch and Hen, 2005). In general, constitutive neurogenesis within the forebrain PVZ and the hippocampal subgranular zone provides new granule-type neurons to the olfactory bulb and dentate gyrus, respectively, which are primarily GABAergic inhibitory neurons. The addition or replacement of new neurons within these regions is highly dynamic and can be modified by hormones and growth factors, afferent neurotransmission, enriched environments and exercise, drugs (e.g. antidepressants), stress, age and genetic background (Ming and Song, 2005). In addition, dynamic regulation of neurogenesis in these regions may be central for

Table 2
Localization of *in vivo* adult neurogenic compartments in vertebrates

Class	Species	Periventricular zone	Non-periventricular zone	References
Teleostei	*Danio rerio*	✓	Major brain subdivisions (Tel, TeO, Hyp, Ce), CMZ	Marcus et al. (1999), Maeyama and Nakayasu (2000), Byrd and Brunjes (2001), Zupanc et al. (2005), Adolf et al. (2006), and Grandel et al. (2006)
	Gasterosteus aculeatus L.	✓	Major brain subdivisions (Tel, TeO, Hyp, Ce), CMZ	Ekström et al. (2001)
	Apteronotus leptorhynchus	✓	Major brain subdivisions (Tel, Ce)	Zupanc and Horschke (1995) and Zupanc et al. (1996)
	Poecilia reticulata	✓	Major brain subdivisions (Tel, Ce)	Kirsche (1967)
	Carassius carassius	✓	Major brain subdivisions (Tel, Ce)	Kirsche (1967)
	Leuciscus idus	✓	Major brain subdivisions (Tel, Ce)	Kirsche (1967)
	Sparus aurata	✓	Ce, TeO	Zikopoulos et al. (2000)
	Carassius auratus	✓	TeO, CMZ	Johns (1977), Johns and Easter (1977), Meyer (1978), Raymond and Easter (1983), Raymond et al. (1983), and Alonso et al. (1989)
	Oryzias latipes	n.a.	TeO	Nguyen et al. (1999)
	Eignemannia sp.	✓	n.a.	Zupanc and Zupanc (1992)
	Salmo gairdneri	✓	n.a.	Alonso et al. (1989)
	Barbus meridionalis	✓	n.a.	Alonso et al. (1989)
	Cyprinus carpio	✓	n.a.	Alonso et al. (1989)
	Sternarchus albifrons	n.a.	IEL	Anderson and Waxman (1985)
Amphibia	*Plethodon cinereus*	✓	OE, VNE	Dawley et al. (2000)
	Ambystoma tigrinum	n.a.	OE	Mackay-Sim and Patel (1984)
	Ambystoma mexicanum	✓	OE	Richter and Kranz (1981)
	Triturus cristatus	n.a.	TeO	Minelli and Quaglia (1968)
	Xenopus laevis	n.a.	CMZ	Straznicky and Gaze (1971), Wetts and Fraser (1988), and Wetts et al. (1989)
	Heleioporus eyrei	n.a.	CMZ	Dunlop and Beazley (1981)
	Rana pipiens	n.a.	OE, CMZ	Graziadei and Metcalf (1971) and Reh and Constantine-Paton (1983)
	Rana esculenta L.	✓	X	Bernocchi et al. (1990)
	Rana temporaria	✓	n.a.	Polenov and Chetverukhin (1993)
Reptilia	*Trachemys scripta elegans*	✓	n.a.	Pérez-Cañellas et al. (1997)
	Psammodromus algirus	✓	n.a.	Peñafiel et al. (2001)
	Tarentola mauritanica	✓	X	Pérez-Cañellas and García-Verdugo (1996)
	Podarcis hispanica	✓	X	García-Verdugo et al. (1989) and Perez-Sanchez et al. (1989)
	Tropidurus hispidus	✓	X	Marchioro et al. (2005)
	Thamnophis sirtalis	n.a.	VNE	Wang and Halpern (1988)
Aves	*Serinus canaria*	✓	X	Goldman and Nottebohm (1983), Nottebohm (1985), Alvarez-Buylla and Nottebohm (1988), and Alvarez-Buylla et al. (1990)
	Malopsittacus undulates	✓	X	Nottebohm (1985)
	Streptopeillia risoria	✓	X	Nottebohm (1985)
	Taeniopygia guttata	✓	X	As reviewed by Nottebohm and Alvarez-Buylla (1993)
	Coturnix japonica	✓	X	As reviewed by Nottebohm and Alvarez-Buylla (1993)
	Gallus domesticus	✓	X	As reviewed by Nottebohm and Alvarez-Buylla (1993)
	Parus atricapillus	✓	X	Barnea and Nottebohm (1994)

Table 2 (*Continued*)

Class	Species	Periventricular zone	Non-periventricular zone	References
Mammalia	*Sminthopsis crassicaudata*	n.a.	SGZ	Harman et al. (2003)
	Macaca mulatta	✓	SGZ	Gould et al. (1999c), Kornack and Rakic (1999, 2001), and Ngwenya et al. (2006)
	Macaca fascicularis	✓	SGZ	Gould et al. (1999a, 1999c), Kornack and Rakic (1999, 2001), and Bernier et al. (2002)
	Saimiri sciureus	✓	SGZ	Bernier et al. (2002)
	Callithrix jacchus	✓	SGZ	McDermott and Lantos (1990) and Gould et al. (1998)
	Apodemus flaviocollis	n.a.	SGZ	Amrein et al. (2004a,b)
	Clethrionomys glareolus	n.a.	SGZ	Amrein et al. (2004a,b)
	Microtus subterraneus	n.a.	SGZ	Amrein et al. (2004a,b)
	Microtus ochrogaster	✓	SGZ	Smith et al. (2001) and Fowler et al. (2002)
	Tupaia belangeri	n.a.	SGZ	Gould et al. (1997)
	Cavia porcellus	n.a.	SGZ	Guidi et al. (2005)
	Orictolagus cuniculus	n.a.	CN	Luzzati et al. (2006)
	Sus scrofa	n.a.	Hyp	Rankin et al. (2004)
	Rattus norvegicus (Sprague–Dawley; Long-Evans hooded; Winstar; Fischer 344)	✓	SGZ	Altman and Das (1965), Altman (1969), Kaplan and Hinds (1977), Bayer et al. (1982), Kuhn et al. (1996), Gould et al. (1999b), Biebl et al. (2000), Liu and Martin (2003), Bauer et al. (2005), and Stranahan et al. (2006)
	Mus domesticus (CF-1; C57BL/6; BALB/c; CD1, 129/F2; CBA, DBA; C3H/HeJ; DBA/2J; NZB/BINJ; SW/COBS)	✓	SGZ, SN[a]	Morshead and van der Kooy (1992), Corotto et al. (1993), Kempermann et al. (1997a,b, 1998, 2003), Tropepe et al. (1997), Rietze et al. (2000), Brown et al. (2003), Liu and Martin (2003), Shingo et al. (2003), Zhao et al. (2003), Amrein et al. (2004a,b), Enwere et al. (2004), Maslov et al. (2004), and Sun et al. (2004)
	Homo sapiens	✓	SGZ	Eriksson et al. (1998), Kukekov et al. (1999), and Bédard and Parent (2004)

() denotes the structures within major brain subdivisions displaying the greatest intensity of proliferation; ✓ denotes the presence of adult neurogenic compartments within the cell layers and/or structures adjacent to the brain ventricles; X denotes the absence of neurogenic compartments observed in this region; n.a denotes the authors did not examine the corresponding zone. Ce, cerebellum; CMZ, ciliary marginal zone of the retina; CN, caudate nucleus; Hyp, hypothalamus; IEL, inner ependymal layer of caudal spinal cord; OE, olfactory epithelium; SN, substantia nigra; SGZ, subgranular zone of the hippocampus; Tel, telencephalon; TeO, optic tectum; VNE, vomeronasal epithelium.

[a] Adult neurogenic compartments in these locations remain controversial.

mediating behavioral tasks that are based on learning or memory (Doetsch and Hen, 2005). An important realization has been that these two adult mammalian neurogenic compartments are composed of a heterogeneous population of cells, many of which are identifiable lineage descendents of neural stem cells (Doetsch et al., 1997; Seri et al., 2004). In addition to the premature neurons, there are astrocytes, GFAP-expressing neural stem cells, ependymal cells, tanycytes, undifferentiated progenitor cells and a small population of cells that are largely unidentified with respect to their function. Other regions of the ventricular neuraxis (third and fourth ventricle and central canal) do not normally undergo neurogenesis. Upon growth factor infusion into the ventricles, stem and progenitor cells surrounding the fourth ventricle and cervical central canal can be induced to generate new astrocytes and oligodendrocytes, but not neurons (Martens et al., 2002). Thus, the specialized cellular architecture and molecular signaling of the lateral ventricle PVZ and subgranular zone of the dentate gyrus imparts a unique capacity for the generation of new neurons that is not conserved in all regions of the nervous system. Whether these cellular features are conserved in neurogenic compartment in other vertebrates remains to be elucidated.

The ongoing detection of adult neurogenesis in the PVZ of all vertebrates has designated this region as a common, and often anticipated, source of new neurons. Despite sharing a common proliferative birthplace in the PVZ, numerous differences in neurogenic compartments between vertebrate classes have been reported distal to this region (non-periventricular zone). By far the greatest number of proliferation zones is found in the teleost fishes (Fig. 2B). Teleost fishes lead all other vertebrate classes by encompassing the largest species diversity for the presence of adult neurogenesis within and external to the CNS (Fig. 1B; Table 2; Kirsche, 1967; Johns, 1977; Johns and Easter, 1977; Meyer, 1978; Raymond

and Easter, 1983; Raymond et al., 1983; Anderson and Waxman, 1985; Alonso et al., 1989; Zupanc and Zupanc, 1992; Zupanc and Horschke, 1995; Zupanc et al., 1996, 2005; Marcus et al., 1999; Nguyen et al., 1999; Maeyama and Nakayasu, 2000; Zikopoulos et al., 2000; Byrd and Brunjes, 1998, 2001; Ekström et al., 2001; Adolf et al., 2006; Grandel et al., 2006; Zupanc, 2006). The most frequently cited explanation for the occurrence of this trait is that bony fishes have indeterminate growth, and therefore the majority of brain and sensory structures continue to enlarge by the addition of newborn neurons during senescence (Zupanc, 1999, 2006). Although this is a plausible rationale to explain the persistence of widespread neurogenesis in teleosts, there are several caveats to this argument. First, in general indeterminate growth of the brain, or at least brain subregions, is not an exclusive property of teleosts. Some species of rodents have been shown to have an increasing number of granule cell neurons in the hippocampus with age (Amrein et al., 2004a). Thus, selected brain regions that harbor neurogenic compartments may be differentially regulated in many animals that have been traditionally defined as exhibiting determinate growth. Second, not all fish species exhibit indeterminate growth, especially with regards to increasing muscle mass with age, which is a hallmark feature of indeterminate growth. For example, two species of the cyprinid genus *Danio*, the zebrafish (*Danio rerio*) and the giant danio (*Danio aequipinnatus*), exhibit distinct larval and adult muscle growth patterns. Whereas the giant danios exhibit indeterminate muscle growth and maintain responsiveness to growth promoting hormones as adults, the zebrafish adults reach a growth plateau as they mature (Biga and Goetz, 2006). Moreover, a senescence-related muscle wasting (sarcopenia), comparable to most vertebrates, has been well documented in zebrafish (Gerhard et al., 2002). Finally, the cellular basis for indeterminate growth is not completely known. Continual growth of the teleost brain could result primarily from increased myelination and/or complexity of the extracellular neuropil in addition (or in contrast) to neurogenesis. Thus, while neurogenesis may have a positive allometric relationship to continued brain growth in some teleost species, the relative contribution of adult neurogenesis to adult brain growth in those species remains to be confirmed.

Neurogenic compartments have been identified in nearly all brain regions of those teleosts examined using detailed mapping studies. For example, in the brown ghost knifefish (*Apteronotus leptorhynchus*) proliferating cells are observed in over 100 different brain regions with over 100,000 new cells produced in any given 2 h period (Zupanc and Zupanc, 1992; Zupanc and Horschke, 1995). This finding is further validated by detailed mapping studies of five additional species showing proliferating neurons in all major subdivisions of the CNS, including *Danio rerio* (zebrafish), *Gasterosteus aculeatus* (three-spinned stickleback), *Poecilia reticulata* (guppy), *Carassius carassius* (common carp), and *Leuciscus idus* (golden ide) (Fig. 2B; Kirsche, 1967; Zupanc and Horschke, 1995; Zupanc et al., 1996, 2005; Maeyama and Nakayasu, 2000; Byrd and Brunjes, 1998, 2001; Ekström et al., 2001; Adolf et al., 2006; Grandel et al., 2006; Zupanc, 2006). Above all, the adult cerebellum has been ascribed as the major neurogenic compartment within the hindbrain of bony fishes, where approximately 75% of all newborn cells are generated (Zupanc and Horschke, 1995; Zupanc et al., 1996, 2005; Zupanc, 1999, 2001b; Ekström et al., 2001). Supplementary zones of marked proliferation are located at or near the surface of the ventricular, paraventricular and cisternal system, as well as in the telencephalon and optic tectum (Kirsche, 1967; Alonso et al., 1989; Zupanc and Zupanc, 1992; Zupanc and Horschke, 1995; Nguyen et al., 1999; Zikopoulos et al., 2000; Ekström et al., 2001; Zupanc et al., 2005; Zupanc, 2006; Adolf et al., 2006; Grandel et al., 2006).

Lastly, the localization and confirmation of neuronal progenitor cells in the caudal-most segment of the normal adult spinal cord of *Apteronotus albifrons* (black ghost knife fish) has been of specific interest (Anderson and Waxman, 1985). This study asserted that single ependymal cells of the inner ependymal layer of the spinal cord act as neuronal progenitor cells, and that following differentiation these cells take on a neuronal phenotype. By contrast, a more recently published study of *Petromyzon marinus* (lamprey) examining proliferation in the adult CNS, found no positively labeled cells for neuronal markers in the ependymal layer of the caudal spinal cord (Pizarro et al., 2004). Ascertaining the mechanisms responsible for differences in the neuronal proliferative capacity in the normal spinal cord of fishes, may prove to be a tractable approach to understanding how to elicit proliferation in the spinal cord of more complex vertebrates.

Despite teleosts being the most diverse and abundant class of modern day fishes, no research has focused on the major brain structures in extant representatives of more ancient groups, such as the lampreys and hagfishes, and cartilaginous fishes including sharks and rays (Zupanc, 2001a). This is paralleled by a corresponding lack of information on some of the most highly evolved teleost fishes, for instance, the advanced perciformes, such as cichlids.

Investigations of amphibian models of adult neurogenesis have established that selected neurogenic compartments do exist in a variety of representative species (Table 2). Proliferation in the main olfactory epithelium is shared by *Plethodon cinereus* (red-backed salamander), *Ambystoma tigrinum* (tiger salamander), *Ambystoma mexicanum* (axolotl), and *Rana pipiens* (leopard frog) (Graziadei and Metcalf, 1971; Richter and Kranz, 1981; Mackay-Sim and Patel, 1984; Dawley et al., 2000). Conversely, neurogenic compartments in the periventricular areas of the telencephalon, and the preoptic recess have been identified in the red-backed salamander and axolotl, *Rana esculenta* L. (European green frog) and *Rana temporaria* (European common frog) (Richter and Kranz, 1981; Bernocchi et al., 1990; Polenov and Chetverukhin, 1993; Dawley et al., 2000). Less common have been reports of neuronal generation in the vomeronasal epithelium and optic tectum as seen in the red-backed salamander and *Triturus cristatus* (crested newt), respectively (Minelli and Quaglia, 1968; Dawley et al., 2000).

Adult retinal neurogenesis continues to be a distinguishing feature of fish and amphibians (anamniotes) compared with modern day vertebrates (see Table 2). Anamniotes maintain

populations of multipotent progenitor cells in the ciliary marginal zone which give rise to the entire suite of retinal cell types in the adult animal (Meyer, 1978; Dunlop and Beazley, 1981; Reh and Constantine-Paton, 1983; Wetts and Fraser, 1988; Wetts et al., 1989; Marcus et al., 1999). Since these animals generate only a small portion of the retina during embryonic development, concentric rings containing all six retinal cell types are added to the periphery of the retina into adulthood (Straznicky and Gaze, 1971; Johns, 1977). In teleosts, in depth studies of the ciliary marginal zone of the retina have taken place in the zebrafish, three-spinned stickleback, and *Carassius auratus* (goldfish), whereas mapping of the ciliary marginal zone of amphibian has occurred in the leopard frog, *Xenopus laevis* (African clawed frog), and *Heleioporus eyrei* (moaning frog) (Straznicky and Gaze, 1971; Johns, 1977; Johns and Easter, 1977; Dunlop and Beazley, 1981; Meyer, 1978; Reh and Constantine-Paton, 1983; Raymond and Easter, 1983; Raymond et al., 1983; Wetts and Fraser, 1988; Wetts et al., 1989; Marcus et al., 1999; Ekström et al., 2001).

Similar to their avian relatives, reptiles contain only one primary neurogenic compartment during maturity. Proliferation in the adult reptilian brain follows a pattern similar to embryonic brain development with the primary neurogenic compartment localized to the PVZ of the lateral ventricular walls (Fig. 2B; García-Verdugo et al., 1989; Perez-Sanchez et al., 1989; Pérez-Cañellas and García-Verdugo, 1996; Pérez-Cañellas et al., 1997; Font et al., 2001; Peñafiel et al., 2001; Marchioro et al., 2005). Within this compartment, the greatest intensity of neuronal proliferation exists in the medial cortex of the telencephalic PVZ, believed to be homologous to the dentate gyrus in the hippocampus in mammals (Alverez-Buylla and Lois, 1995; Cayre et al., 2002; García-Verdugo et al., 2002; Nacher et al., 2002; Marchioro et al., 2005). Inside the medial cortex, the sulcus septomedialis has been compared with the 'hot spot' in the ventricular walls of birds (Font et al., 2001; García-Verdugo et al., 2002). Within the medial cortex, nearly 14% of all new neurons are generated in the medial cortex PVZ of the lacertid lizard (Font et al., 2001). In one of the few studies examining the common garter snake (*Thamnophis sirtalis*) neurogenic compartments have also been observed in the adult vomeronasal epithelium, as seen in the red-backed salamander (Wang and Halpern, 1988; Dawley et al., 2000). The vomeronasal system in these animals is highly specialized for the chemosensory detection of molecules, such as prey chemicals and pheromones (Halpern and Martinez-Marcos, 2003). To date the most detailed studies of reptilian adult neurogenesis have been limited to *Podarcis hispanica* (wall lizard) and *Tarentola mauritanica* (Moorish wall gecko), and one species of turtle, *Trachemys scripta elegans* (red-eared slider) (Fig. 1C; Table 2; García-Verdugo et al., 1989; Perez-Sanchez et al., 1989; Pérez-Cañellas and García-Verdugo, 1996; Pérez-Cañellas et al., 1997; Font et al., 2001). However, data are entirely lacking for the majority of lizard families, crocodiles, and snakes.

Detailed investigations of adult neurogenesis in the avian CNS have principally focused on *Serinus canaria* (canaries) and *Taeniopygia guttata* (zebra finches) (Nottebohm, 2002b). Songbirds have played a pivotal role in avian research, sparked by the seminal work of Nottebohm in the 1980s (Goldman, 1998). In all bird species studied thus far only one neurogenic compartment within the entire CNS has been observed and is restricted to the PVZ of the lateral ventricles within the forebrain (Fig. 2B; Table 2; Goldman and Nottebohm, 1983; Nottebohm, 1985, 2002a; Alvarez-Buylla and Nottebohm, 1988; Alvarez-Buylla et al., 1990; Nottebohm and Alvarez-Buylla, 1993; Barnea and Nottebohm, 1994; Rousselot et al., 1997; Goldman, 1998). Greater mitotic activity occurs in the ventral aspect of the ventrolateral wall and, to a lesser extent, in the dorsolateral tip of the wall (García-Verdugo et al., 2002). These discrete proliferative regions ('hot spots') within the PVZ produce new neurons throughout the entire lifespan of the animal (Doupe, 1994; Cayre et al., 2002).

It was not until the implementation of the thymidine analog, 5′-bromo-2′-deoxyuridine (BrdU) in the 1990s that adult neurogenesis was confirmed, and more importantly accepted, in the adult rodent (Nowakowski and Hayes, 2001; Gould and Gross, 2002). As seen in Table 2 (see also Fig. 1C), at present the most comprehensive studies of adult neurogenesis have been restricted to rodents (laboratory bred rats, mice: Altman and Das, 1965; Altman, 1969; Kaplan and Hinds, 1977; Bayer et al., 1982; Morshead and van der Kooy, 1992; Corotto et al., 1993; Kuhn et al., 1996; Tropepe et al., 1997; Kempermann et al., 1997a,b, 1998, 2003; Gould et al., 1999b; Biebl et al., 2000; Rietze et al., 2000; Brown et al., 2003; Liu and Martin, 2003; Shingo et al., 2003; Zhao et al., 2003; Enwere et al., 2004; Maslov et al., 2004; Sun et al., 2004; Bauer et al., 2005; Stranahan et al., 2006) and primates (macaque monkey: Gould et al., 1999a,c; Kornack and Rakic, 1999, 2001; Bernier et al., 2002; Koketsu et al., 2003; Ngwenya et al., 2006), although other animal models have been examined (McDermott and Lantos, 1990; Gould et al., 1997, 1998; Lavenex et al., 2000; Smith et al., 2001; Fowler et al., 2002; Harman et al., 2003; Amrein et al., 2004a,b; Rankin et al., 2004; Guidi et al., 2005; Luzzati et al., 2006; Ponti et al., 2006). Investigations on postmortem humans have only been initiated in the last 10 years, however the results, thus far, have been consistent with the data from other mammalian species (Eriksson et al., 1998; Kukekov et al., 1999; Bédard and Parent, 2004). Compared with anamniotic vertebrates, mammals show a significant decrease in the brain structures supporting neurogenesis into adulthood. From the data compiled two neurogenic compartments harboring adult neural stem cells have been confirmed in adult mammals (Zupanc, 2001a). These compartments include the telencephalic PVZ lining the lateral ventricles, and the subgranular zone of the dentate gyrus of the hippocampus (Fig. 2B; reviewed by Taupin and Gage, 2002).

Recently, research using rodent models has suggested the existence of two additional neurogenic compartments located in the adult mammalian brain. First, studies of mice have revealed newborn dopaminergic projection neurons within the adult substantia nigra, though proliferative activity was characteristically lower than seen in the PVZ and subgranular zone (Zhao et al., 2003). These results remain controversial,

however, since a follow up report was unable to confirm these initial findings, with the claim that no new dopaminergic neurons are generated in the substantia nigra (Frielingsdorf et al., 2004). Secondly, investigations of the PVZ layers in the posterior olfactory bulbs of adult rats have led to the notion that these layers may represent a *bone fide* neurogenic compartment in the mammalian CNS (Liu and Martin, 2003). One interpretation of this data is that the lateral ventricle subependyma extends rostrally to within the olfactory bulb itself, allowing the possibility for varying degrees of proliferative activity along this neurogenic axis. However, further support for in situ olfactory bulb neurogenesis comes from a recent study of the adult postmortem human olfactory systems (Bédard and Parent, 2004). Thus, new olfactory bulb neurons in adulthood may be derived intrinsically or via the rostral migratory stream.

Comparative investigations must be extended to all major invertebrate and vertebrate groups in order to underpin the diversity and plasticity of adult neurogenesis. Taking this approach will yield insight into questions such as why phylogenetically older vertebrates (i.e. fish) display more neurogenic compartments than modern vertebrates (i.e. mammals), and whether these compartments are permanent throughout adulthood or if populations of adult neural stem cells become quiescent over time. The ability to discern newborn neurons and their place of birth may be limited however, by how quickly technological advancements proceed to permit visualization of neurogenic compartments within the CNS, peripheral nervous system, and sensory systems (Gage, 2002). A systematic approach may prove useful, in particular, between members of the same class, in order to maintain consistency during comparative studies (Rakic, 2002). It is certain that continuing to rely solely upon the current model organisms will impede our ability to delineate the full complement of neurogenic compartments.

4. Taxonomic variation in adult neurogenic compartments

Given the animal models studied to date, it is well known that variation in neurogenic compartments and the migratory destination of proliferating cells exists between major invertebrate and vertebrate phyla and classes. For example, a significant distinction exists in features of adult neurogenesis between the five major classes of vertebrates including the rate, location, and number of neurogenic compartments and migratory streams. Still, these differences are not startling when considered at such a high taxonomic level since most of this variation could be attributed to the evolutionary lineage of each group. However, when inter-class and species-specific variation arises within a closely related group of species, this dissimilarity becomes a much more challenging question to address. Here, we highlight some of the defining examples, which have surfaced in the literature, and led us to contemplate alternate driving forces behind this trait.

4.1. Inter-class evidence from insects, crustaceans and reptiles

Adult neurogenesis in holometabolous (complete metamorphosis) and hemi-metabolous (incomplete metamorphosis) insects provide a first look at inter-class variation. It has generally been thought that following eclosion in adult holometabolous insects, neurogenesis is an extremely rare event compared with hemi-metabolous insects (Fahrbach et al., 1995). Contrary to this belief, studies have shown the occurrence of this trait in the mushroom bodies of the rove beetle, whereas no traces of adult born neurons have been identified in the adult honeybee (*Apis mellifera)* (Bieber and Fuldner, 1979; Fahrbach et al., 1995). Likewise, within hemi-metabolous insects, family-specific differences are also evident. While species of the family Gryllidae (i.e. house cricket) and several Coleopteran (i.e. beetles) families have revealed adult mushroom bodies as the central neurogenic compartment, the same has not been found in the migratory locust (Family: Acrididae) and American cockroach (Family: Blattidae) (Cayre et al., 1996). Collectively, these data demonstrate the need for a more rigorous pursuit of alternative explanations for this variation, including genetics, life history, and environmental factors. At this stage it would seem that phylogenetics (e.g. locust versus crickets) and the behavioral complexity found in social insects (e.g. honeybee) fail to explain differences in the presence or absence of adult neurogenesis (Cayre et al., 2002).

The presence of inter-class variation in adult neurogenesis is additionally reinforced by the work of Schmidt and Harzsch (1999) in species of decapod crustaceans. Whereby all species display neurogenic compartments in the lateral soma cluster of the brain, BrdU labeling in the ancestral spiny lobster (*Panulirus argus*) has shown that this species is exceptional in containing a proliferative site in the medial soma cluster (Schmidt and Harzsch, 1999; Schmidt, 2001). Given this discrepancy, one might posit that this proliferative site has been secondarily lost in more recently evolved species of decapod crustaceans.

Evidence for regional and inter-class variation in brain structures recruiting newly differentiated neurons and neurogenic compartments have also been presented in the class Reptilia. An earlier comparative review of the wall lizard, the Moorish wall gecko, and the red-eared slider exposed differences in the rate of neuronal incorporation into target sites, and the final migratory destinations of newborn neurons (Font et al., 2001). The rate of neuronal recruitment was greatest in the nucleus sphericus of the wall lizard, compared with the Moorish wall gecko where this was highest in the medial cerebral cortex. Furthermore, unlike the brain structures integrating newly developed neurons in the Moorish wall gecko, evidence for olfactory bulb and cerebellar neurogenesis also exists in the adult wall lizard and red-eared slider (García-Verdugo et al., 1989; Pérez-Cañellas et al., 1997; Font et al., 2001). Of the lizard species examined to date, *Thamnophis sirtalis* (common garter snake) is the only known species to contain neurogenic compartments in the adult vomeronasal and

olfactory epithelium (Wang and Halpern, 1988). Curiously, this is more typical of the neurogenic compartments reported for amphibians than the PVZ of reptiles (Pérez-Cañellas and García-Verdugo, 1996; Font et al., 2001). We infer that the lifestyle of these species is responsible for much of the observed variation. This is particularly true in the case of the garter snake, where chemical cues are used to communicate with one another and to locate potential mates (Shine et al., 2000; LeMaster et al., 2001).

4.2. Species-specific evidence from mice strains and crustaceans

Evidence for species-specific variation in adult neurogenesis is still in its infancy. The scarceness of examples stems from the general lack of recurring studies using the same models under identical captive or laboratory conditions. However, comparisons of mice strains offer us a glimpse of how the genetic background of a species may shape proliferation rates, neurogenic compartments, and the functionality of new neurons. Work on neurogenic compartments in decapod crustaceans also supports the notion that species-specific variability persists. Even though it may seem premature to probe for such attestation, examples of species-specific variability provide a realization of the extent of plasticity and potential of adult neurogenesis.

Work by Kempermann et al. (1997b) addressed the hypothesis that the genetic makeup of a species may in fact contribute to the degree of adult neurogenesis. By examining proliferation, survival, and neuronal differentiation in the dentate gyrus of the hippocampus of four strains of laboratory bred mice (C57BL/6, BALB/c, CD1 (ICR), 129/SvJ), the authors noted variability in proliferation, survival, differentiation, and total cell counts. Specifically, proliferation was greatest in C57BL/6 mice, while the survival rate of newborn cells was highest in CD1 mice. Moreover, the greater rate of proliferation of C57BL/6 mice was counterbalanced by a greater production of granule cells over a 6-day period. It is of interest, however, that despite the above differences data was non-significant between strains with respect to neuronal differentiation 4 weeks after BrdU application, and during comparisons of neuronal density (Kempermann et al., 1997b). This study indicates that at the species level, the genetic background of the animal strongly influences various facets of adult neurogenesis in the hippocampus. These results were supported by findings in Tropepe et al. (1997), which showed that forebrain subependymal neurogenesis *in vivo* and neural stem cell proliferation *in vitro* in the mixed strain B6129/F2 was significantly different than that of the SW/COBS. Given that all of the strains used have been reared in a highly standardized environment for multiple generations, it is unlikely that the observed variations in neurogenesis in laboratory mouse strains are a result of selection. Rather, these data indicate that variations can arise at random, can be tolerated by the overall program of hippocampal and subependymal neurogenesis and are heritable. In the laboratory, this variation may arise as a result of genetic drift. In contrast, although variation in rates of hippocampal neurogenesis in wild mice has been well documented (Amrein et al., 2004a,b), in this context variations would likely be subjected to selective pressures and have a higher probability of persisting in the population because they confer a selective advantage to hippocampal- or olfactory-dependent behaviors.

A second example of species-specific variation comes from studies of adult neurogenic compartments in decapod crustaceans. By comparing literature on adult true crabs, research by Schmidt and Harzsch (1999) showed a lack of BrdU-positive staining in the lateral soma clusters of three large adult crabs (*Cancer pegurus*), compared with commonly observed labeling in the lateral soma clusters of smaller adult crabs (*Cancer pegurus*, *Carcinus maenas*) (Schmidt, 1997; Schmidt and Harzsch, 1999; Hansen and Schmidt, 2001). Given these results, it has been postulated that this species-specific variation might be caused by a lack of newly generated olfactory projection neurons throughout the entire lifespan of some animals (Schmidt and Harzsch, 1999). Thus, since larger species are correlated with a greater age-class, neuronal birth may in fact halt or slow down during senescence, as has been observed to occur in adult laboratory and wild rodents (Kuhn et al., 1996; Tropepe et al., 1997; Amrein et al., 2004a,b).

Two major steps forward are needed to resolve the driving forces underpinning taxonomic variability in adult neurogenesis. First, we must encourage research focusing on new laboratory models. It is imperative that these models are both representative and in sufficient number for each invertebrate and vertebrate class, especially at the family and genus taxonomic levels. Secondly, we must expand studies of adult neurogenesis beyond the laboratory, and consider how this trait is influenced by the natural environment and social interactions (see Section 5). At this point, we can expect to see significant progress towards the value of adult neurogenesis and more importantly why it is likely to persist in some animals compared with others throughout adulthood. Moreover, we may be able to elucidate whether the primary source of variability responsible for taxonomic differences is attributed to species lineages, environmental factors, or a combination of both.

5. Adult neurogenesis in natural populations

Exploring the effects of environmental influences, animal behavior, and social interactions on adult neurogenesis is becoming a major initiative in the field. Collectively, these factors constitute a number of combined forces acting on brain plasticity, and ultimately, the rate and location of neurogenesis in adulthood. Even though many of these studies have taken place under simplified laboratory conditions, they have been instrumental in identifying a variety of natural mechanisms influencing the rate of adult neurogenesis in animals. These mechanisms are commonly divided into exogenous and endogenous cues, and include environmental enrichment and sensory inputs (Barnea and Nottebohm, 1994; Kempermann et al., 1997b, 1998; Gould et al., 1999b; Sandeman and Sandeman, 2000; Scotto-Lomassese et al., 2000; Hansen and Schmidt, 2001; Fowler et al., 2002; Scotto-Lomassese et al.,

2002; Brown et al., 2003; Hansen and Schmidt, 2004; Magavi et al., 2005; Meshi et al., 2006; Segovia et al., 2006), seasonal variation (Alverez-Buylla and Lois, 1995; Clayton, 1998; Dawley et al., 2000; Nottebohm, 2002a,b; Hansen and Schmidt, 2004; Hoshooley and Sherry, 2004), temperature and photoperiod (Ramirez et al., 1997; Peñafiel et al., 2001), physical activity (Bernocchi et al., 1990; van Praag et al., 1999a,b), stressful experiences (Gould et al., 1997, 1998; Tanapat et al., 2001; Bain et al., 2004; Mirescu and Gould, 2006), social status (Kozorovitskiy and Gould, 2004), hormones and sex differences (Doupe, 1994; Smith et al., 2001; Fowler et al., 2002; Margotta and Caronti, 2005), programmed cell death (Morshead and van der Kooy, 1992; Harzsch et al., 1999; Biebl et al., 2000; Amrein et al., 2004a; Sun et al., 2004; Lehmann et al., 2005; Lossi et al., 2005) and senescence (Altman and Das, 1965; Kara, 1994; Seki and Arai, 1995; Kuhn et al., 1996; Tropepe et al., 1997; Gould et al., 1999c; Amrein et al., 2004b; Mackowiak et al., 2004; Enwere et al., 2004; Maslov et al., 2004; Marchioro et al., 2005; Buckwalter et al., 2006; Chadashvili and Peterson, 2006; Driscoll et al., 2006; Luo et al., 2006). Taken together these data suggest that from insects to mammals, both the daily behavior and immediate environment of the species are intimately related with the addition of new neurons throughout adulthood. We begin this section by first commenting briefly on senescence, an endogenous mechanism that has received much attention in recent years for its effect on cell proliferation and neuronal differentiation. Many excellent recent reviews on the molecular and cellular regulation of adult neurogenesis exist (for example, Ming and Song, 2005; Hagg, 2005). We do not wish to replicate this vast information here. Rather, this section is meant to highlight the fact that intrinsic changes over time (e.g. gene expression) will likely interact with the environment to regulate adult neurogenesis, but our understanding of this interaction is in its infancy. More importantly, in this section we comment on natural population studies, and the implications of laboratory raised models, as a way of defining the exogenous mechanisms that control adult neurogenesis.

5.1. The effect of senescence on neurogenesis

Senescence is a naturally occurring process that begins after embryogenesis is complete and continues until the death of an organism. This endogenous process is generally thought to contribute to the overall decline or slowing of mental processing, and in the context of adult neurogenesis appears to exert an age-related decline in neurogenic capacity. Only in the last 10 years has senescence been considered in the same light as adult neurogenesis, implicating reductions in neuronal birth with age-related diseases and mental disorders. Coupling senescence with adult neurogenesis gives rise to many intriguing questions. First, does an age-related threshold of adult neurogenesis exist during the lifespan of an animal? Given the evidence to date, this would appear to be the case. However, whether this is equally prevalent in all neurogenic compartments remains uncertain. Furthermore, do all neurogenic compartments age at a similar rate, and what role does species variation play in this regard? Considering the variation in senescence across animals, it would be unreasonable to assume that neurogenesis is not affected differentially. However, most puzzling may be the functionality of this process in animals characterized by negligible senescence or indeterminate growth, such as many species of decopod crustaceans, teleosts, amphibians, reptiles, and a small number of mammals. In the proceeding paragraphs, we summarize some of the foremost findings showing conducive evidence for the role of senescence in age-related decline in the rate of adult neurogenesis.

Nearly all age-related studies have employed rodent models, and a combination of *in vivo* and *in vitro* approaches, to ascertain the effects of senescence on neuronal birth and migration to target structures. Seki and Arai (1995) were the first to clearly demonstrate a significant age-related decline in newly formed and developing granule cells in the dentate gyrus of young to old-aged adult rats. With few exceptions, recent literature has supported these initial findings using several BrdU protocols. These studies have pointing towards an age-related decline in neurogenesis in the forebrain PVZ, and dentate gyrus, comparing young (2–7 months) and old (23–27 months) adult animals (Kaplan et al., 1985; Kuhn et al., 1996; Tropepe et al., 1997; Jin et al., 2003; Bondolfi et al., 2004; Heine et al., 2004; Maslov et al., 2004). Corresponding reports of olfactory neurogenesis in mice have provided additional proof that aged mice (24 months) have fewer new interneurons in the olfactory bulb than young adult mice (2 months) (Enwere et al., 2004). Despite this decline, 24-month-old adults showed no difference in their ability to discriminate between two discrete odors compared with young adults, although fine olfactory discrimination was impaired in this group. Interestingly, Kempermann et al. (2003) showed that following pulse labeling with BrdU in 2–11-month-old mice, levels of BrdU-labeled neurons remained at a steady state in the granule cell layer. In comparison with the aforementioned studies, one interpretation of these latter results is that the onset of attenuated neuronal proliferation or survival is initiated at some time point between 11 and 23 months. One particularly important study by Kempermann et al. (1998) illustrated that an enriched environment can in part rescue age-related declines in mitosis and the production of adult born neurons. These investigators showed that by switching 6- and 18-month-old mice from standard housing to an enriched environment, with opportunities for social and physical interaction, and exploration, survival of BrdU-labeled cells increased by 68% in 6-month-old mice and 32% in 18-month-old mice in the dentate gyrus. Nevertheless, these data consistently demonstrate that the efficacy of the enriched environment on neuronal proliferation is diminished in older animals.

What mechanisms might be responsible for the observed age-related differences in adult neurogenesis? While there are likely many working hypotheses on this subject, several studies have suggested that neuronal differentiation is delayed with advancing age given the percentage of cells that do not express a neuronal phenotype 1 month after their birthday (Lichtenwalner et al., 2001; Nacher et al., 2003; Bondolfi et al., 2004;

Heine et al., 2004; Kempermann et al., 2004). Recent evidence has shown that for the maturation of neuronal phenotypes, specific growth factors secreted by astrocytes within their surrounding niche or target migratory site may be required. A study of young adult and aged rat brains showed that astrocyte populations in the mammalian PVZ and subgranular neurogenic compartments express high levels of fibroblast growth factor-receptor-2 (FGFR2) protein, and that FGF signaling could be involved in maintaining neurogenesis at later stages of adulthood (Chadashvili and Peterson, 2006). These authors observed an age-related decrease in FGFR2 in the olfactory bulb and hippocampus, which may indicate that expression of this receptor at the final migrating destination of developing neurons could be required for proper differentiation into mature and functional neurons. In a separate study, increases in transforming growth factor-beta 1, a cell cycle regulator that increases after injury and with age, secreted from astrocytes, was also shown to strongly inhibit hippocampal neurogenesis in aged transgenic mice (Buckwalter et al., 2006). Aside from growth factors, several hormones and neurotransmitters, including glucocorticoids, corticosterone and glutamate have also been associated with age-related declines in cell proliferation in the hippocampus of rats (Sapolsky, 1992a,b; Lupien and McEwen, 1997; Nacher et al., 2003; Abrous et al., 2005). Taken together, these data offer a glimpse towards potential intrinsic mechanisms that may be associated with changes in neurogenesis at varying stages of adulthood. As a rational basis for further investigating the phenomenon of neurogenic senescence, it is reasonable to posit that diminished neurogenesis is a byproduct of increasing age, rather than the alternative notion that decreased neurogenesis is somehow required for age-related function. Regardless, these studies must be extended to other major vertebrate and invertebrate populations before any meaningful insight is achieved.

5.2. *Towards the future of natural population studies*

Based on our knowledge from laboratory experiments we now must ask: How does adult neurogenesis occur in natural populations when animals are not restrained to specific conditions? Thus far only a handful of studies have examined free-living species (Barnea and Nottebohm, 1994; Lavenex et al., 2000; Amrein et al., 2004a,b; Hansen and Schmidt, 2004; Hoshooley and Sherry, 2004; Barker et al., 2005). A first step would be to consider whether laboratory data is upheld during investigations of the species in its natural environment (Amrein et al., 2004a, and see next section). If this is not the case, what exogenous factors are impinging on adult neurogenesis, and what are the most likely causes of this disparity? To prove successful, an integrative approach such as this would necessitate the collaboration between ethologists, evolutionists, anatomists, physiologists and neurobiologists.

Bridging the gap between the natural ecology of a species, population, or community with the associated changes in neuronal proliferation in adulthood may be closer than we think. In May 2000, Toronto, Canada played host to a workshop on ‘‘Hippocampal Neurogenesis in Natural Populations’’ in an effort to spearhead the need for more studies on the fundamental purpose and function of adult neurogenesis in mammals (Boonstra et al., 2001). The consensus of the workshop was that in order to predict the purpose and function of neurogenesis in humans, we must first unravel the mystery of how adult neurogenesis is correlated with the natural behavior of animals. We advocate that such a forward thinking approach should be applied to all past, current, and future invertebrate and vertebrate models of adult neurogenesis.

Tracking studies have been proposed to compare laboratory findings of neuronal replacement with those in the natural habitat of the species (Nottebohm, 2002b). For example, capture–release–recapture experiments can be designed, in which a sample of individuals is captured, injected with a birth date marker, released, and then recaptured following a predetermined time period. As an extension of this, we recommend additional detailed observations of activity patterns, social interactions, foraging mode, and environmental conditions both leading up to, and following injection with the cell proliferation marker. This may be accomplished by either field observations or by implanting a microchip able to record specific species-related or environmental data within the animal. One obstacle of integrative studies however, is the difficulty in pinpointing individual sources of variation leading to differences in proliferative activity, rate, and location of adult neurogenesis. This caveat may in part be overcome by designing more sophisticated laboratory paradigms where multiple cooperative factors can be tested simultaneously on a multifactorial model and compared with the results obtained from natural population studies.

Fish are excellent models to pursue questions surrounding the interplay between animal behavior, the immediate environment, and the generation of adult born neurons, given that these animals add new neurons to a large collection of brain areas throughout their lives (Fig. 2B; Scharff, 2000). An elegant study of cichlids in the Victoria, Malawi, and Tanganyika freshwater lakes of East Africa provide an ideal natural population to delineate how microhabitat selectivity can produce modifications in brain plasticity, and to posit whether such changes are a result of adult neurogenesis (Huber et al., 1997; Kotrschal et al., 1998). The first of three major trends showed that piscivores had larger olfactory bulbs and optic tecta than insectivores and zoo-planktivores. Secondly, the optic tectum was smallest in species from deep water habitats and largest in pelagic species, while the cerebellum was largest in pelagic species. Finally, the telencephalon also increased in size from deep to shallow waters. From these results, it is tempting to conjecture that adult neurogenesis may be responsible for the differences observed in brain size in response to feeding specialization and water depth. However, to date the likelihood of this hypothesis remains speculative. These neuroanatomical trends substantiate the need for further investigations into predator–prey relationships, sensory modalities, activity patterns, biological rhythm, mating, and foraging of species in their natural environment. It has become widely accepted that these shared factors are likely to play a central role in shaping the presence of adult neurogenesis.

5.3. Implications of laboratory raised models

An important concern that has surfaced in the field is the question of how representative are laboratory studies when contrasted with those in the natural environment of a species. The possibility that laboratory-bred or captive animals may display differences in their rate of adult neurogenesis compared with free-ranging animals first arose during studies of black-capped chickadees by Barnea and Nottebohm (1994). These investigators discovered a nearly two-fold decrease in cell labeling in the hippocampus of captive birds compared with wild birds. This same trend was reported in a similar study by Hansen and Schmidt (2004) on adult shore crabs. Crabs kept in captivity for a period of 12 weeks before BrdU injection showed a general decline in the number of BrdU-immunoreactive cells than crabs processed shortly after being caught. Therefore, it is critical that we approach the results of laboratory-bred or captive animals with caution and not take for granted that the same findings will be paralleled in the wild. It has been suggested that this issue may best be dealt with by consistently including a wild-sample (captured–injected with a birth date marker–released) of the model organism of interest to reveal the extent to which new neurons are added in the adult brain under typical, free-ranging conditions (Nottebohm, 2002b). This approach would allow direct comparisons to be made as well as aid in modifying the laboratory environment during subsequent studies so that they can be conducive to the behaviors of animal in their natural habitat. However, in many cases a free-ranging control is impractical for a single laboratory to support, in which case collaborative initiatives could be sought. Since Barnea and Nottebohm (1994) published their work on black-capped chickadees, a number of invertebrate and vertebrate papers studying animals under impoverished and enriched living conditions have been put forth (Kempermann et al., 1997b, 1998; Sandeman and Sandeman, 2000; Scotto-Lomassese et al., 2000). Although these experiments did not compare free-ranging and laboratory animals, the data consistently show that animals living in enriched environments display a greater presence of adult neurogenesis.

At least two considerations must be taken into account when evaluating the reliability of laboratory data in comparison to data from the natural habitat of an animal. First, laboratory-bred animals lack the complete assortment of stimuli during development leading up to adulthood, which would otherwise be available under natural conditions. Hence, for this reason alone we should anticipate differences in the distribution of adult neurogenesis between laboratory-bred and wild animals. Second, when considering an ‘‘enriched laboratory environment’’, it is unlikely that this simulated habitat parallels that present in the natural habitat of the animal. For instance, interactions that persist in the natural environment of a species, including predation, competition for mates and territory, and environmental stochasticity cannot be recreated under artificial laboratory conditions with laboratory-bred animals (Boonstra et al., 2001). While laboratory studies are extremely useful in isolating individual variables contributing to the persistence of adult neurogenesis, the constant bombardment of complex multimodal stimuli common to all animals, including humans, can only be found in the natural environment.

The interactions between multiple mechanisms regulating levels of neurogenic activity in adulthood within natural populations are of great interest. Such questions however, pose a serious challenge because of the difficulty of ascertaining to what degree each mechanism contributes to the observed changes in proliferation. Moreover, whether multiple mechanisms have a synergistic or antagonistic effect on levels of mitotic activity, and in which combination, is poorly understood, but is likely to occur in the wild. Recent work by Gould and colleagues have highlighted that the effect of positive and negative neurogenic mechanisms alone, known to affect levels of proliferation, interact to influence one another in combination (Stranahan et al., 2006). Their study demonstrated that the positive effects of physical activity, such as running, on the rate of newborn neurons in the rat dentate gyrus is severely attenuated in animals housed in social isolation compared to those housed in groups. This indicates an additive effect of physical activity and social interaction, and the requirement of a social environment for increased neurogenic activity. This study illustrates the need for designing more complex assays to test the interactions between multiple mechanisms that are currently known to influence the levels of adult neurogenesis alone.

Asserting the primary behaviors and activity-patterns of a species within their natural habitat will undoubtedly facilitate our ability to uncover the function of adult neurogenesis and how it is modified by such behaviors (Scharff, 2000). By combining tracking studies with continuously improving laboratory techniques, it is conceivable to expect significant advancements in this area over the next 10 years. Nevertheless, to do so investigators must be willing to go beyond the laboratory. The importance of environmental influence on adult neurogenesis may be confirmed by altering the natural environment of the animal. Animals could either be reared to adulthood in the novel environment, or transferred to such an environment at a specific developmental stage, with birth date labeling performed accordingly. Comparisons between the typical environment of the species and the novel environment could then be assessed.

The benefits of natural population studies are two-fold. First, they are ideal for testing the accuracy of laboratory experiments to confirm whether the same results are obtained under natural conditions. Such data is central to testing whether differences exist in the number of neurogenic compartments in laboratory-bred animals compared with those examined in the wild. Presently, strong evidence supports the claim that adult neurogenesis is more plentiful in animals in their natural environment compared with laboratory-bred or captive animals (Barnea and Nottebohm, 1994; Hansen and Schmidt, 2004). Second, natural population studies provide useful data on how the daily behavior of individuals, populations, and communities lead to an increase or decrease in adult neurogenesis within their true habitat; that is, the ‘‘dynamics’’ of adult neurogenesis. However, the limited number of different species studied to date

in the laboratory, and especially in the wild, does not allow us to corroborate whether this logic can apply to a more general population of animals.

6. Functional significance of adult neurogenesis

The intrinsic ability of synapses to undergo rapid activity-dependent refinement of their microstructure is crucial for the formation of neural circuitry during embryogenesis (Hensch, 2005). Moreover, microstructural changes in the mature brain, and in particular changes in synaptic morphology, occur in response to sensory stimuli and are required for learning and memory formation (e.g. Feldman and Brecht, 2005). In general, synaptic morphology (e.g. number of dendritic spines and size of post-synaptic densities) appears to be quite labile and correlates with changes in behavior. Thus, the formation, modification and elimination of synapses can play a fundamental role in information processing in the CNS.

In conceptualizing this common notion of neural plasticity, one usually invokes an image of a neural circuit containing a stable number of neurons that undergo alterations in their synaptic connectivity. However, elimination and formation of synapses can be the direct result of the removal and replacement, respectively, of entire neurons. This expanded view of neural plasticity, one that includes cell loss, addition or replacement, is only now receiving more attention given the interest in the field of adult neurogenesis. Nonetheless, there is a paucity of theoretical and experimental insight into the potential role of neuronal replacement as a mechanism of neural circuit plasticity.

Many other excellent reviews have recently documented our current understanding of the potential role of neurogenesis in brain function (Kempermann et al., 2004; Doetsch and Hen, 2005). We will not review this vast literature here and instead refer the reader to these reviews for more information. Our intention here is to provide a few select examples of the challenges that are faced with integrating neurogenesis into a more complete understanding of neural plasticity and to highlight the value of using a comparative approach to facilitate our progress in this area.

6.1. Ascribing a functional role for neurogenesis in distinct brain regions

Theories describing the function of adult neurogenesis are strongly influenced by our understanding of the overall function of the brain region that contains neurogenic compartments. For example, most of the current research focus on adult neurogenesis is aimed at understanding how the generation of new neurons contributes to the processes related to learning and memory. Given the presence of neurogenesis in anatomical areas such as the mammalian hippocampus and avian song nuclei, it seems reasonable to test functional hypotheses within this cognitive framework. However, the facility with which neurogenesis can be altered by various hormones (Gould et al., 1998; Shingo et al., 2003), exercise (Kempermann et al., 1997b; van Praag et al., 1999a,b) and enriched environments in both vertebrates and invertebrates (van Praag et al., 1999b; Scotto-Lomassese et al., 2000) indicates that neurogenesis may, in fact, have a predominant role in modifying circuitry related to the processing of sensory information. Here the use of other species of animals might be particularly relevant because of the presence of neurogenesis in regions of the brain or ganglia that are not principally involved in cognition. For example, unilateral olfactory and visual sensory deprivation can reduce neurogenesis independently of changes in hormone levels in the mushroom bodies of adult crickets (Scotto-Lomassese et al., 2002). Mushroom bodies are typically considered to mediate learning and memory in some arthropods, but neuroanatomical and functional evidence suggests that the mushroom bodies may be multimodal sensory integration centers that project to the protocerebrum (Ito et al., 1998).

Recently, Kempermann (2002) has posited that the function of new neurons in the mammalian hippocampus is to modify hippocampal circuitry in order to enhance its power for processing information that will eventually be stored as memories in the isocortex. This theory is somewhat limited because it focuses primarily on the addition of new neurons into existing circuitry, which is only one aspect of the continuum of cellular history that defines neurogenesis. For example, the loss or steady state replacement of neurons in the hippocampus has not formally been addressed. Nonetheless, this ‘‘gateway’’ hypothesis is appealing because it ascribes a function for neurogenesis based on the detailed function of hippocampal circuitry as a transient memory gateway for the brain and not based on a behavioral readout (e.g. spatial memory in a water maze test) that likely is the result of multiple interacting neural circuits, some of which may not be modified by neurogenesis. Neurogenesis in the adult retina, cerebellum, or diencephalic nuclei of amphibians and teleosts present a similar challenge for formulating functional hypotheses that are based on the detailed function of the local neural circuitry.

The presence of neurogenic compartments between homologous brain regions in different groups of animals, such as the PVZ surrounding the telencephalic lateral ventricles in amniotes, which generates neurons migrating to pallial and subpallial areas, cannot be used *a priori* as evidence for common functional requirements for persistent neurogenesis in these regions. For example, in rodents the telencephalic PVZ is the main source of interneurons that are recruited along the rostral migratory stream toward the olfactory bulb, and whose long-term survival depends on olfactory bulb activity (Petreanu and Alvarez-Buylla, 2002). However, in songbirds, the telencephalic PVZ primarily contributes new neurons to forebrain nuclei related to song acquisition (Alvarez-Buylla et al., 1992). Furthermore, evidence for the functional requirement of neurogenesis for avian olfaction is largely unexplored, despite the fact that many bird species, such as the homing pigeon (*Columba livia*) and domestic fowl (*Gallus domesticus*), have olfactory systems that are functionally and anatomically homologous with those of mammals (Jones and Roper, 1997).

Perhaps the ultimate question is whether we can identify a non-trivial, universal theory for the functional significance of

adult neurogenesis. Until we have a detailed understanding of how neurogenesis affects the function of neural circuitry in a variety of distinct brain regions, we cannot assume that there is a common explanation for adult neurogenesis.

6.2. Intrinsic modulation of neurogenesis

At the interface between environmental cues, such as social interactions and seasonality, and progenitor cells in the PVZ lies the local anatomical circuitry that controls, in part, the behavioral response to these cues. Evidence for the role of local circuitry as a proximate regulator of adult hippocampal neurogenesis has been accumulating since the demonstration that blockade of NMDA-type glutamate receptors or lesioning of the entorhinal cortex (afferent projections to the dentate gyrus) resulted in an increase in progenitor cell proliferation (Cameron et al., 1995). Recent studies have extended these observations by providing direct evidence that excitatory neuronal activity can regulate the production of new neurons and that this mechanism may play a prominent role in the storage and/or clearance of memories (Deisseroth et al., 2004). However, the production of new neurons is only one aspect of adult hippocampal neurogenesis and there is now strong evidence that excitatory neuronal activity can modulate neuronal differentiation (Tozuka et al., 2005), circuit integration (Ge et al., 2006) and the survival of newly generated (and perhaps newly integrated) neurons (Tashiro et al., 2006). Together, these studies provide compelling evidence for complex intrinsic regulation containing both feed-back and feed-forward signaling to control the production, differentiation and survival of new neurons. Whether such a model can be applied to all regions of the brain that maintain neurogenic activity remains to be determined, but these types of investigations will allow us to gain insight into the functional consequences of neurogenesis in the relevant context of cellular interactions within a circuit as opposed to an inappropriate view of neurogenesis as an isolated phenomenon within the tissue.

6.3. Active versus induced neurogenesis: unpredictable sources of neuronal replacement

Despite the widespread evidence for adult neurogenesis among a diverse array of metazoans and the strong evidence for the primacy of stem cell function towards maintaining adult neurogenic compartments, we continue to be surprised by this biological phenomenon. One surprise comes from studies demonstrating the neurogenic potential of anatomical loci that normally do not exhibit active (or homeostatic) neurogenesis.

One recent study examined the potential role that neurogenesis may have in memory recovery in the hippocampus after an ischemic lesion (Bendel et al., 2005). Adult neurons are very susceptible to ischemic damage because of their high metabolic demand for oxygen and their poor glycogen storage capacity. Pyramidal neurons of the CA1 region of the rat hippocampus degenerate after an ischemic event leading to behavioral deficiencies. Ischemia actually enhanced neurogenesis in the subgranular zone of the dentate gyrus, but these new neurons did not repopulate the degenerated CA1. Instead, new neurons destined for the CA1 were derived from PVZ precursors that were induced to proliferate as a result of the ischemic insult. This region harbors quiescent neural stem cells that can be re-activated if removed from their *in vivo* environment (Seaberg and van der Kooy, 2002) or induced to generate new neurons *in vivo* (Nakatomi et al., 2002), but does not produce new CA1 neurons under homeostatic physiological conditions. Regeneration of CA1 neurons after at least 90 days is associated with restoration of CA1-dependent learning and memory tasks, suggesting that the neurons are at least partially functionally incorporated. Thus, despite the regenerative potential of the PVZ regions of the rat hippocampus, neurogenesis in the CA1 does not occur under normal circumstances. One implication of this finding is that homeostatic neurogenesis has no functional role in CA1 physiology.

Another example of the presence of quiescent stem cells *in vivo* in regions with no active neurogenesis is the mammalian retina. The peripheral ciliary margin in the adult rodent and human retina harbors a stem cell population with the capacity to generate new retinal neurons (e.g. rod photoreceptors) *in vitro* (Ahmad et al., 2000; Tropepe et al., 2000; Coles et al., 2004) or after transplantation *in vivo* (Coles et al., 2004), but remains inactive *in vivo*. A comparative analysis of neurogenesis in homologous regions of other vertebrates may reveal the molecular and cellular properties of these neurogenic zones in order to understand why the mammalian counterparts have undergone quiescence. For instance, in teleost fish, adult neurogenesis is evident in the lateral PVZ of the telencephalic area dorsalis *in vivo* (Ekström et al., 2001), a region that is functionally homologous to the mammalian hippocampus (Rodriguez et al., 2002). Moreover, the molecular and cellular basis of neurogenesis in the postembryonic ciliary marginal zone of teleosts, amphibia and even recent studies in chick (reviewed in Hitchcock et al., 2004) are very important foundations for understanding the biology of adult ciliary marginal zone neurogenesis and for discovering the mechanism that prevents active neurogenesis in the adult mammalian retina.

Finally, conventional wisdom tells us that adult neurogenic zones are, by and large undifferentiated and periventricular in nature, or at least very well circumscribed with a clear embryonic delineation from a periventricular germinal matrix (Alvarez-Buylla et al., 2001). Likewise, the primary mode of neuronal replacement is the emigration of progenitors from these zones. Although there is fairly strong evidence for an environmental niche that maintains adult neurogenesis (see Doetsch, 2003), there is evidence for *in situ* neurogenesis in regions that are relatively distant from the PVZ and involve little or no progenitor cell migration, such as retinal rod progenitors (Mack and Fernald, 1995) or telencephalic progenitors (Mueller and Wullimann, 2002) in teleosts. In these examples, the sources of the new neurons appear to be committed progenitors that do not reside in the PVZ. Although antecedent migration of these quiescent progenitors from a germinal zone during postembryonic or adult stages is formally possible, these findings indicate that at least some new neurons in the adult brain might be produced *in situ* from resident precursors. Multipotent progenitors with colony-

forming properties *in vitro* have been isolated from many regions of the postembryonic rodent brain, but most appear not to persist in adulthood (Seaberg et al., 2005). However, a recent report indicates that non-periventricular (*in situ*) neurogenesis may exist in adult mammals as well. Luzzati et al. (2006) show that there is a rare population of radial glial-like cells located in the parenchyma of the adult caudate nucleus of the rabbit with the capacity to generate new neurons *in vivo*. Given that neural stem cells do not appear to be localized within the parenchyma of the adult rodent striatum (Morshead et al., 1994), these findings suggest that this rare population of neuronal progenitor cells may be derived from the striatal PVZ. Moreover, since adult neuronal progenitors can actively migrate into the striatal parenchyma after growth factor infusions in the lateral ventricles (Craig et al., 1996), it is possible that these relatively quiescent progenitors are derived from PVZ stem cells in adulthood, rather than existing as a remnant of embryonic neurogenesis. From a comparative standpoint, the identification of alternative (and sometimes unpredictable) sources for new neurons in the adult brain will provide a deeper understanding of the species variation in adult neurogenesis that exists and possibly lead to novel evolutionary models to explain the adaptive significance of adult neurogenesis.

6.4. Species-specific neurogenesis and behavior

An examination of mushroom body neurogenesis in the adult brains of two different species of insects provides a particularly poignant example of the challenges we face in understanding the behavioral significance of neurogenesis. The function of the mushroom bodies is associated with learning and memory as well as multimodal sensory integration and there is evidence for structural plasticity during insect behavioral development (Zars, 2000). Studies using the adult house cricket (*Acheta domesticus*) have clearly demonstrated neurogenesis in the adult mushroom bodies (Cayre et al., 1996). However, in the adult honeybee (*Apis mellifera*), there is no apparent neurogenesis in the mushroom bodies (Fahrbach et al., 1995). Given the importance of the insect mushroom bodies for learned behavior in both species, this drastic difference reveals that neurogenesis, as a substrate for structural plasticity in the brain, may be highly adaptable and not a pre-requisite for functional plasticity. However, given the evidence for quiescent stem cells in regions of the brain where neurogenesis does not occur under baseline physiologic conditions, it is possible that neurogenesis can be induced in the honeybee mushroom bodies under non-homeostatic conditions, such as lesion-induced degeneration. Further studies will be required to determine the extent to which region-specific neurogenic potential is observed in the absence of homeostatic neurogenesis in both invertebrates and vertebrates.

6.5. Neuronal turnover

Neuronal turnover is a key feature of homeostatic neurogenesis and has been examined most extensively in mammals. Cellular homeostasis (or turnover) can be defined as the death of mature neurons in a local circuit in order to compensate for the insertion of a newly recruited neuron. However, evidence indicates that the vast majority of newly generated neuronal progenitor cells die before they have become functionally incorporated within a local circuit. Thus, neurogenesis is balanced by extensive cell death of progenitor cells as well as mature neurons. Volumetric constraints impinge upon the continuous growth of most brain structures, thus programmed cell death becomes an important regulatory mechanism in many animals. However, we still know little about the functionality of this process in animals characterized by negligible senescence or indeterminate growth, such as teleosts, some amphibian species, and decapod crustaceans. A reasonable prediction may be that lower relative rates of apoptosis are present in these species compared with mammals where adult neurogenesis has been significantly reduced.

Much of what we know regarding the association between apoptosis and neurogenic regulation arises from investigations of the neurogenic compartments of rodent models. For example, work by Morshead and van der Kooy (1992) used a combination of retroviral lineage tracing and BrdU labeling to show strong evidence for the occurrence of postmitotic death of constitutively proliferating cells in the PVZ of the adult mouse brain. Likewise, in the dentate gyrus of the adult mouse hippocampus, by employing Bax knock-out mice Sun et al. (2004) were recently able to confirm that the proapoptotic gene Bax is crucial to ongoing apoptosis for adult born hippocampal neurons. Moreover, BrdU labeling along with deoxy-uridine triphosphate-nick end (dUTP-nick end) labeling in the dentate gyrus and olfactory bulb of adult rats revealed that continuous neuronal incorporation and cell death is present in these structures (Biebl et al., 2000). However, because the same population of newly incorporated BrdU-positive neurons were not double-labeled with dUTP-nick end labeling, it is difficult to state whether the high rates of programmed cell death recorded in this study, especially those in the olfactory bulbs, are indicative of the same population of neurons. These and other studies provide strong evidence that the number of adult born neurons that undergo migration to become integrated into neuronal circuits is mediated by apoptotic mechanisms.

In wild-living rodents, correlations between cell proliferation and cell death have also been presented. Amrein et al. (2004a) evaluated granule cell number, cell death and cell proliferation in the dentate gyrus across yellow-necked wood mice, bank voles, and European pine voles compared with six strains of laboratory mice. All species showed a significant relationship between the number of dUTP-nick end-stained cells and the number of pyknotic cells. A correlation between the number of pyknotic cells and proliferation was also noted in the dentate gyrus. As previously shown by Cameron and Gould (1996) in rats, the current study implies that in general, cell generation in the dentate gyrus is intimately linked with levels of apoptosis amongst these rodent models. Variation in the number of pyknotic and apoptotic cells between wild and laboratory-bred species were also observed, supporting the notion that differences exist between captive-bred and free-ranging animals.

Another example of the integral role of apoptosis with adult neurogenesis comes from a study of the lobster deutocerebrum.

Examinations of the central olfactory pathway of the American lobster have confirmed that birth and death of olfactory interneurons appear to be coupled together (Harzsch et al., 1999). In 7-year-old animals cell death was observed in a small group of projection interneurons bordering near the accessory lobes, a common site of recruitment of newly differentiated neurons. These researchers suggested that this continual turnover of olfactory interneurons may be linked with the continuous turnover of olfactory receptor. Given this finding, it would seem that newborn olfactory interneurons might function foremost to replace those interneurons eliminated during pruning of olfactory circuits in order to respond to novel olfactory cues. However, this intriguing hypothesis of the interdependence of peripheral and central neurogenesis in the olfactory pathway may be species-specific, and in particular only occur in crustaceans that molt throughout adulthood. In a recent study of the crab, *Libinia emarginata*, which unlike decapod crustaceans does not molt throughout adult life, the addition of new olfactory receptor neurons was shown to cease after the terminal molt, while olfactory interneurons in the brain continued to be generated (Sullivan and Beltz, 2005). Thus, peripheral neurogenesis is not absolutely required for the regulation of central neurogenesis in the olfactory system.

It has been postulated that without homeostatic mechanisms, such as cell death, the integration of newly recruited neurons into local circuitry over time could lead to detrimental effects on circuit function, such as seizures or erroneous memory recall (Meltzer et al., 2005). Novel computational methods will be an important aspect of modeling how neuronal turnover impacts on behavior (Chambers et al., 2004), which will form the basis for testing hypotheses in real neural circuits, such as within the hippocampus. Many questions remain to be answered with respect to the relationship of cellular turnover and the regulation of circuit function and, ultimately, behavior. For example, although proliferating astrocytes represent a relatively small population of cells within these neurogenic zones, it is not clear to what extent these cells contribute to neural circuit function or maintenance, or whether they play a purely supportive role in ensheathing the progenitor cells and maintaining a blood–brain barrier. Moreover, the relationship between maturation of newly recruited neurons and behavioral changes dependent on neurogenesis is not clear. Recent evidence indicates that maturational progression of newly generated dentate gyrus granule neurons in the rhesus monkey takes five times longer to complete compared to a similar progression in rat (Ngwenya et al., 2006). How does this difference compare to the rate of hippocampal-dependent learning and memory acquisition between the two species? Answers to these and other questions will lead to a deeper understanding for the role of neurogenesis in circuit plasticity and behavior.

7. The origin of adult neurogenesis: searching for evolutionary clues

The evolution of adult neurogenesis continues to elude us. Its presence and functional requirement (at least in some species) nonetheless implies that it is of fundamental biological importance rather than simply an inherited, vestigial character. Unraveling the origin of this trait and the selection pressures that have given rise to its presence or absence in the adult nervous system poses by far the greatest challenge today. This challenge is perpetuated by the need to understand, within a comparative context, the life history of the species and the evolutionary development of the structures retaining this plasticity (Gage, 2002). As has been advocated during studies of CNS evolution, an initial step to addressing the phylogenetics of adult neurogenesis should start by making structural and functional homologies between simple and more complex animals (Holland, 2003). In cooperation with the role of natural selection, and other underlying driving forces, which presumably promote the fitness of this trait, the evolutionary origin of adult neurogenesis may thereby be within reach (Boonstra et al., 2001).

Among vertebrates, there is convincing evidence that adult neurogenesis is an evolutionary conserved trait. The picture is less clear however, in the case of invertebrates that have been plagued by few studies of representative groups (see Fig. 1). For instance, in the class Mammalia, species such as mice, marmosets, macaques, humans and more recently non-eutherian marsupials, have demonstrated the persistence of this phenomenon (McDermott and Lantos, 1990; Eriksson et al., 1998; Kornack and Rakic, 1999; Harman et al., 2003). Comparisons across vertebrate taxa suggest that adult neurogenesis is likely to have arisen in a common ancestor of today's chordates (Zupanc, 2001a). However, collectively, more derived vertebrate species (i.e. birds, mammals) have undergone a remarkable reduction in this plesiomorphic trait compared with ancestral vertebrates. A point worth considering is that reptiles and birds, which are phylogenetically closely related, also share a single common neurogenic compartment localized in the cells of the lateral ventricular walls (see Figs. 1C and 2B; Pérez-Cañellas and García-Verdugo, 1996; Rousselot et al., 1997; Goldman, 1998; Font et al., 2001; Nottebohm, 2002a). Thus, lineages that have evolved or radiated within an overlapping time period may be a principal indicator of shared properties of adult neurogenesis. Cladistic analysis of such trends would be indispensable in deducing the significance of these relationships.

Comparisons of the evolution of adult retinal neurogenesis in concert with adult neurogenesis in the CNS of animals are useful in attempting to expose some overarching trends of this biological phenomenon. In the CNS of vertebrates, the consensus is that as one moves from anamniotes to amniotes there is an obvious reduction in the number of neurogenic compartments and brain structures recruiting new neurons. The end product is a general decrease in the percentage of adult neural stem cells born and dispersed throughout the brain. Likewise, the potential for regeneration also appears to have a phylogenetic origin. Fish and amphibian are known to regenerate entire brain regions following removal or damage, which parallels their capacity for continual neurogenesis throughout adulthood (Zupanc and Ott, 1999; Gotz et al., 2002). By comparison, the ability to regenerate selective brain regions is, for the most part, lost in reptiles, birds, and mammals. In

adult retinal neurogenesis, a similar trend can be attributed to phylogenetic lineage. In the case of adult retinal progenitor cells, amniotes contain populations restricted in their proliferative potentially *in vivo*, unlike fish and amphibians. In birds, multipotent adult retinal progenitor cells can only generate amacrine and bipolar cells up to 2 weeks post-hatching, whereas mammals preserve only a dormant, albeit multipotential, population of adult retinal progenitor cells in the pigmented ciliary margin of the ciliary body after birth (Morris et al., 1975; Ahmad et al., 2000; Fischer and Reh, 2000; Tropepe et al., 2000; Kubota et al., 2002).

The ongoing generation of adult retinal progenitor cells observed in fish and amphibians is explained by the limited growth of the retina during embryonic development; thereby leading to the addition of all retinal cell types to the retina in adulthood (Straznicky and Gaze, 1971; Johns, 1977). The widespread presence of adult neurogenesis in the CNS of these classes can similarly be linked to the continuous growth of these animals (Easter, 1983). On the other hand, the perinatal limitations of proliferation and phenotypic constraints of adult retinal progenitor cells in modern vertebrates seem to include quiescence or loss of stem cells. However, considering that retinal histogenesis in warm-blooded vertebrates is completed perinatally, these limitations may not come as such a surprise (Teakle et al., 1993; Fischer and Reh, 2000). Compartments still housing actively proliferating adult neural stem cells in adult mammals, such as the hippocampus, may therefore represent evolutionary conserved plasticity, since these areas may benefit the fitness of the species, as has been described in songbirds (Nottebohm, 1985, 2002a; Barnea and Nottebohm, 1994).

There is no simple mechanism to explain the origin of adult neurogenesis. The precise driving forces and selection pressures contributing to the perseverance of this biological phenomenon may in fact remain blurred until we bridge the gap between the plasticity of this trait and its function in the natural environment. In doing so however, we must be mindful of the distinction between original function and current fitness when considering the adaptive significance of adult neurogenesis (Font et al., 2001). It has been suggested that because of the resemblance of regulatory mechanisms during adult and embryonic neurogenesis, the possibility that this trait, in adulthood, is a remnant of embryonic development rather than an adaptation to specific selective pressures in adult life, should not be disregarded. However, there are major differences in adult neurogenesis compared to embryonic neurogenesis and consequently, regulatory mechanisms may have been partly co-opted for a specifically adapted adult function. In an effort to determine the evolutionary origin of adult neurogenesis, future systematic reassessment of the major evolutionary lineages of invertebrates and vertebrates may prove invaluable in uncovering relationships between the biological characteristics of this process.

8. Conclusion

Adult neurogenesis is a fascinating biological trait, which has captivated the minds of many researchers since its debut in the field over 40 years ago. Its species-wide diversity forces us to question its evolutionary roots. In this review, it has been our aim to provide a comparative framework for understanding the biological principles of adult neurogenesis by emphasizing the robust nature and variation of this trait across the animal kingdom. We firmly believe that by taking a comparative, multi-disciplinary approach, we will more readily address the evolutionary, anatomical and functional implications of adult neurogenesis.

Acknowledgements

Although we attempted to cite the appropriate articles throughout this manuscript, we invariably missed important contributions in some sections while in other sections we purposely limited our discussion to highlight only a few representative examples due to overall space limitations. We apologize to our colleagues for these omissions. We thank the anonymous reviewers for helpful comments on this manuscript. Financial support from the Canada Foundation for Innovation, the Ontario Innovations Trust, the Canadian Stem Cell Network, and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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