Adult neurogenesis in the brain of higher vertebrates: implications of the paradigm shift

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The recent research on the mammalian brain, along with sustained research on the avian brain and older research on the rodent brain, has brought about one of the greatest paradigm shifts in neuroscience. The discovery of neuronal stem cells in neurogenic sites that migrate, differentiate and get recruited into functional circuits has upset a fundamental principle of science. Adult neurogenesis in hippocampal and extra-hippocampal circuits is attenuated or enhanced in response to diverse environmental, behavioural and physiological conditions, has implications for learning and memory mechanisms, and awakens possibilities for repair of injured brain tissue and treatment of neurodegenerative disorders.

ONE of the dogmas of neuroscience has been that higher vertebrates and humans are born with their full complement of neurons, with restricted postnatal neurogenesis taking place in the first few months of life and none thereafter. Throughout the twentieth century, this basic principle has prevailed and attempts to suggest otherwise thwarted, primarily because neurons are highly differentiated post-mitotic cells. Neuroscientists provided evidence to support that learning and formation of new memories entailed a rewiring of a pre-wired neuronal circuitry available at birth, which is an established fact. During most of the second half of the last century, the plastic brain thinking ruled supreme; neurons undergo plastic changes, varied degrees of activity-dependent plasticity either progressive (dendritic spouting) or regressive (pruning of redundant synapses), long-term potentiation (LTP), long-term depression (LTD), changes in ion channels and their properties, transmitter concentrations, gene expression, protein synthesis and long-term phenotypic changes[1–11].

That the adult brain also maintains a population of immature neuronal stem cells (NSCs), shows that the brain has varied strategies to change. The birth of new neurons in the adult brain, or adult neurogenesis as the phenomenon is called, includes cell proliferation; survival of neuronal precursors, differentiation of neurons and incorporation of these newly generated neurons in specific brain structures. Adult neurogenesis in lower vertebrates such as fish, snakes, lizards and amphibians did exist. Some evidence going against the static-plastic brain theory, and demonstrating adult neurogenesis in different brain regions of birds such as the canary, zebra finch, budgerigar and chickadee, rodents such as rat, mouse, other mammals such as cats, marmosets, primates such as macaque and rhesus monkeys and in humans, exists since four decades, but most has been rapidly accumulating in the last few years, and has implications of adult neurogenesis in experiential learning and memory, in replacement of lost brain tissue, and in the treatment of neurodegenerative disorders.

Avian neurogenesis

During the early eighties, while experimenting on song learning in canaries, Nottebohm showed something that most held for years as insignificant as far as implications for rodents, primates and humans were concerned. Song learning and production in this singing bird involved a robust adult neurogenesis and was all set to bring down a long-held dogma crashing. The canaries (*Serinus canaria*) sing throughout the breeding season during spring and early summer. During late summer–early autumn moulting season, they 'shed' their songs, or 'forget' them. During next spring, the same canaries sing a new song repertoire[12]. The canary is called therefore an 'open-ended' learner, while others such as zebra finches (*Poephila guttata*, *Taeniopygia guttata*) that learn their songs during a restricted period during development and retain the stereotyped song repertoire for life are called 'restricted' learners (Figure 1). The spring learning period for the canary correlated with a significant increase in volume (more than double the size) in certain caudal forebrain nuclei involved in song-learning and production, such as the HVc (high vocal centre; upper panel, Figure 2) by about 99% and RA (robust nucleus of the arcopallium) by about 76% (lower panel, Figure 2) when compared to the non-breeding moult birds.

This was akin to the changes reported earlier in the same brain regions in testosterone-administered female canaries that produce male-like song. It was hypothesized then (in keeping with the extant thought-paradigm), that the acquisition of a new song repertoire was probably facilitated by the growth of new dendritic segments and synapses, which they were; but the neurons were newly

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generated ones that were replacing old or dead neurons. It was subsequently demonstrated using [³H]-thymidine, which when injected gets incorporated into the DNA being manufactured during mitosis, and therefore labels newly generated cells[13], that the canary birds were producing thousands of new neurons every day in the ventricle (V; upper panel Figure 3 and inset Figure 4) and showing widespread neurogenesis. These cells were migrating and replacing older ones in the telencephalon of adult canaries[14], proved to be neurons based on morphology and physiology, and were being recruited into a functional song-learning circuit in the adult brain[15].

Song is a learned behaviour used by birds to attract mates and to defend breeding territories. In oscine passerines (songbirds), song behaviour is contributed by a network of discrete, interconnected brain regions or nuclei. HVc and RA are two telencephalic nuclei of a circuitry consisting of about 24 nuclei from the ear to the syrinx and respiratory muscles that subserve song and other vocalizations in birds. Among these, the song-learning pathway (also called anterior forebrain pathway) includes the HVc located in the caudal forebrain, Area X and lMAN located in the frontal telencephalon, and a thalamic nucleus DLM. HVc projects to Area X and lMAN projects to RA. The song production pathway includes the HVc, RA and brain stem nuclei that project to syrinx and respiratory muscles (Figure 3).

The new neurons that are generated in the ventricular zone in the adult brain in canaries as well as in zebra finches (not typical photoperiodic seasonal breeders), song sparrows (typical photoperiodic seasonal breeding, age-limited learners), towhees, juncos, budgerigars and certain other birds at a seemingly constant rate, are incorporated into the HVc and most of them later constitute either the interneurons of the HVc or the HVc → RA projection neurons, depict responses of auditory stimuli[15], and incorporate injected, labelled testosterone.

Increased cell death results in increased incorporation of new neurons into the HVc, which are responsible for song production during next spring. The ensuing moult season comprises a decrease in photoperiod, reduced levels of testosterone, apoptosis and loss of song. The spring season is marked by an increase in photoperiod, increase in testosterone levels, adult neurogenesis and acquisition of new song[12]. Thus, neuronal turnover is seasonally regulated, an increase in circulating sex steroids decreases turnover, increases survival of HVc neurons, thus increasing their number during the breeding season. The song of the canary does seem to contain some of the previous years' elements, but its structure is new[16], while that of the song sparrow loses its stereotypy during the non-breeding season and the zebra finch maintains stereotyped song.

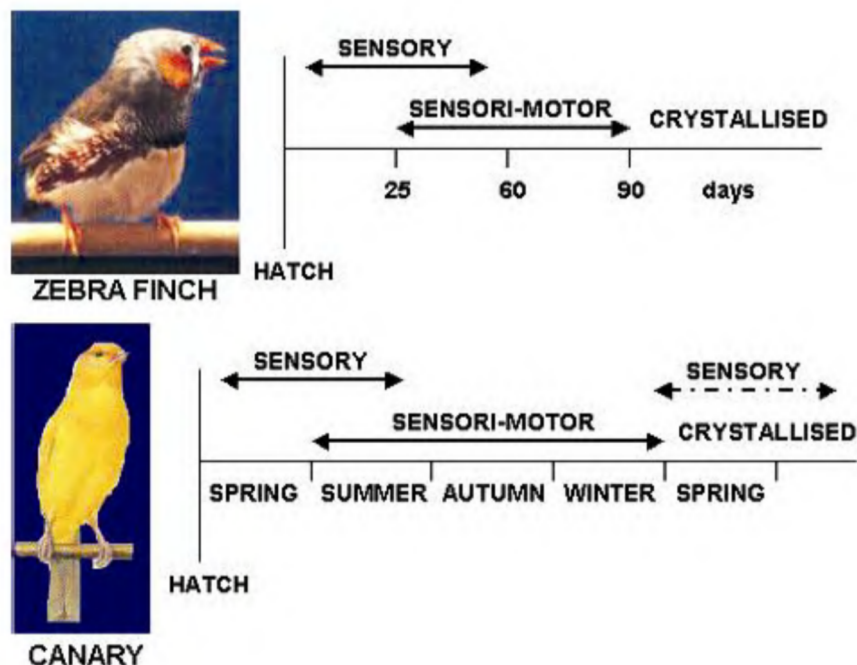That such changes in the volume of certain other brain regions such as the hippocampus (Figure 4) implicated in

Figure 1. Schematic representation of phases in song-learning in zebra finch (from hatch to about day 120), a 'restricted' learner and the canary (from hatch to a little more than 1 year), an 'open-ended' learner. Sensori-motor indicates a phase during which song is plastic, after which it becomes crystallized or stereotypy is attained. In the phase when the canary is singing a stable song repertoire, the next sensory phase marked by neuronal incorporation begins (shown with punctated line).

spatial memory are also induced by changes in environment, was seen when brains of chickadees held in cages were compared to those in the wild: the free-ranging chickadee, which had to avoid predators and forage for food and store it in food caches, had a larger number of neurons in the hippocampus than the caged chickadees[17]. This study demonstrated an increased level of [3H]-thymidine labelling in birds caught in autumn from the wild when food-caching activity is at a high level, than in early spring when food-caching is no longer necessary, indicating a correlation between a memory-related task and neurogenesis. The hippocampus, a site of memory formation and storage, is detrimental to remembering stored food caches during winter; so the new neurons were functioning at times when memory was crucial. The avian hippocampus has been considered homologous to its mammalian
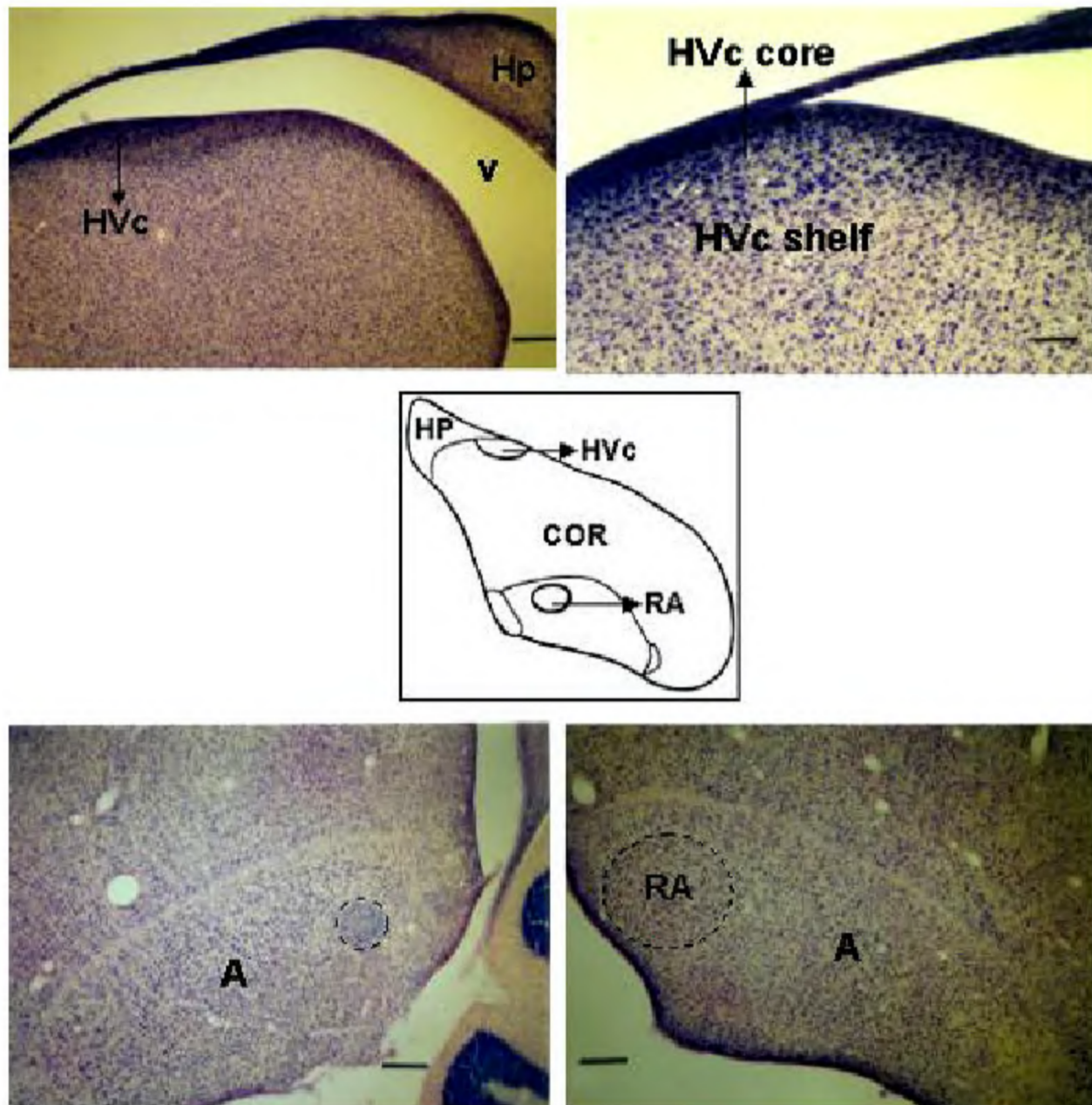

Figure 2. Upper panel: Left, HVc of a male zebra finch stained with giemsa, a nissl. stain; bar scale 200 μm; V, Ventricle (Right) Magnification showing core and shelf regions; bar scale 80 μm. Middle panel: Transverse section of the bird brain depicting location of HVc as well as RA in the caudal telencephalon HP, Hippocampus; COR, Areas with cortical equivalents. Lower panel: Left, RA of a female zebra finch. (Right) RA of a male zebra finch; bar scale 200 μm; A, Arcopallium RA of a zebra finch female is similar to that of a canary male during the moult season, and RA of a male is similar to that of a canary male during the spring–summer reproductive season.

counterpart (Figure 4) based on embryological, hodological, morphological and functional evidence[18–20]. LTP, a putative neurophysiological correlate for learning and memory, has been demonstrated in the hippocampus of various birds[21–23]. The avian hippocampus has been implicated in spatial memory during navigation in homing pigeons[24], and in imprinting, a stable, early learning process[25–27].

Food storers undertake food caching during fall, for retrieval and consumption when food is scarce. Hundreds to thousands of food items are stored per year individually across a widespread territory, the borders of which (trees, other landmarks) provide the visuo-spatial cues for memory. Hippocampal lesions impair recovery, while if food caching is prevented during development, growth is affected[28]. This behaviour is widespread among various temperate-region birds such as marsh tits (*Parus palustris*), red-breasted nuthatches and blue jays; *Parus major*, a non-food storer does not demonstrate increase in hippocampal volume[29]. Thus a comparison between storing and control birds indicates that the experience of storing or non-storing affects hippocampal growth (neurogenesis) and attrition (apoptosis)[28].

Whether a canary has to evolve a new song repertoire each year to attract a female, or a black-capped chickadee has to remember numerous food caches in order to recover food during the winter, both are existential problems that require recruitment of extra neurons. The discovery that adult birds give birth to a steady stream of new brain cells meant that neurons filled with old memories were being exchanged for new ones, which was difficult to envisage for the primate or even the human brain[30]. The idea of adult neurogenesis was also considered unusual, since strokes and other brain injuries are irreversible; lost neurons are not regenerated like other cells such as glia. Therefore, this was thought to be a

Figure 3. Avian vocal or song control system shown in sagittal section. The forebrain pathway involved in song acquisition is called the anterior forebrain pathway, shown in pink and red hues, while the motor control pathway is shown in blue hues. DLM, Nucleus dorsolateralis, anterior thalami, pars medialis; IMAN, Lateral magnocellular nucleus of the nidopallium; NIF, Nucleus interfacialis; nXIIts, Tracheosyringeal portion of the hypoglossal nucleus.

unique phenomenon among birds, with no implications for other higher vertebrates. But studies on the canary and the chickadee, along with some rodent studies conducted earlier (see below), had led to the questioning of the no-new-neurons dogma and to a rethinking of the forms of plasticity existing in the adult brain to adapt to environmental demands beyond just plasticity that entailed a remodelling of dendrites and synapses.

Rodent and primate neurogenesis

The phenomenon had not just been seen in birds, but had also been demonstrated in mammals using the same technique. [^{3}H]-thymidine autoradiographs of young adult rats after electrolytic lesions combined with intracranial injections of the marker, showed accumulation of reduced silver grains over the nuclei of a few neurons in the neocortex and over the granule cells of the hippocampus[31]. Subsequently, formation of new cells in the granule layers of the dentate gyrus (Figure 4) of the hippocampus, and olfactory bulb following intraperitoneal or intraventricular injections in normal adult rats and cats was also shown[32,33]. The latter study showed an increase in silver-grain accumulation following injections of tritiated testosterone, but the nature of these cells was doubted.

Kaplan, who used electron microscopy with [^{3}H]-thymidine technique, showed that the newly generated cells in the olfactory bulb and the dentate gyrus of four-month-old rats possess structural properties of neurons[34], and showed the same for new neurons found in layer IV of the visual cortex of three-month-old rats[35,36]. However, when brains of young and adult monkeys (six months to eleven years) injected with labelled [^{3}H]-thymidine were studied and no new cells were observed[30], it was suggested that the long-standing dogma should continue to remain, that by the time a monkey (or a human being) reached a few months of age, its full neuron complement was attained, unlike in avian and rodent species that may display variable degrees of post-developmental neurogenesis.

Adult neurogenesis in the olfactory bulb and the dentate gyrus of the hippocampus was repeated for young and adult[37–39] and in adrenalectomized[40,41] rats. While the former studies suggested that the newly generated cells were substantiating an increase in the neuronal population in the hippocampus (no significant change was noted in the olfactory bulb), the latter showed that new neurons were being generated to compensate for the ones dead due to enhanced levels of glucocorticoids. With new and more convincing techniques (immunohistochemical localization of dividing cells and their progeny using bromodeoxyuridine–BrdU and specific fluorescent markers/ antibodies specific to the neuron cell type such as neuronal nuclei, neuron specific enolase, microtubule-associated protein, turned-on-after-division 64 kDa protein, calbindin, etc.), adult neurogenesis has since been demonstrated
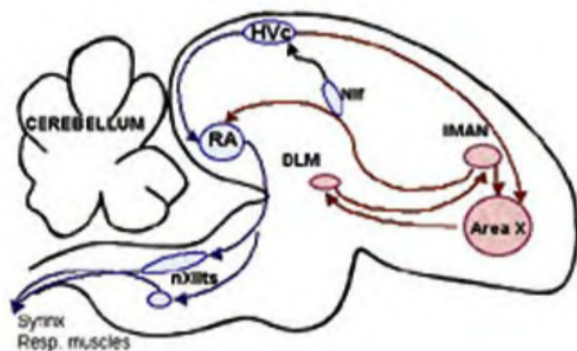
in the mammalian olfactory bulb, and dentate gyrus of the hippocampus from rodents to tree shrews, marmosets, rhesus and macaque monkeys[42,43], though the reliability of these methods has also been questioned[44].

Besides these phylogenetically older mammalian brain structures, adult neurogenesis in other higher-order associative regions of the neocortex of the adult primate (macaque), such as the prefrontal, inferior temporal and posterior parietal cortex that are responsible for language and complex thought, has been demonstrated[45]. These new cells were shown to migrate through the white matter from the subventricular zone (SVZ) to the cortex and extend axons there, though other studies have shown this to occur only after apoptosis was induced[46]; also survival of these neurons was doubtful. In the hippocampus however, where adult neurogenesis has been detected in rats[47] and in macaque monkeys[43], it has lately been convincingly shown that the new neurons generated in the subgranular layer (SGL), which migrate to the dentate gyrus have neuronal morphology, display passive membrane properties and action potentials, and possess functional synaptic inputs similar to those found in mature dentate granule cells[48].

Mammalian studies showed that the phenomenon is widespread with progenitors found in septum, striatum, spinal cord, cerebral cortex, corpus callosum, optic nerve, eye, etc., indicating that the potential exists in all these regions, but signals necessary for neurogenesis are lost or inhibitory mechanisms may be in place. The studies also showed that adult NSC properties include extensive proliferative ability, self-renewal, differentiation of progeny into neurons and other cells. This generalized potential has yielded formation of chimeric chick–mouse embryos and cells of all the germ layers[49]. Two neurogenic sites for true stem cells were identified (SGL in the dentate gyrus of the hippocampus and SVZ that surrounds the fluid-filled ventricles found in the centre of the brain and spinal cord), though a more recent study indicates that SGL cells have a rather limited proliferative potential and that true hippocampal stem cells lie dorsally in a collapsed ventricle[50]. Moreover, the mammalian studies demonstrated that adult neurogenesis is enhanced by exercise, stimulating environs, low levels of corticosteroids (adrenalectomy) and attenuated by stress, increased levels of steroids, ageng, etc.
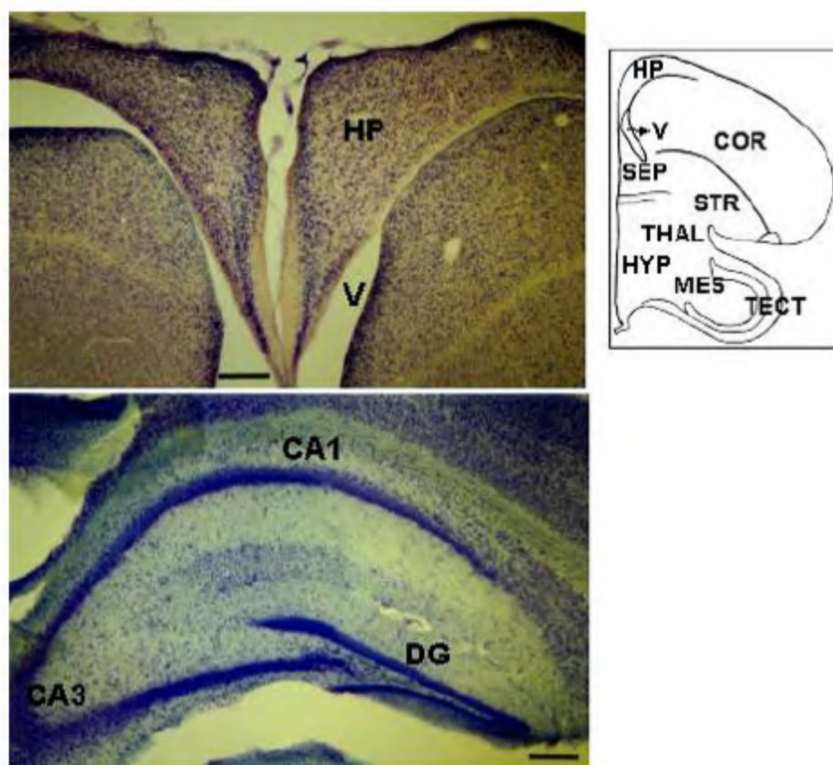

Figure 4. (Left panel) Photomicrograph of avian (giemsa-stained) and rodent (thionin-stained) hippocampi. Similarities are not readily discernible; various authors have found regions in bird hippocampus homologous to those in mammals. Volume of the hippocampus is increased in food-storing birds. (Right panel) Avian hippocampus is found dorso-lateral to the ventricle, the avian neurogenic site. The mammalian neurogenic site is found ventral to the dentate gyrus (DG). Bar scale 200 μm. CA, Cornu Ammonis; SEP; Septum; STR, Striatum; THAL, Thalamus; HYP, Hypothalamus; MES, Mesencephalon; TECT.

Human neurogenesis

It was assumed that adult neurogenesis was likely to play a diminished role in human beings, whose behaviour is determined by complex social and cognitive interplay. Moreover, human behaviour is the outcome of memories stored over the lifetime of an individual. If new neurons were replacing older ones, as was the case in birds and rodents, human beings could not be expected to rely on past experience to aid in present or future adaptational situations involving social and cognitive behaviour[30].

A study on cancer patients using BrdU technique showed the contrary[51]. BrdU is used in cancer patients to trace tumour progress. Five patients between the ages of fifty-seven and seventy-two, who had cancer of the throat or the larynx, demonstrated accumulation of the marker in post-mortem sections of the brain. Primitive neural stem cells had divided and created about five hundred to thousand new cells each day in the dentate gyrus.

Implications of the paradigm shift

This study along with earlier primate work, spurred NSC research among neuroscience groups and idle speculation among the laity and in the media. Foremost among the implications is the significance that the phenomenon of adult neurogenesis in the hippocampus has for humans. Efforts are on to screen for stimulators and attenuators of neurogenesis. The implications for learning and memory are apparent. The attenuation in neurogenesis due to stress and its increase when provided with stimulating environments is also apparent. However, the promise it holds for reversals or damage repair from strokes, injury to the brain/spinal cord and other neurodegenerative disorders using cell replacement therapy from stem cell cultures, is what humanity at large will benefit from.

Learning and memory

Certain types of events, such as learning of new song repertoires or enhanced memory capacities for food caches or even hormonal (testosterone) changes in the reproductive season, appear to stimulate neurogenesis in the adult brain; estrogen, which has been shown to boost memory, is formed from testosterone in the brain by action of the enzyme aromatase, and leads to a transient increase in the number of newly-generated cells in the female rat[52]. That the phenomenon had enormous potential and could be important for learning and memory in higher vertebrates, had been suggested much earlier[12,32,34] and was recently reiterated[53,54]. Studies on canaries, where a new song repertoire is acquired from a new pool of proliferating neurons, have implications in other vocal learning contexts; for example, in phoneme acquisition and retention in mimic-

king birds[55], and possibly also in the learning of a new language or a new task in humans.

Direct evidence for the involvement of adult neurogenesis in the formation of trace memories in hippocampal-dependent memories was shown in mice treated with methylazoxymethanol acetate, a cell-proliferating toxin and DNA-methylating agent. Here, new neurons that appear in the SGL get integrated into the existing hippocampal circuitry essential for certain types of memory that involve timing and temporal order of events. Reduction in the number of newly generated neurons in adult rats impairs hippocampal-dependent trace conditioning, where animals are required to associate stimuli separated in time[54,56]. The study that demonstrated adult neurogenesis in neocortical areas[45], however, did not demonstrate any significant effect on behavioural or cognitive functioning in a higher primate like the macaque.

Stress and depression

Stress, for instance, is a common trigger for depression and a potent suppressor of neurogenesis; it promotes the release of glucocorticoids, which inhibit new cell development and its proliferation rate in the dentate gyrus of the hippocampus in monkeys[42]. The hippocampus has a high level of corticosteriod receptors; patients with bouts of clinical depression have smaller-volume hippocampi than their normal counterparts. Regular exercise and a stimulating environment, both factors that might act to suppress depression or are counteractive to stress, have been shown to promote neurogenesis in rats[47]. Also, newly formed cells died when the animal was exposed to the scent of a predator, which acted as a releaser for fear or social subordination. Other experiments demonstrated that age affects the production of new neurons in rats[57]. Earlier, enriched and impoverished environments have been shown to affect dendritic morphology either progressively or regressively[58,59].

Neurodegenerative disorders – cell replacement – clinical implications in humans

Due to the long-established fact that human brains cannot replace dead neurons, brain damage is considered irreversible, and neurological diseases in the elderly unstoppable. Various clinically relevant insults to the mammalian brain (e.g. seizures, ischaemia, traumatic brain injury, etc.) show an increase in proliferation of putative stem/progenitor cells within neurogenic niches. However, somewhat paradoxically, such an apparent recapitulation of development or attempt at a regenerative response fails to result in cellular replacement at the injured site. It is supposed that certain tumour-suppressor mechanisms may be in place.

New brain cells mean new approaches to neurological problems and diseases, and there is wild speculation of the implications of what even a minute turnover of adult NSCs could have for humans. If new neurons could integrate themselves as successfully into the brains of adult humans as they do in adult birds, researchers may be able to influence them using trophic factors to develop in a particular manner and replace dying or failing cells. For example, they could be coaxed to proliferate into mid-brain dopaminergic cells and grafted into the striatum to treat Parkinson's disease. Alzheimer's disease, where the principal area affected is the neurogenic-site-containing hippocampus, could possibly be treated with its own pool of progenitor cells.

In this manner, the brain could be 'trained' to repair itself with its own NSCs, if the endogenous trophic factors could be administered, and the neurochemistry of the surrounding cells and migratory routes discerned[60]. Adult NSCs under a variety of culture conditions can be induced to proliferate and differentiate into glia or neurons in the presence of fibroblast growth factor and to a lesser extent, the epidermal growth factor. Retinoic acid and cAMP appear to be crucial for differentiation, while neurotrophins such as NGF, BDNF and NT-3 influence neuronal differentiation and transmitter phenotype[61].

The modus operandi may be different for neurogenic-site and non-neurogenic-site containing brain regions; for instance, stem cells from the spinal cord require high concentration of growth factors to demonstrate neurogenesis. Culture studies indicate that astroglia from neurogenic sites could induce neurogenesis in non-neurogenic sites such as the spinal cord, since GFP-engineered NSCs isolated from the adult rodent hippocampus, and cultured with astrocytes of newborn hippocampus, proliferated by a factor of eight and their progeny steered into becoming neurons[62], while GFAP-labelled astroglia derived from radial glia that probably still possess progenitor potential have given rise to new neurons in the SGL of the hippocampus[63]. Adult NSCs cultured with adult neurons and neonate and adult astrocytes develop into electrically active neurons and integrate into the neuronal network, indicating that mature astrocytes promote neuronal maturation and synapse formation[64].

Information from bird-brain studies indicates that neural precursors during adulthood give rise to a variety of, but not all, neuronal phenotypes[65]. Most adult-born neurons fit the characteristics of those added later on in development, like interneurons or neurons with short projection targets within the same structures like in the olfactory bulb, HVc, HVc–RA projection neurons, hippocampal granule cells and intracortical projection neurons in primates. In mice though, where neurogenesis is spontaneous only in the olfactory bulb and the hippocampus, adult neural precursor cells have been induced to change fate: photolytic lesions in layer VI of the cortex induced SVZ stem cells to form pyramidal projection neurons[46].

Targeted apoptotic lesions of select neural pathways of mammalian and avian central nervous systems have resulted in the proliferation of endogenous neural stem/ progenitor cells, migration of these cells to the site of injury, and subsequent cellular replacement. Following elucidation of spatial and temporal conditions that permit functional regeneration of the adult nervous system, a population of cells could be induced to replace cells and neuronal circuits lost after experimental brain injury. While animal studies *in vitro* and *in vivo* have certainly made progress and met with some success, in humans clinical application of adult NSCs is far from imminent.

While this envisages the use of new neurons for neuronal replacement therapies and repair of damaged tissue in humans, it has been suggested that in nature, new neurons were not meant for replacement but rather in response to existential behavioural problems on which hinge the functional significance of adult neurogenesis in higher vertebrates, including man[66].

Functional significance of adult neurogenesis

What has emerged as significant from this sojourn, besides the fact that a long-standing myth has dissolved[67] and brought about a drastic change in our thinking of the plastic strategies available to the brain, is the functionality of these new neurons. While the mammal studies used laboratory-bred mice or rats or primates held in captivity, where laboratory conditions even with an enhanced enrichment would not mirror conditions in the wild[47], the bird studies screened for neurogenesis in what one may term natural circumstances, during the breeding season and during food-caching in the field[29]. That the newly formed cells differentiate and have a purpose, has been unequivocally shown in birds. What their specific function may be and how they are particularly involved in learning and memory, and whether they change the functionality of brain regions such as the olfactory bulb, hippocampus and song control pathway in birds, has brought forth various theories[66,68].

Olfactory bulb

That neurogenesis is widespread and persistent in the olfactory discrimination centres of insects, crustaceans, rodents and primates has been well established. In mice, the olfactory neurons with odour-specific olfactory receptors project to glomeruli of each bulb. These project onto mitral or tufted cells, which are inhibited by granule cells. Neuronal production in the SVZ and migration to the olfactory bulb continue even in the absence of the bulb. Therefore, cell birth and migration here do not seem to depend on olfaction or activities within the bulb.

In adult mice forebrain, NSCs of the SVZ migrate along the rostral migratory stream to the olfactory bulb and form olfactory interneurons there. Pregnancy and postpartum induce such a neurogenesis in the olfactory bulb of mice: at gestation day 7, there is an increase in cell proliferation by about 65% and by postpartum day 7 about 35%; the peaks correlating with peaks in circulating prolactin (PRL) levels. Here again, as in canaries and black-capped chickadees, the new neurons are thought to help in solving existential problems[69,70]; the mother needs to evolve an olfactory discrimination for her altricial offspring to elicit successful maternal behaviour. It is suggested that production of new olfactory interneurons is a maternal adaptation initiated early on in pregnancy and mediated by PRL, and may have important functional consequences such as offspring recognition and maternal behaviour[71].

Hippocampus

The dentate gyrus of the adult hippocampus generates neurons throughout life. Here, new granule cell layer neurons are formed from resident neuronal stem or progenitor cells and get integrated into the trisynaptic circuitry of the hippocampus. Voluntary exercise increases cell proliferation and the number of surviving neurons[48]; mice given access to a running wheel in standard laboratory cages had increased rates of cell proliferation than control animals as well as those that participated in a spatial learning task, left to swim or exposed to enriched environs. The voluntary runners showed more surviving neurons after four weeks, but not significantly more than those held in enriched environs, indicating that voluntary exercise and enriched environs stimulate adult neurogenesis; however, learning did not necessarily correlate with or lead to neurogenesis.

Another study showed that enriched environs (larger cages with toys) also engender neurogenesis in young mice compared to those reared in deprived conditions, i.e. standard laboratory cages, and that the former demonstrate better spatial learning compared to the latter. This increase in the total neuron number and volume of the granule cell layer persisted into adulthood[47], and the rate of survival was greatly enhanced by housing young adult/aged animals in enriched environments. Further, when rats trained on a hippocampal-dependent associative task were compared with those trained on a hippocampal-independent associative task and controls and showed higher rates of neurogenesis in the hippocampus[56], it was proposed that postnatal neurons play a specific role in learning and that learning specifically can increase or enhance adult neurogenesis. Whether the contrary, i.e. deprived laboratory cage conditions and/or training in a hippocampal-independent task downregulated hippocampal neurogenesis, was not tested.

Whether adult neurogenesis in the rodent or mammalian hippocampus increases memory per se is still questionable, but a reduction in newly generated cells in the hippocampus affecting a hippocampal-dependent task, while sparing a hippocampal-independent task has been shown[56], indicating that if new cells are not put to use, they undergo apoptosis. In keeping with earlier postulates on memory indicating a sieve-like role for the hippocampus, which categorizes information and passes it on to appropriate extra-hippocampal circuits[72], these newly generated cells in the hippocampus are proposed to act as gatekeepers controlling the inflow of new memory[68]. LTP, the electrophysiological measure of learning, is enhanced in the same mice in which physical activity enhanced neurogenesis, indicating that there is an activity-dependent regulation of adult neurogenesis in hippocampus of mammals as also shown earlier for birds; the food storers had larger volumes of hippocampus than did non-storers of a related species.

Food caching, which leads to increased cell incorporation in the hippocampus in birds, demonstrates a correlation between changes in behaviour and adult neurogenesis. When food-storing activity is highest, the daily rate of neuronal incorporation in the ventral hippocampus is highest. Behavioural and lesion studies on bird hippocampus have implicated it in spatial memory, and when birds relying on spatial memory were observed incorporating new cells into the hippocampus, the structure–function subservience and the homology (avian and mammalian hippocampus) issue seemed to be strengthened. In contrast to the song control system that has been extensively studied and causative and disruptive factors of adult neurogenesis discerned, studies on hippocampal circuitry are not as many. Moreover, it has been argued that if birds require additional neurons to acquire memory, they may need the same number to recover them[29]. In fact, during retrieval hippocampal volume is on the decrease. This may be due to memory being subsequently stored in extra-hippocampal, probably cortical circuits, though this has not yet been shown. So hippocampal neurogenesis does not increase memory per se in birds either.

Whether incorporation of adult-generated neurons in the hippocampus during food-storing activity or during training in a hippocampal-dependent task is due to learning, requirement of increased memory capacities or due to increased use of the neural structures that subserve these behaviours, remains to be determined[70]. However, what has emerged as significant from these studies is that an enriched environment or rather, a challenging environment effects upregulation of adult neurogenesis, and activity contributes to the survival and purpose of these neurons.

Song control pathway

In song learning too there exists a positive correlation between the plastic phase of song learning in the canary

and the rate of cell proliferation. The correlation is also temporal; it is the time when canary song is changing dramatically. It also correlates with high levels of testosterone. What has been observed in the canary and other songbirds is a spontaneous replacement of neurons during post-natal development of song, and thereafter during every breeding season. The neurons being replaced are found mainly in the HVc, besides the frontal forebrain song control centre, Area X. The number of neurons in the HVc remains the same, indicating that existing neurons are being culled. Thus it is apoptosis that engenders neurogenesis, as was also shown in rats; but in the canary some existing neurons are also being culled.

There is an argument that neurogenesis in the songbird brain is seasonal[73]. The phenomenon, however, has also been shown in non-seasonal birds such as the zebra finches; the purpose of these new cells here though, needs to be ascertained[74]. We know that despite HVc showing regular neuronal addition in adult zebra finches they maintain stereotyped song, indicating that the phenomenon is tightly regulated[75,76]. As in the canary, induced cell death in the zebra finch results in an increased incorporation of new neurons into the HVc, while neuronal incorporation into the HVc is decreased following deafening[65]. In the zebra finch, therefore, the newly generated neurons do not seem to induce learning, but may strengthen an existent but highly active pathway. In the canary, however, longer photoperiods induce increases in levels of testosterone, which has an impact on song-learning and on the generation of new neurons. If birds are prevented from singing, the new neurons will not survive, indicating again that it is only when they have a purpose that they survive, and that survival is activity-dependent. Nottebohm suggests that a spontaneous neuronal recruitment as seen in HVc and the hippocampus is essential to rejuvenate key brain circuits and could hold the key to new, long-term memory[77].

Conclusion

The picture that is emerging regarding the functionalities of these newly generated neurons is their primary role in renewal. They are being recruited to replace old, dying or dead cells as seen in the HVc of birds and visual cortex of mice. Or they are involved in the acquisition of new and the renewal/'updating' of older memories in the hippocampus of both birds and mammals. They also act as storage sites of the new or renewed song repertoire in birds, or for new odours as in the olfactory bulb of female mice after parturition[66,68,69,71].

Secondly, the survival of these newly generated neurons seems to be activity-dependent. Active regions seem to incorporate most of the proliferating cells and new cells in these active regions will survive if they have a purpose. This is reminiscent of development where experience leads to the laying out of a neuronal network and the esta-

blishment of neuronal connections that are renewed[78–80]. While there may exist differences in the mechanistics and time-frame for differentiation of adult-generated cells into functionally mature neurons from the processes that occur during development and post-natal development, factors such as experience, behavioural changes, responses to existential problems that dictate the proliferation, differentiation, functioning and survival of adult-generated neurons seem to be remarkably similar to those leading to activity-dependent postnatal development of neuronal networks.

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The sugarcane woolly aphid, *Ceratovacuna lanigera* Zehntner (Hemiptera: Aphididae): its biology, pest status and control

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Sugarcane woolly aphid, *Ceratovacuna lanigera* Zehntner has been recently reported in outbreak proportions from western and southern India. Though the pest was first reported from West Bengal in 1958 and later from other parts of Northeast India, it had not made its way to other parts of India. The pest breeds on plants of the family Poaceae, but has been also observed on members of Bixaceae, Theaceae and Combretaceae. It has been recorded on ten species of plants in India. It reproduces parthenogenetically and has an anholocyclic (absence of sexually producing generation) life cycle. Thirty-eight natural enemies have been recorded on the aphid from different parts of the world.

Recent surveys in the pest-affected areas of Maharashtra (western India) and Karnataka (southern India) have yielded several indigenous predators which include coccinellids, neuropterans, syrphids and a pyralid. Integrated pest management involving mainly mechanical and biological control appears to be the best option. There is ample scope for more directed work on this important emerging pest, especially in the areas of pest ecology and distribution. The role of resistant varieties, and biological, cultural and mechanical control in managing the pest needs to be carefully evaluated.

SUGARCANE is attacked by several aphid species in India. Raychaudhuri[1] listed 17 species of aphids associated with sugarcane of which seven belong to subfamily Aphidinae; five to Pemphiginae; two to Drepanosiphinae and three to Hormaphidinae. Among the three hormaphidine species in the genus *Ceratovacuna* Zehntner, *Ceratovacuna lanigera* Zehntner is a serious pest of sugarcane in several parts of the Oriental region. The species is known from India, Nepal, Bangladesh, East and South Asia, Fiji and Solomon Islands[2] (Table 1). It has been recorded on other members of the family Poaceae like bamboo and

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