Opinion piece

Adult hippocampal neurogenesis of mammals: evolution and life history

Substantial production of new neurons in the adult mammalian brain is restricted to the olfactory system and the hippocampal formation. Its physiological and behavioural role is still debated. By comparing adult hippocampal neurogenesis (AHN) across many mammalian species, one might recognize a common function. AHN is most prominent in rodents, but shows considerable variability across species, being lowest or missing in primates and bats. The latter finding argues against a critical role of AHN in spatial learning and memory. The common functional denominator across all species investigated thus far is a strong decline of AHN from infancy to midlife. As predicted by Altman and colleagues in 1973, this implies a role in transforming juvenile unpredictable to predictable behaviour, typically characterizing mammalian behaviour once reproductive competence has been attained. However, as only a fraction of mammalian species has been investigated, further comparative studies are necessary in order to recognize whether AHN has a common unique function, or whether it mediates species-specific hippocampal functions.

Keywords: adult neurogenesis; evolution; life history; adult development; behaviour; flexibility

1. INTRODUCTION

Within the brain of adult mammals, proliferation of neurons occurs spontaneously in the walls of the lateral ventricle and the subgranular layer of the hippocampus. Cells from the ventricle walls migrate and integrate into the olfactory bulb, whereas new neurons in the subgranular layer differentiate into dentate gyrus granule cells of the hippocampus (figure 1). The functional significance of adult-born neurons in the hippocampus is still debated; several studies have found opposite results with respect to the role of newly generated cells in hippocampus-dependent learning and memory tasks (Saxe et al. 2006; Imayoshi et al. 2008). This raises the question of how important adult neurogenesis might be for animals living in their natural context, and to what extent experimentally obtained insights into the regulation and function of adult hippocampal neurogenesis (AHN) can help us to understand its relevance in the healthy and diseased human brain (Nottebohm 2002; Lindsey & Tropepe 2006). An obvious approach would be to compare wild species with differential demands for cognitive abilities and check for their levels of AHN, expecting those species excelling to exhibit extreme levels of AHN.

2. FUNCTIONAL CORRELATES OF ADULT HIPPOCAMPAL NEUROGENESIS IN WILD MAMMALIAN SPECIES

The vast majority of studies of adult neurogenesis have been carried out in domesticated laboratory mice and rats. Both species show pronounced strain differences in their basal AHN, whose range of variation exceeds by far the known strain differences in behaviour (Kempermann et al. 1997; Perflieva et al. 2001). AHN can be visualized immunohistochemically by endogenous proteins (figure 2a) or incorporated markers such as bromodeoxyuridine (BrdU). The direct comparisons of basal AHN rate among studies or species, however, are rare due to differences in markers, staining protocols, lack of standardization or missing unbiased counting procedures (for more details see Amrein et al. 2008). Still, AHN in wild rodents is well documented. Considerable species differences can be observed (figure 2a), and in some cases, different levels of AHN as predicted by their environment were found. High adult proliferation rates (up to 20 000 new cells daily) were found in wood mice patrolling large territories (figure 2a(i),(iv),b(i)) while lower levels were found in bank voles (figure 2a(ii),(v),b(ii)), and pine voles (Amrein et al. 2004). Studies in two squirrel species, with different territory sizes and caching behaviour, showed that chipmunks with small territories with a single food cache had lower basal proliferation rate than squirrels using multiple storage places located in larger territories (Barker et al. 2005). Seasonally changing requirements for spatial memory did not lead to altered neurogenesis in wild squirrels (Lavenex et al. 2000). Most bats lack neurogenesis in the hippocampus (figure 2a(ii),(v),b(iii)), and Amrein et al. 2007), despite showing precise spatial memory for food sources in the wild and laboratory (Thiele & Winter 2005). Possibly, spatial, episodic and contextual memory may be more dependent on neurogenesis than spatial navigation (Wojtowicz et al. 2008). This might be particularly important for predators that must constantly relate danger to changing locations and stimuli, thus creating a particularly high demand for AHN. However, the attempt of linking extreme rates of AHN with any type of hippocampus-dependent cognitive abilities faces one big problem: primates, and in particular humans, show comparatively low levels of AHN (Eriksson et al. 1998; Gould et al. 1999), which, in humans, seemingly becomes rudimentary after 30 years of age (Fahrner et al. 2007).

3. IS AGE DEPENDENCY OF MAMMALIAN ADULT NEUROGENESIS ASSOCIATED WITH BEHAVIOURAL CHANGES IN LIFE HISTORY?

Thus far, an age-dependent decline of AHN is the only common finding in all species investigated. Protracted neurogenesis of granule cells peaks at puberty and declines dramatically thereafter, as documented in mice, rats and monkeys (Kuhn et al. 1996; Gould et al. 1999; Ben Abdallah et al. in press), albeit with considerable species differences. Wild old wood mice, voles, chipmunks and squirrels show a decline in ongoing proliferation compared with that of young...
Figure 1. Neurogenesis in the hippocampus. Progenitor cells divide in the subgranular layer of the hippocampus (a). Newborn neurons migrate a short distance into the granule cell (DG) layer (b) where they attain full mature state (c) by forming dendrites towards the molecular layer, receiving inputs from layer II of the entorhinal cortex (light blue), and connecting via mossy fibre pathway (red) to pyramidal cells of CA3. CA3 pyramidal cells send the information via Schaffer collaterals (green) to pyramidal cells of CA1, which in turn feedback the information to subiculum and deep layers of entorhinal cortex (dark blue). Neurogenesis occurs in the bottleneck of the unidirectional, trisynaptic loop of the hippocampus.

Figure 2. (a) Extremes in hippocampal proliferation activity as revealed by Ki-67 immunohistochemistry. Adult yellow-necked wood mice (*Apodemus flavicollis*; (i),(iv)) show extreme proliferation activity in the dentate gyrus (i) and the rostral migratory stream, RMS (iv). In adult bank voles (*Myodes glareolus*, formerly *Clethrionomys glareolus*; (ii),(v)), proliferation activity in the dentate gyrus is lower (ii), but equal to wood mice in the RMS (v). In the hippocampus of a pale spear-nosed bat (*Phyllostomus discolor*; (iii),(vi)), a few Ki-67 positive cells can be seen in the hilus, but not in the subgranular layer of the dentate gyrus (iii). Proliferation activity in the RMS (vi) is similar to that in the mice. Sagittal sections, scale bar = 50 µm. (b) Similar sized mammals with extremes in AHN and lifespan. (i) Short-lived yellow-necked wood mice and (ii) bank voles show high and low level of AHN. (iii) Long-lived pale spear-nosed bats do not have proliferation activity in the hippocampus. Photo (i) and (ii): Rollin Verlinde; photo (iii): Katja Rex.

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and adults (Amrein et al. 2004; Barker et al. 2005). In
shrews, neurogenesis ceases completely once the
animals have overwintered (Bartkowska et al. 2008).
A decline in ongoing proliferation appears to be a
truly general phenomenon in laboratory bred as well
as wild animals and humans (Seress et al. 2001; 
Fahrner et al. 2007). In order to understand the
functional relevance of AHN across species, age,
lifespan and mortality rate of the animals must be
taken into account. Age dictates basal cell prolifer-
ation rates, average lifespan might be correlated with
the number of precursor cells, and mortality rate
might indicate how essential young neurons in the
hippocampus are for the survival of the animals.

Therefore, one would expect AHN in many mamm-
alian species to be associated with the change of
behavioural traits that characterize the transition from
juvenile to adult behaviour. The idea is not new:
Altman and colleagues noted that the function of
hippocampal maturation might be ‘transforming reck-
less juveniles into cautious adults’ (Altman et al. 1973).
Later on, Lipp & Wolfer (1995) tried to fit
adult changes in hippocampal circuitry to evolutionary
mechanisms. They hypothesized that high behavioural
flexibility during late adolescence and young adult-
hood improves the chance of establishing ecological
and social niches facilitating reproduction. After hav-
ing found such niches, however, radical changes of the
behavioural profile are not likely to enhance reproduc-
tive success. Thus, brain processes that strengthen
acquired habits probably increase the thresholds for
behavioural change. The age-dependent decline in
AHN might reflect a late form of selective develop-
mental stabilization (Changeux & Danchin 1976).

Networks containing newly formed dentate granule
cells might form a mosaic of differentially activated
channels along the many parallel intrahippocampal
(trisynaptic) loops (figure 1). Continued neuronal
activity along these channels might then result in local
downregulation of granule cell proliferation, resulting
in predictable and stable topographical patterns of
hippocampal activity. Ultimately, this leads to
increased predictability of activities characterizing
mature adult behaviour. Late developmental disap-
pearance of AHN would thus correspond to a slow
form of neuronal plasticity—a morphological learning,
possibly accompanied by other age-dependent changes
in the hippocampal mossy fibre system (Wolfer & Lipp
1995) and other brain structures controlling the
behaviour such as the prefrontal cortex.

This hypothesis might explain a considerable por-
tion of the differential dynamics of AHN in mammals.
Most rodents are short-lived species with a reproduc-
tive peak lasting one season only. This leaves a period
of few months during which locally appropriate beha-
vioural habits can be developed. These behavioural
habits must relate to available food sources, predator
pressure and social interactions with conspecifics.

Once acquired, they may be useful for another year at
best. On the other hand, bats have a long life, but
acquire sexual maturity in a few months, so they
acquired during a few months may be sufficient for
the rest of life, not needing further modifications.
Finally, primates with their (genetically determined)
protracted period of development may have a longer
window of AHN and routine forming, but reaching
sexual maturity and full reproductive sexual status will
reduce eventually this process to very low levels.

Clearly, such hypotheses require comparative verifi-
cation. An obvious step is to investigate long- and
short-living rodent species sharing a similar environ-
ment. Another one would be to compare predators
versus predated species, including small variants such
as weasels versus mice, or large animals such as lions
versus antelopes. Finally, the search may be extended to
include species with socially complex versus solitary
lifestyles. Whatever the outcome will be, it offers the
promise to eliminate—as shown for bats—hypotheses
about a general physiological role of AHN in mammals.
Hopefully, a general rule of function will emerge.

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