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CHAPTER 8

Environmental enrichment and the brain [1]

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Introduction

An intriguing feature of the adult brain is its capacity for structural and functional modification in response to external stimuli. This plasticity of the adult nervous system has been the focus of research efforts for decades. The historical antecedents of ideas about brain changes in relation to experiential factors can been traced back to ancient Greece (Rosenzweig, 1996; Diamond, 2001) and has captured the imagination of scientists, philosophers and writers. It was in the 18th century when it was hypothesised that nervous tissue can respond to exercise by physical growth. The impact of the environment on the brain was alluded by Charles Darwin (1874) in his description of wild rabbits having increased brain size compared to domesticated rabbits. Nature is repleted with examples of how wild animals like sheep, ducks, and pigs differ in brain measures compared to their domesticated relatives. A dramatic illustration of nature's experiment on how some species of animals can display differential brain architecture as a result of environmental influences is that of the blind cave dwelling fish *Amblyopsis spelaea* and its relative *Chologaster agassizi*. The former lives in dark caves while the latter lives above ground in swamps and streams. Comparison of the brains of these two related species of fish revealed that the ground dwelling *A. spelae* had degenerate eyes and a smaller optic tectum. Since the species uses smell more than vision, the olfactory tract and related telencephalon were enlarged, as was the cerebellum. By contrast, the *C. agassizi* living near the watersurface in daylight had a large tectum and well-formed eyes (Poulson, 1963). That evolutionary pressures can orchestrate such structural changes in the brains of related species is self-evident. This can further be exemplified by observations of measurable differences in brains of, for example, domesticated and wild rats (Kruska, 1975), turkeys (Ebinger and Röhrs, 1995), pigs (Plogmann and Kruska, 1990) and silver foxes (Popova et al., 1991).

What was not expected is that in the laboratory rats relatively minor variations in housing environment at adulthood could induce chemical and anatomical changes in the brain, as Bennett and colleagues demonstrated in the early 1960s. These studies, influenced by the initial speculations and observations of Hebb (1949), were discordant with the then prevailing view that at adulthood the brain

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[1] This paper is dedicated to Dr. Edward L. Bennett, University of California, Berkeley, on the occasion of his 80th birthday.

is fixed and static and therefore not susceptible to modification by environmental influences. The investigators found that housing adult rats in an environment rich in sensory stimuli induces measurable changes in gross brain structure and levels of the enzyme acetylcholinesterase (Krech et al., 1960; Bennett et al., 1964a,b; Diamond et al., 1964, 1966; Rosenzweig and Bennett, 1969). This was followed by demonstrations of environmentally induced neuroanatomical changes of finer structures, such as dendritic branching, dendritic length and dendritic spine density (Globus et al., 1973; Diamond et al., 1976). These seminal observations stimulated much research on the influence of enriched environment on different aspects of brain function and behaviour. As a result, a voluminous literature from the last four decades exists. Recent discoveries concerning environmentally induced increase in adult neurogenesis (Van Praag et al., 2000) have given this paradigm a new resonance, resulting in a further increase in reports. In this review, we will survey some of the work on the influence of enriched environment on the adult brain, and provide new unpublished findings.

Effects on the cortex

In the enriched environment condition (EC) devised by Bennett et al., 10–12 rats are placed in large cages (76 × 76 × 46 cm) containing some stimulus objects such as balls, running wheels, tunnels, and ladders (Bennett et al., 1964a, 1974; Rosenzweig and Bennett, 1969, 1996; Diamond, 1988). The 'toys' are changed daily. In contrast to this environmental complexity the impoverished environment condition (IC) consisted of housing the animals singly in small cages. In between these two environmental conditions a standard environment (SC) is employed and consists of housing three or four rats in laboratory group cages. Variations of environmental enrichment housing exists and have been used in different laboratories.

In the initial studies, it was observed that differential housing of rats from 25 to 55 days of age resulted in different brain weights between littermates housed in EC and IC environments (Rosenzweig et al., 1962; Bennett et al., 1969; see also reviews by Bennett, 1976, Bennett and Rosenzweig, 1970, and Diamond, 1988). This finding was replicated by the Berkeley group and several other groups. It also appeared that the differences in brain weight could not be attributed to differences in body weight as the EC animals, which had higher brain weights, had lower body weights than the IC animals. The largest EC–IC difference was found with respect to the occipital cortex (9.4%), and this led these investigators and others to a systematic examination of various measures in the occipital cortex induced by EC. In the different layers of the visual cortex analyses were made of environmentally induced changes in neuronal soma size, neuronal density, length of dendritic branches, dendritic spine density, length of synapses and glial cell counts. In layer I, no differences were found, while in the deeper layers consistent differences between EC and IC rats were observed. It was found that rats from the enriched environment developed significantly thicker and longer cerebral cortices compared to littermates from the impoverished and standard environments (Bennett et al., 1964a,b, 1970; Diamond et al., 1964, 1966, 1967, 1972; Altman et al., 1968; Walsh et al., 1971, 1973).

EC animals had more glial cells, increased size of neuronal perikarya and nuclei in the cortex (Altman and Das, 1964; Diamond et al., 1966, 1967, 1975). These changes were largely seen in the occipital cortex. Dendritic branching in occipital layer II stellate neurones was increased in EC animals (Holloway, 1966). Further work showed that in pyramidal neurones and stellate neurones of the occipital cortex EC rats had more higher order dendritic branches than their IC littermates. Differences in dendritic branching patterns in the visual cortex were also observed predominantly in the basal dendrites (Greenough and Volkmar, 1973). Changes in number of dendritic spines were induced as a result of environmental enrichment (Globus et al., 1973), and similarly the differences were larger in the basal dendrites. In cortical layers II and III the basal dendrites in pyramidal neurones of EC animals showed an increase in length of terminal segments of the dendrites and increased branching (Uylings et al., 1978). The alterations in dendritic branches and spines suggested changes in individual synapses. Studies on dimensions of the synapses revealed that in layer III and layer IV, EC animals had longer post-synaptic thickening than IC rats (Mollgaard et al., 1971; West and Greenough, 1972; Diamond et al., 1975). The neuroanatomical

changes in the visual cortex could at least in part be mediated by neurotrophins, as their levels increased in the visual cortex of EC rats (Torasdotter et al., 1996, 1998), and the nerve growth factor inducible (NGF-IA) immediate early gene, which is also induced in EC animals' visual cortex (Wallace et al., 1995). Changes in mRNA levels in the brains of EC animals were demonstrated in earlier studies (Ferchmin et al., 1970; Bennett, 1976; Ferchmin and Eterovic, 1986).

These neuroanatomical changes are likely to have functional consequences. Speculations that plastic changes occurring at synaptic sites could be related to long-term memory have been entertained by some investigators at different times — from Tanzi and Cajal to Hebb and Kandel (for reviews see, e.g. Rosenzweig, 1996; Diamond, 2001). Increased synaptic density and larger synaptic sites appear to be associated with enhanced capacity for learning, as studies have repeatedly shown that EC animals perform better than IC animals in a variety of mazes, such as the Hebb–Williams maze, the Krechevsky Hypothesis apparatus, the Radial arm maze and the Morris water maze.

In addition to its effect on the visual cortex, EC induces subtle neuroanatomical and biochemical changes in different brain regions of adult rats, such as the hippocampus, the entorhinal cortex, and cerebellum, of which the hippocampus has received the greatest attention.

Effects on the hippocampus: from neurotrophins to neurogenesis

A considerable body of literature links the hippocampus to various plasticity related phenomena, and particularly with learning and memory. Yet earlier studies of the influence of EC on gross measures in the hippocampus were equivocal with some groups reporting changes in hippocampal measures (Walsh et al., 1969; Walsh and Cummins, 1979), others failing to see such differences (Diamond et al., 1976), and still others reporting differences in dendritic branching in dentate granule cells, but only in female EC rats (Juraska et al., 1985, 1989). Furthermore, increases in granular cells, dendritic branching and overall size of the dendritic field were observed in enriched juvenile, but not in adult rats (Fiala et al., 1978).

Recent studies have generated convincing evidence of environmentally induced changes in the hippocampus of EC rats as compared to IC rats, in a wide array of biological variables. These studies have shown that EC induces hippocampal changes in gene expression and/or protein levels of neurotrophins (Falkenberg et al., 1992; Mohammed et al., 1993; Torasdotter et al., 1996, 1998), glucocorticoid receptors (Mohammed et al., 1993; Olsson et al., 1994), the Alzheimer amyloid precursor protein (Huber et al., 1997), immediate early genes (Mohammed et al., 1993; Olsson et al., 1994), serotonin receptors (Rasmuson et al., 1998), AMPA receptor binding (Gagné et al., 1998) as well as in neurogenesis (York et al., 1989; Kempermann et al., 1997, 1998a,b; Nilsson et al., 1999). Exposure to a complex environment induces increased spine densities in the hippocampal CA1 pyramidal cells (Moser et al., 1994). The hippocampus involvement in plasticity related phenomena, such as learning, has been the focus of intensive investigation. Neurotrophins, for example, have been of special interest in this regard as they are abundantly expressed in the hippocampus and have been implicated as mediators of plasticity in this and other brain regions (Thoenen, 2000). The members of the nerve growth factor family of neurotrophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are abundantly expressed in the hippocampus, where they are localised in pyramidal cells and dentate granule cells (Barde, 1990; Ernfors et al., 1990; Maisonpierre et al., 1990; Ernfors et al., 1988). Behavioural studies have revealed both BDNF and NGF to be importantly involved in mediating learning and memory (Henriksson et al., 1992; Ma et al., 1998; Mizuno et al., 2000; Woolf et al., 2001). There are numerous studies indicating involvement of these neurotrophins in synaptic plasticity in the hippocampus and other brain regions, such as the somatosensory and visual cortex (McAllister et al., 1995; Schuman, 1999; McAllister, 2000). Of interest are observations that NGF regulates cell body size, dendritic arborisation and dendritic spine density (Cuello, 1996; Sofroniew et al., 2001), changes that are also induced by environmental enrichment. Similarly there is the intriguing observation that the dendritic growth of pyramidal neurones in the developing visual cortex is dynami-

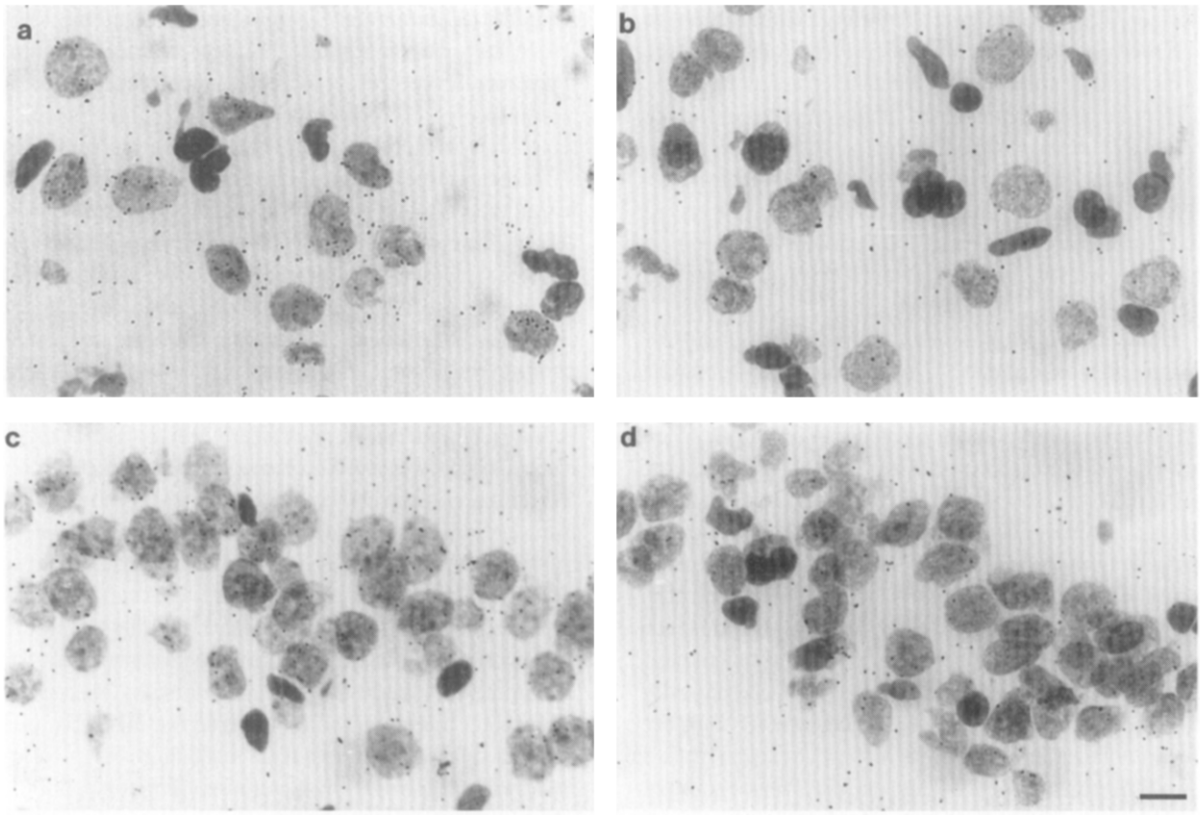


Fig. 1. Photomicrographs showing the expression of NGF mRNA in the layer IV of the rat occipital cortex (a,b) and pyramidal layer of hippocampal CA1 region (c,d) of the adult rats (50 days old) housed for 1 month in enriched environment (a,c) and impoverished environment (b,d). Note the increased hybridisation signal (black dots) on neurones of the enriched animals. Scale bar: 10 μm. (Reproduced from Torasdotter et al., 1998.)

cally regulated by BDNF and NT-3, whereby BDNF stimulates growth in layer IV, while NT-3 stimulates growth in layer VI (McAllister et al., 1997). Age-related loss of dendritic spines in the neocortex could be counteracted by 4 weeks administration of NGF, which restored dendritic spine densities (Mervis et al., 1991). Also treatment with NGF increased dendritic branching in the pyramidal neurones in layer V of the cortex, and increased dendritic spines (Kolb et al., 1997a,b).Taken together these findings suggest that neurotrophins may be importantly involved in mediating changes in dendritic morphology of enriched rats.

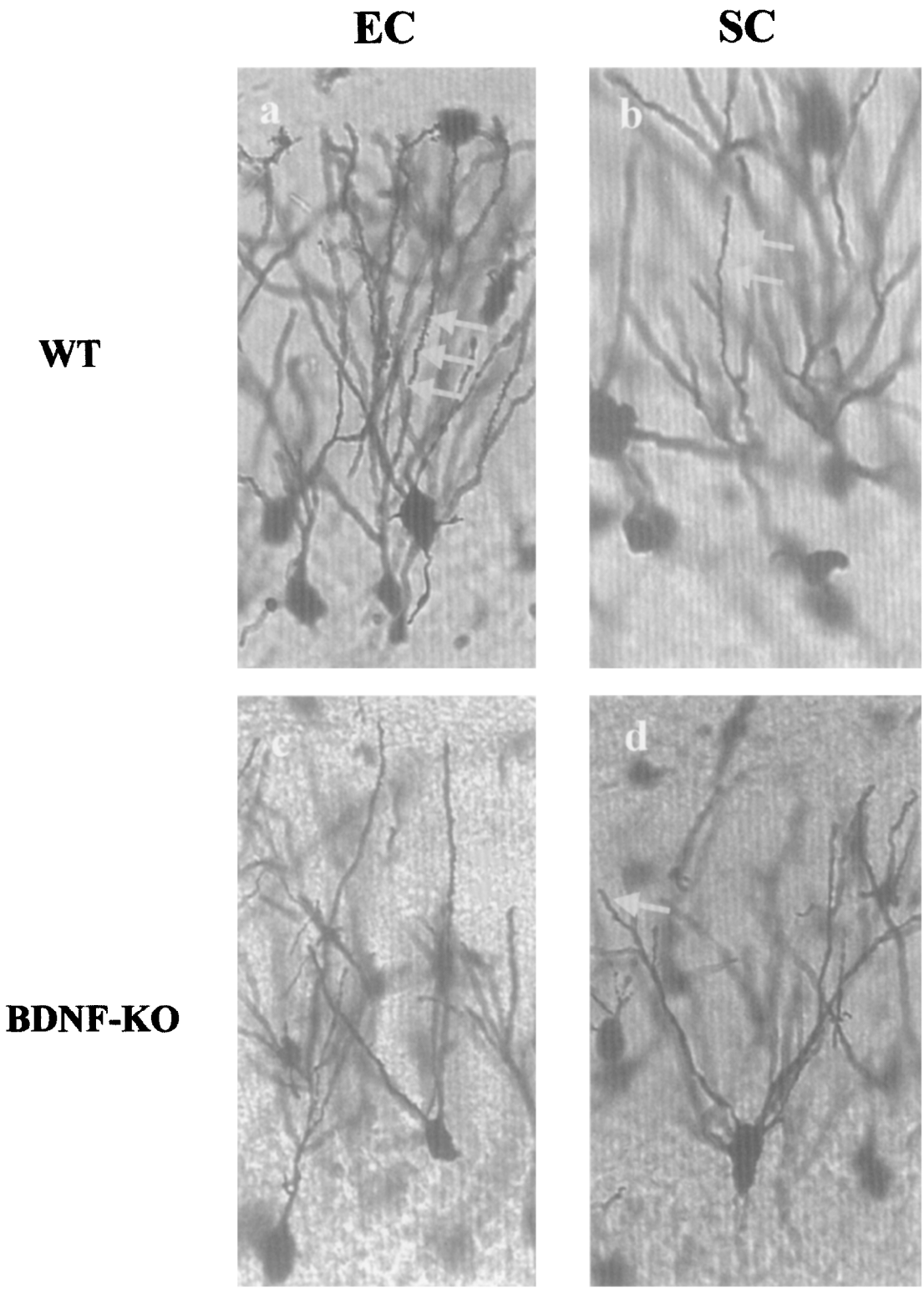
For a number of years we have been analysing influences of environmental enrichment on neurotrophins at both protein and mRNA levels. We found that housing adult rats in an enriched environment increased NGF levels in the hippocampus (Mohammed et al., 1993; Pham et al., 1999a,b; Ickes et al., 2000). The mRNA expression for NGF was increased in the hippocampus and visual cortex of enriched animals (Torasdotter et al., 1998). Similarly, the mRNA expression for NT-3 was elevated in enriched rats (Torasdotter et al., 1996). Fig. 1 shows results of in situ hybridisation for NGF mRNA in the hippocampus and visual cortex of adult rats that had been in EC or IC for 1 month.

The expression of mRNA for BDNF was also increased in the hippocampus of enriched rats (Falkenberg et al., 1992). Several studies point to an important role of BDNF in maintaining hippocampal plasticity. This includes the demonstration that BDNF can modulate physiological activity in the hippocampus CA1 region (Patterson et al., 1992,

1996; Kang and Schuman, 1995, 1996; Figurov et al., 1996). BDNF increases the density of apical dendritic spines and the number of synapses per neurone in slice cultures of the rat hippocampus (Tyler and Pozzo-Miller, 2001) and enhances dendritic growth and branching in slice cultures of the ferret visual cortex (McAllister et al., 1995). It is therefore reasonable to infer that the neuroanatomical changes induced by EC at the synaptic level involve a release of BDNF. To explore the purported role of BDNF in EC-induced neuroanatomical changes we have used knockout mice lacking the BDNF gene. These mice are impaired in spatial learning (Linnarsson et al., 1997). We exposed BDNF knockout mice and their wild-type controls in EC or SC for 2 months. The animals were behaviourally tested for exploratory behaviour and habituation in the open-field and hole-board. After behavioural tests, animals were killed, their brains removed and processed for Golgi Cox staining and the dendritic spine density in the dentate gyrus was measured. Environmental enrichment in wild-type mice caused increased dendritic spines in the hippocampal dentate gyrus neurones. This effect was attenuated in the BDNF mutant mice. Thus while there was a clear difference in number of dendritic spines between the wild-type enriched animals and standard housed animals, in the mutant mice this difference was reduced. Fig. 2 shows a Golgi section of neurones in the dentate gyrus of BDNF knockout mice and wild-type mice from EC and SC.

Behavioural analysis showed that both EC and SC BDNF knockout mice were hyperactive in the open field, but SC animals were slower to habituate in the open field. Knocking out the BDNF gene did not completely abolish enrichment effects on behaviour and on dendritic spines, suggesting, in addition to BDNF, the participation of other factors in regulating the EC induced brain and behavioural changes. For example, glutamate, which is also elevated in EC animals (Myhrer et al., 1992) is found to regulate dendritic growth (McAllister et al., 1996; McKinney et al., 1999). Available evidence indicates that the dendritic branching patterns are controlled by both intrinsic and extrinsic mechanisms. The extrinsic mechanisms include neurotrophins, such as NGF, BDNF and NT-3 (McAllister, 2000), hormones such as thyroxine (Gould et al., 1990), cell adhesion molecules such as cadherins which regulate synaptic plasticity (Tang et al., 1998), Notch 1 (Redmond et al., 2000) and a host of genes, recently identified in *Drosophila* sensory neurones, which regulate specific aspects of dendritic growth. These include (1) *prospero* which regulates dendritic outgrowth; (2) *kakapo*, a large cytoskeletal protein involved in axonal outgrowth; and (3) *flamingo*, belonging to the protocadherin subclass of the cadherin superfamily (Gao et al., 1999). Proper expression of *flamingo* is required for the formation of normal dendritic fields (Gao et al., 2000). In addition, environmental enrichment causes significant changes in a large number of genes, which can be linked to neuronal structure, plasticity and neurotransmission (Rampon et al., 2000a).

For more than a century, a central dogma of neuroscience has been that no new neurones are added to the adult mammalian brain (see Gross, 2000). In recent years, this dogma has been overturned by the weight of evidence showing that in the dentate gyrus of the hippocampus neurones are continuously produced. The generation of new cells occurs not only in phylogenetically less advanced animals, but also in mammals, such as rats (Altman and Das, 1965; Kaplan and Hinds, 1977), tree shrews (Gould et al., 1997), marmosets (Gould et al., 1997), macaques (Gould et al., 1999; Kornack and Rakic, 1999) and even humans (Eriksson et al., 1998). That experience can modify the morphology of the hippocampus has been shown in birds whereby the volume of the hippocampus and its neurone number are larger in food-storing birds than in related non-storing birds (Clayton and Krebs, 1995). Other studies have demonstrated that new neurones are added daily to the hippocampus of the adult black-capped chickadees' brain, which appears to be modulated by environmental complexity and learning experience (Barnea and Nottebohm, 1994, 1996). The first study to examine the influence of environmental enrichment in adult rodents on cell proliferation was performed by Altman and Das (1964), who, by using autoradiography, found an increase in labelled glial cells in the corpus callosum, but could not detect new neurones being formed in the cortex. Later York et al. (1989), using ^{3}H-thymidine to label dividing neurones in the brains of rats housed in EC or SC from 60 to 90 days of age, saw evidence of increased neurogenesis in the dentate gyrus. A definitive proof


EC
SC
WT
BDNF-KO
a
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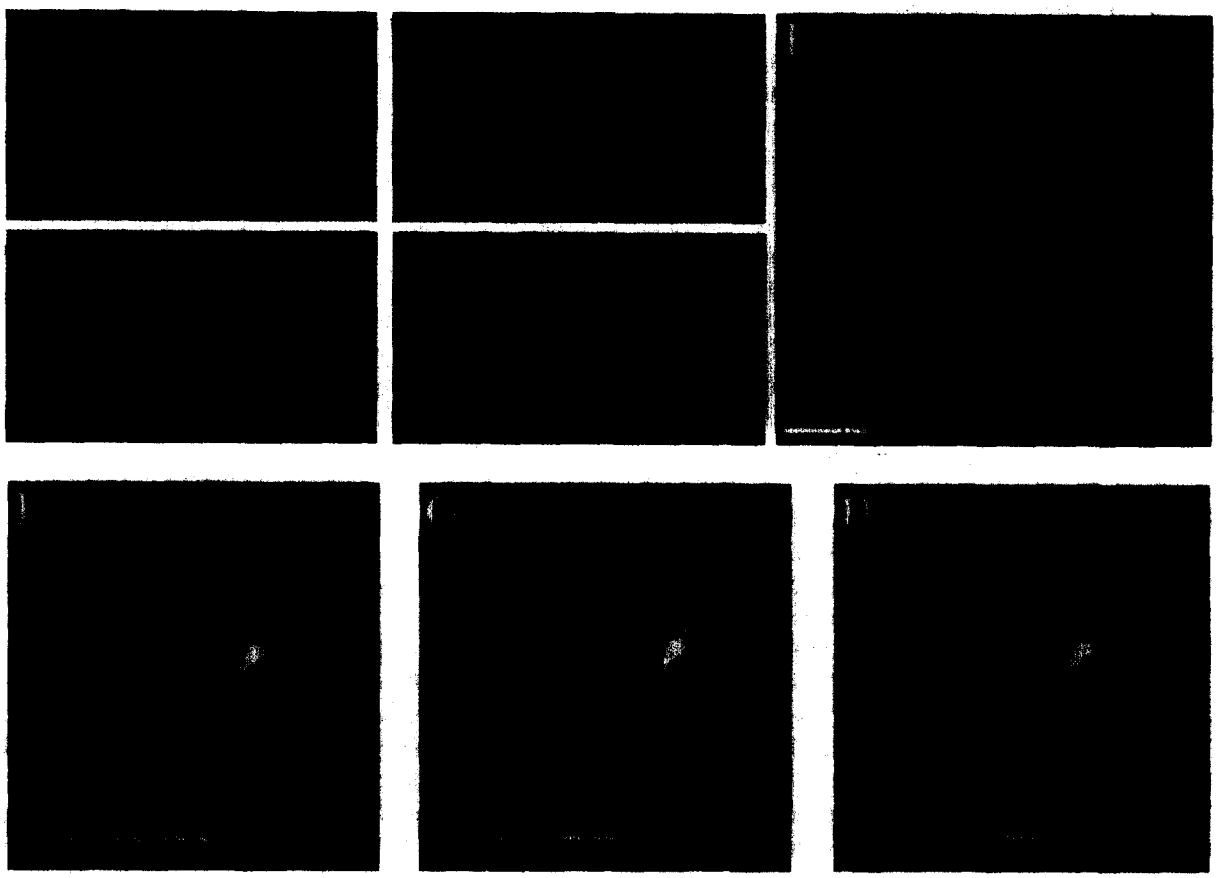

Fig. 3. BrdU-labelled cells in the dentate gyrus. (A) BrdU-labelled nuclei in the dentate gyrus in adult rats (70 days old) housed in enriched environment (EC) 4 weeks after injections. (B) BrdU-labelled nuclei in the dentate gyrus in animals housed in impoverished environment (IC) 4 weeks after injections. Proliferation (C) and survival (D) 4 weeks after discontinuation of BrdU injections. The nuclei are dark and irregularly shaped 1 day after the last BrdU injection (C). Four weeks later, the number of BrdU-positive cells has decreased, and the remaining nuclei have a more rounded appearance and resemble the chromatin structure of mature granule cells (D). The nuclei are frequently found within the granule cell layer 4 weeks after BrdU injections. Confocal images of cells with neuronal phenotype (Calbindin-positive; red) (E). Newborn granule cell (arrow) in the adult dentate gyrus double-labelled with BrdU (green) and Calbindin (red) analyzed with a Z-series through the dentate gyrus using scanning laser microscopy (F–H). Scale bars: 50 μm. (Reproduced from Nilsson et al., 1999.)

of increased neurogenesis in the hippocampal dentate gyrus of mice was provided by Kempermann et al. (1997, 1998a) and in rats by Nilsson et al. (1999). Using the proliferation marker bromodeoxyuridine (BrdU) these investigators found that enrichment increases neurogenesis in the dentate gyrus of adult mice and rats. Fig. 3 depicts the observed increase in neurogenesis in the dentate gyrus of adult EC rats.

In their first study, Kempermann et al. (1997) examined young mice while in their later study

Fig. 2. Photomicrographs of the dentate granular cells stained by Golgi–Cox method in the adult wild-type (a,b) and BDNF knockout (c,d) mice housed in enriched environment (a,c) and social (standard) environment (b,d) for 60 days. The black arrows indicate the position of the spines on the apical dendrites of granular cells. Note that the enriched environment increased the density of dendritic spines in both the wild-type (3 × arrows) and BDNF knockout (2 × arrows). However, it is clear that the wild-type enriched mice have greater spine density; while the BDNF knockout standard housed mice almost lack dendritic spines.

aged mice were analysed. These findings have generated considerable interest as they suggest functional implications of neurogenesis both in young and aged animals. For example, increased neurogenesis in the dentate gyrus has been associated with learning (Shors et al., 2001), while stress has been found to cause reduction of neurogenesis (Gould et al., 1997). Environmental enrichment does not seem to affect proliferation of progenitor cells, rather it appears to promote survival of the dentate granule cells.

The role of the hippocampus in learning and memory has been the focus of increased research interest. The multitudinous changes induced in the EC animals' hippocampus, such as increased gene expression for glucocorticoid receptors and neurotrophins, may contribute to the enhanced cognitive function of these animals that has been observed in several behavioural tests such as performance in the Hebb–Williams maze (Mohammed et al., 1986; Galani et al., 1997), the Morris water maze (Whishaw et al., 1984; Mohammed et al., 1990) and in the radial arm maze (Galani et al., 1998). The entorhinal cortex is the origin of the major cortical inputs to the hippocampus; and there is evidence implicating its involvement in memory (Scovile and Milner, 1957; Eichenbaum et al., 1994; Otto et al., 1997). Other work suggests that structures within the hippocampal formation are not similarly involved in spatial learning and memory (Galani et al., 1998). The entorhinal cortex of enriched animals is thicker than that of IC animals (Diamond, 1988) and levels of glutamate levels in the entorhinal cortex of EC animals are increased (Myhrer et al., 1992). In addition middle-aged rats that had spent 1 year in enrichment had higher levels of NGF in the entorhinal cortex compared to IC animals. The EC animals had significantly higher levels of NGF in the hippocampus and entorhinal cortex, as well as in the visual cortex. (Pham et al., 1999a). All these changes could have an impact on neurones in these brain regions known to be critically involved in cognitive function.

Insulin growth factor-1 (IGF-1) is another neurotrophin that has been shown to be important in maintaining neuronal survival, glial differentiation and facilitating release of acetylcholine (Dore et al., 2000). IGF-1-like immunoreactivity and IGF1-mRNA have been identified in different brain regions, and IGF-1 receptor sites have been visualised throughout cortical and subcortical regions, with high densities in all cortical regions and the hippocampus. Of interest also is the recent observation of IGF-1 causing increased neurogenesis in the dentate gyrus (Åberg et al., 2000). We have employed autoradiography to analyse the influence of environmental enrichment on density of IGF-1 receptors in 49 brain regions.

Fig. 4 shows the laminar distribution of IGF-1 binding sites at the level of the occipital cortex in EC and IC adult rats that had been exposed to differential housing for 1 month. The density of binding sites in the occipital cortex layers of EC animals was increased as compared to IC animals. EC animals also had more binding sites in the entorhinal cortex. Table 1 presents the results of all regions analysed.

Effects on the cerebellum

The cerebellum of EC rats also had a higher density of IGF-1 receptors than that of IC animals. The cerebellum has been found to display plastic properties in response to environmental influences. Given the well known function of the cerebellum in maintaining motor coordination and learning (Glickstein, 1993), and since the EC animals are actively engaged in exploring, climbing and balancing, it is reasonable to expect particular changes in the cerebellum of these animals. Complex motor skill learning leads to an increase in synapse number in the cerebellar cortex (Kleim et al., 1997, 1998). Changes in morphology of cerebellar Purkinje cells in response to environmental stimulation have been noted. Rearing monkeys in a stimulating environment, in contrast to isolated environment, resulted in more extensive spiny branchlets of Purkinje cells (Floeter and Greenough, 1979).

Effects on the amygdala

In several behavioural studies, it is evident the EC animals differ from IC rats in emotional aspects of behaviour. In tests on diversity of exploration IC rats interacted less with objects in a free exploration situation than EC rats (Renner and Rosenzweig, 1987). In open-field tests, IC rats display increased locomotor activity and reduced habituation, which is indicative of increased arousal and emotionality

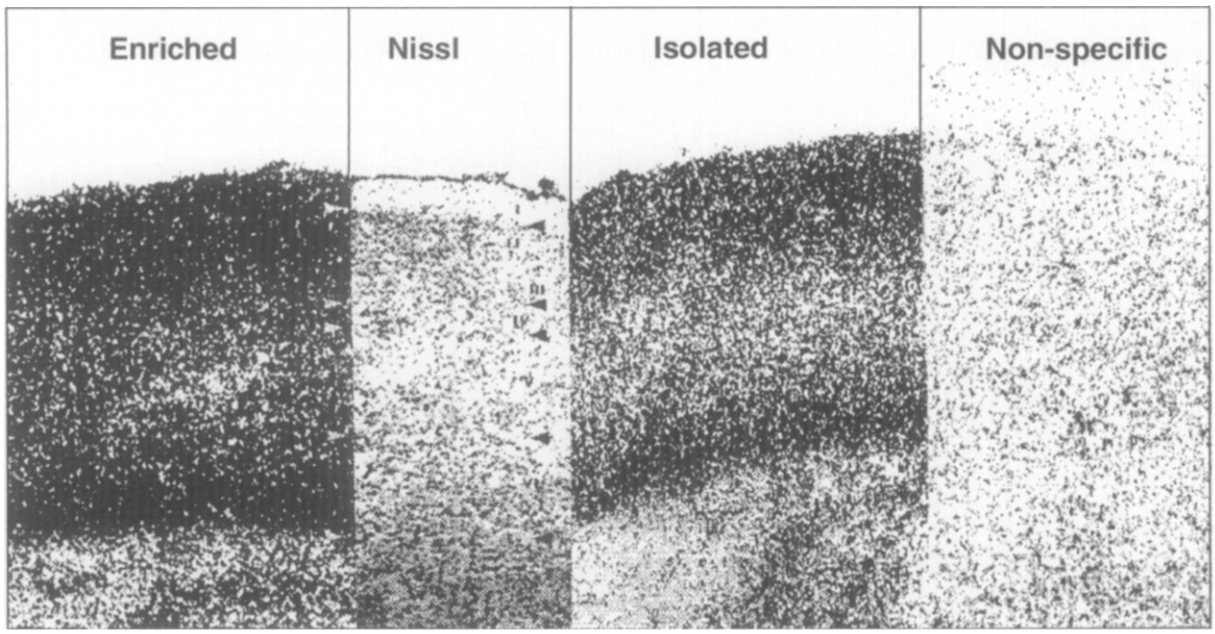

Fig. 4. Photomicrographs of the autoradiographic film labelled by ^{125}I-insulin-like growth factor 1 in the occipital cortex of the adult rats (3 months old) housed for 30 days in enriched or isolated environment. Note the increased IGF-1 receptor binding sites throughout all the cortical layers, but predominantly in layers I–III and layer VI of enriched housed rats.

(Mohammed et al., 1990; Falkenberg et al., 1992). A key brain region thought to be critical for generating behavioural responses to emotionally arousing stimuli is the amygdala. The amygdaloid complex consists of several nuclei which differ in their cyto- and chemi-architectonic, and in their intra- and extra-amygdaloid connectivities (Pitkanen et al., 1997). Studies employing classical and instrumental conditioning paradigms have highlighted the differential roles of various substructures of the amygdaloid complex in emotional learning. The amygdala shows plastic properties in response to environmental influences. Morphological changes in both synapses and neurones in the medial amygdaloid nucleus were observed following manipulation of the pheromonal environment (Ichikawa et al., 1993). Functional activity in different brain regions can be studied by employing expression of the immediate early gene c-*fos* and its protein product c-Fos (Kaczmarek and Chaudhuri, 1997). Studies on aversive learning have revealed differential expression of c-Fos in some amygdaloid nuclei (Kaczmarek, 1993). To map functional activity in the amygdaloid complex and other brain regions of differentially housed rats we examined expression of c-Fos following exposure to aversive stimuli. Since the differentially housed rats differ in emotional behaviour as indicated above, we hypothesised the animals would respond differently in fear conditioning as revealed by c-Fos expression in brain regions known to be important for mediating emotional behaviour. Virtually no c-Fos expression could be detected in various brain structures in the naive animals, and in the rats 24 h after the exposure to the footshocks. By contrast, elevated c-Fos expression was observed in the amygdala, thalamus and hypothalamus of the rats sacrificed 2 h after the exposure to the aversive stimuli. On the other hand, lack of c-Fos expression was observed in the hippocampus at the same time point. Detailed analysis of c-Fos immunolabeling of various amygdala subnuclei in EC and IC animals revealed significant differences in their responses to the conditioning procedure. The most pronounced c-Fos expression was observed within the medial amygdala and amygdaloid-striatal transition area, in which the IC animals displayed higher c-Fos levels than the

TABLE 1

Anatomical distribution of ^{125}I-IGF-1 receptor binding sites in the brains of adult rats (3 months old) housed in enriched ($n = 8$) or impoverished ($n = 8$) environment for 30 days

Regions		^{125}I-IGF-1 receptor binding (fmol/mg wet weight)	
		Enriched	Isolated
Frontal 1	superficial I–III	2.97 ± 0.1	2.63 ± 0.22
	deep IV–VI	2.7 ± 0.14	2.47 ± 0.15
Frontal 2	superficial I–III	3.03 ± 0.2	2.72 ± 0.1
	deep IV–VI	2.69 ± 0.17	2.55 ± 0.11
Frontal FL	superficial I–III	3.55 ± 0.03	3.28 ± 0.22
	deep IV–VI	3.16 ± 0.15	2.82 ± 0.22
Frontal HL	superficial I–III	3.05 ± 0.33	3.13 ± 0.19
	deep IV–VI	2.9 ± 0.39	2.76 ± 0.19
Parietal 1	superficial I–III	2.78 ± 0.10	2.63 ± 0.06
	deep IV–VI	2.53 ± 0.12	2.32 ± 0.02
Parietal 2	superficial I–III	2.91 ± 0.07	2.83 ± 0.18
	deep IV–VI	2.54 ± 0.06	2.25 ± 0.12
Temporal 1	superficial I–III	3.83 ± 0.18 [a]	3.09 ± 0.08
	deep IV–VI	3.1 ± 0.06 [b]	2.42 ± 0.14
Temporal 2	superficial I–III	4.52 ± 0.24 [a]	3.53 ± 0.15
	deep IV–VI	3.26 ± 0.06 [a]	2.84 ± 0.08
Occipital 1	superficial I–III	3.45 ± 0.11 [a]	2.96 ± 0.12
	deep IV–VI	2.92 ± 0.01 [b]	2.58 ± 0.05
Occipital 2	superficial I–III	3.7 ± 0.18 [a]	2.87 ± 0.10
	deep IV–VI	2.9 ± 0.05 [a]	2.54 ± 0.11
Gustatory	superficial I–III	2.85 ± 0.11	2.73 ± 0.16
	deep IV–VI	2.58 ± 0.08 [a]	2.17 ± 0.09
Entorhinal	all layers	4.16 ± 0.28 [a]	3.39 ± 0.14
Perirhinal	all layers	3.78 ± 0.19 [a]	3.08 ± 0.15
Insular	Ag A superficial I–III	3.58 ± 0.15	3.4 ± 0.12
	deep IV–VI	3.29 ± 0.39	2.77 ± 0.11
Insular	Ag P superficial I–III	3.18 ± 0.04	3.14 ± 0.16
	deep IV–VI	2.76 ± 0.21	2.37 ± 0.10
Piriform	all layers	3.11 ± 0.17	2.90 ± 0.09
Cingular 1	all layers	2.3 ± 0.09	2.3 ± 0.17
Cingular 2	all layers	2.51 ± 0.15	2.36 ± 0.13
Cingular 3	all layers	2.54 ± 0.1	2.71 ± 0.07
RSA anterior	all layers	1.82 ± 0.14	1.87 ± 0.19
RSA posterior	all layers	2.88 ± 0.15 [a]	1.97 ± 0.17
RSG anterior	all layers	1.45 ± 0.10	1.68 ± 0.07
RSG posterior	all layers	2.76 ± 0.05 [b]	2.24 ± 0.07
Olfactory	bulbar granular layer	2.96 ± 0.72	3.1 ± 0.4
Olfactory	anterior nucleus	3.07 ± 0.42	2.98 ± 0.29
Olfactory	posterior nucleus	3.18 ± 0.23	3.19 ± 0.02
Olfactory	tuberculum	2.93 ± 0.65	1.8 ± 0.36
Claustrum		3.38 ± 0.02	3.29 ± 0.18
Endopiriform	nucleus	3.33 ± 0.22	2.89 ± 0.18
Caudatus-putamen		1.76 ± 0.20	1.10 ± 0.14
Accumbens	shell	3.25 ± 0.1	2.13 ± 0.64
Septum	lateral + medial	1.45 ± 0.2	1.07 ± 0.62
Amygdala	basolateral	3.04 ± 0.5	2.3 ± 0.3
Amygdala	corticomedial	4.06 ± 0.27	3.66 ± 0.3
Thalamus	VP + MD	2.11 ± 0.3	2.8 ± 0.1
Hypothalamus		1.9 ± 0.12	2.15 ± 0.09

TABLE 1 (continued)

Regions		^{125}I-IGF-1 receptor binding (fmol/mg wet weight)	
		Enriched	Isolated
CA1	all layers	2.22±0.33	2.4±0.12
CA2	all layers	3.09±0.18	2.94±0.03
CA3	all layers	3.4±0.19	3.4±0.27
CA4	all layers	2.7±0.23	3.07±0.43
Dentatus	all layers	2.87±0.12	2.93±0.23
Colliculus superior		2.28±0.11	2.13±0.17
Medial genicular body		3.17±0.26[a]	2.08±0.05
Mesencephalon	tegmentum	1.53±0.28	1.11±0.24
Pons	tegmentum	1.30±0.20	1.01±0.27
Medulla oblongata		1.51±0.13	1.39±0.08
Cerebellum	cortex	2.86±0.17[a]	2.29±0.16
Corpus callosum		1.78±0.13	1.59±1.1
Plexus choroideus		6.31±0.16	6.53±0.13

Data were obtained from analysis of autoradiograms. Note the significant increase obtained in the posterior cortical regions: temporal, occipital, retrosplenial, entorhinal, perirhinal and gustatory cortex; non-cortical regions: medial genicular bodies and cerebellum. Data are presented as mean ± S.E.M. [a] $P < 0.05$; [b] $P < 0.01$ (Fischer PLSD test following one-way ANOVA).

EC animals (Nikolaev et al., 2001). These findings are compatible with the notion that the IC animals take longer than the EC animals to recover from a stressful experience.

Influence on the aging brain and injured nervous system

The brain retains its capacity for chemical and anatomical plasticity into old age. The effects of enrichment on the visual cortex that were observed in adult rats can still be seen in aged rats. Thus aged rats housed in EC compared to those housed in IC have larger brain weights, and thicker and longer cortices (Cummins et al., 1973; Diamond et al., 1985a; Van Gool et al., 1987) and they are better in learning tasks (Winocur, 1998). Dendritic measurements in 600–630-day-old rats revealed significantly longer sixth-order dendrites in EC animals as compared to SC animals (Connor et al., 1981). Moreover, the aged EC animals have more cortical dendritic branching and higher spine densities than their IC counterparts (Kolb et al., 1998). In aged rats (24–26 months old) EC increased spiny branchlets and it was subsequently shown that in comparison to IC animals the EC rats had more material in the mid-region of spiny branchlets and less at the end (Greenough et al., 1986). These studies indicate that housing aged rats in an EC helped the animals preserve dendritic growth in the cerebellum (Greenough et al., 1986). Changes in glial cells can be induced in aged animals by EC (Soffie et al., 1999); and cognitive dysfunction associated with aging can be attenuated by enriched environment (Escorihuela et al., 1995; Fernandez-Teruel et al., 1997). It has been demonstrated that enrichment enhances survival of hippocampal dentate gyrus neurones in aged mice (Kempermann et al., 1998b). Forepaw representation in the primary somatosensory cortex of rats housed in standard laboratory conditions is drastically altered during the aging process, and environmental and social interactions could partially offset the age-related breakdown of somatosensory cortical maps (Coq and Xerri, 2001).

In a recent study we placed 22-month-old rats in EC or SC for 30 days and examined dendritic spines in the hippocampal dentate gyrus, entorhinal cortex and visual cortex. Fig. 5 shows photomicrographs of Golgi sections of the three different brain regions, namely the visual cortex, the entorhinal cortex and hippocampal formation from enriched and socially housed aged rats.

In all the three regions there were increased dendritic spine densities in the EC rats as compared

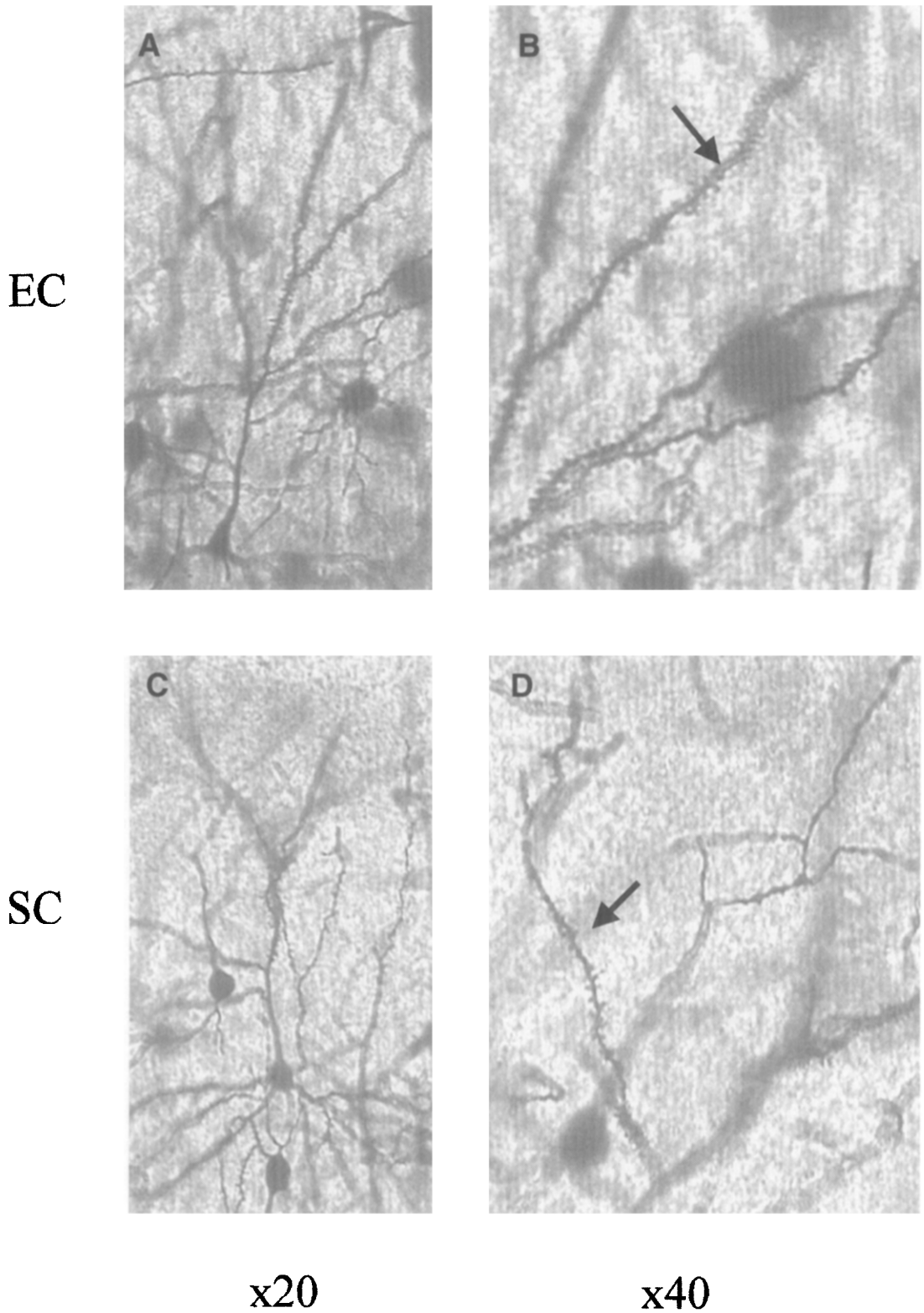

Fig. 5. (A–D) Photomicrographs of the occipital secondary cortex.

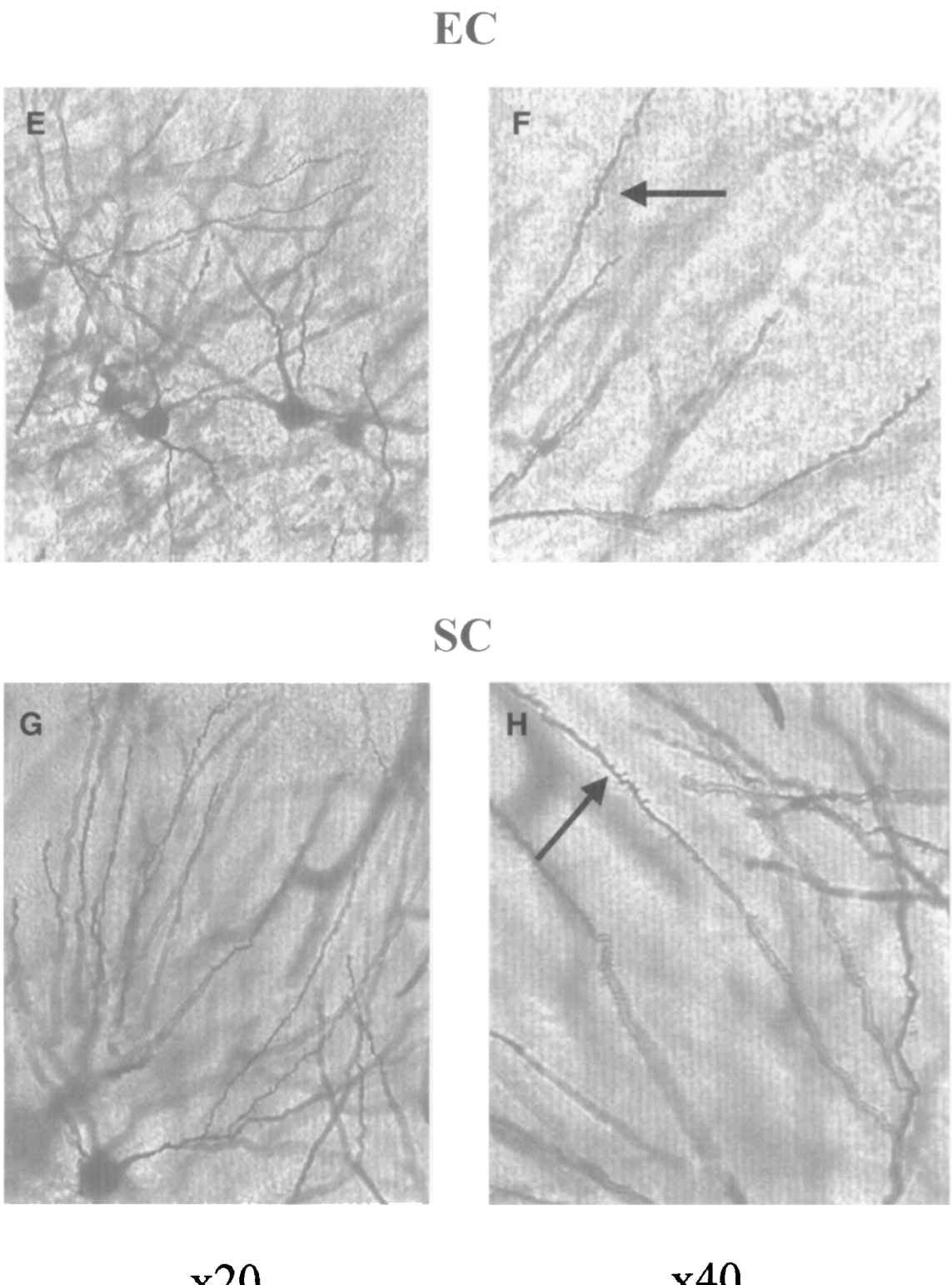

Fig. 5. (E–H) Photomicrographs of the entorhinal cortex layer II.

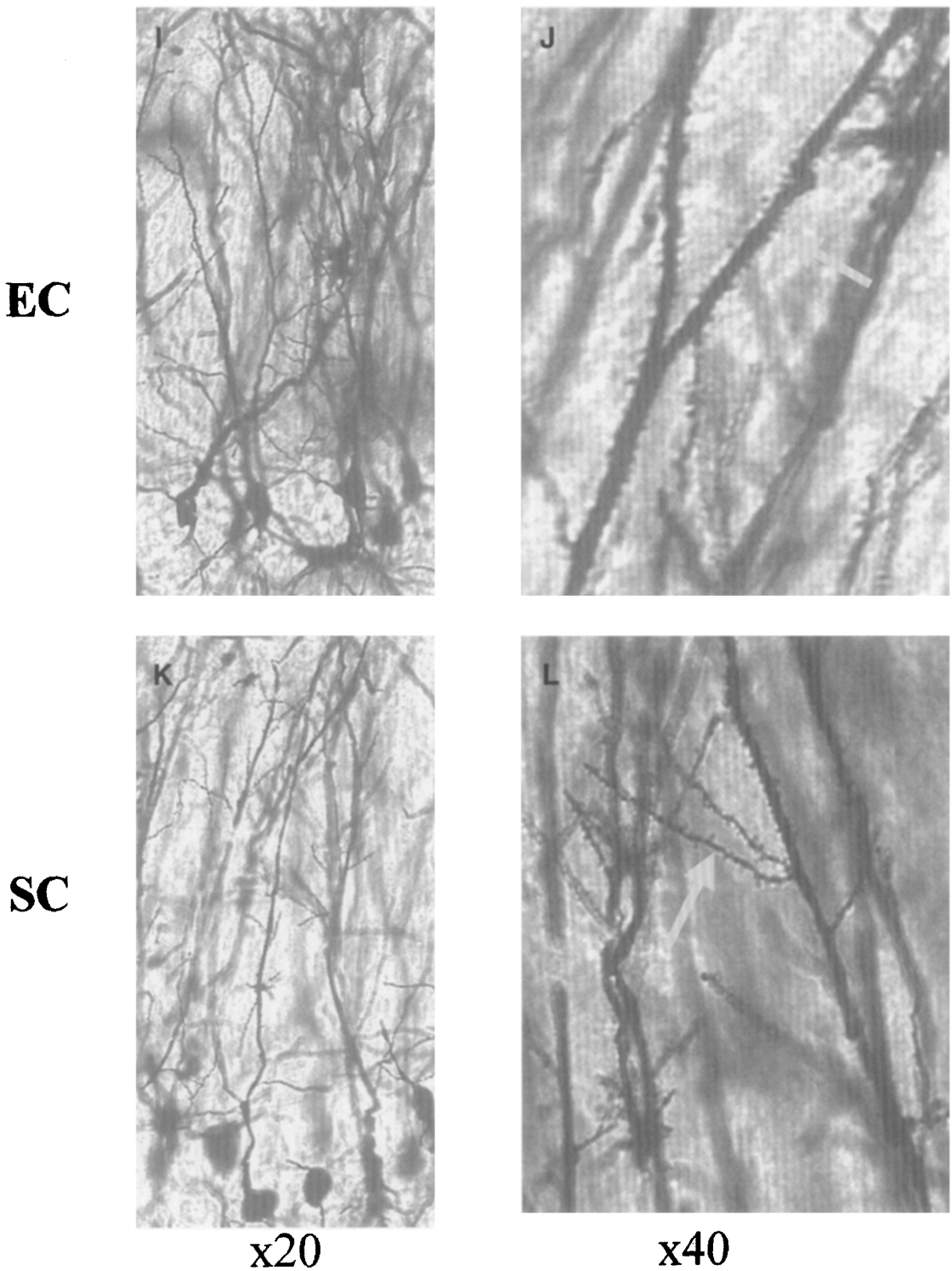

Fig. 5. (I–L) Photomicrographs of the pyramidal layer CA1.

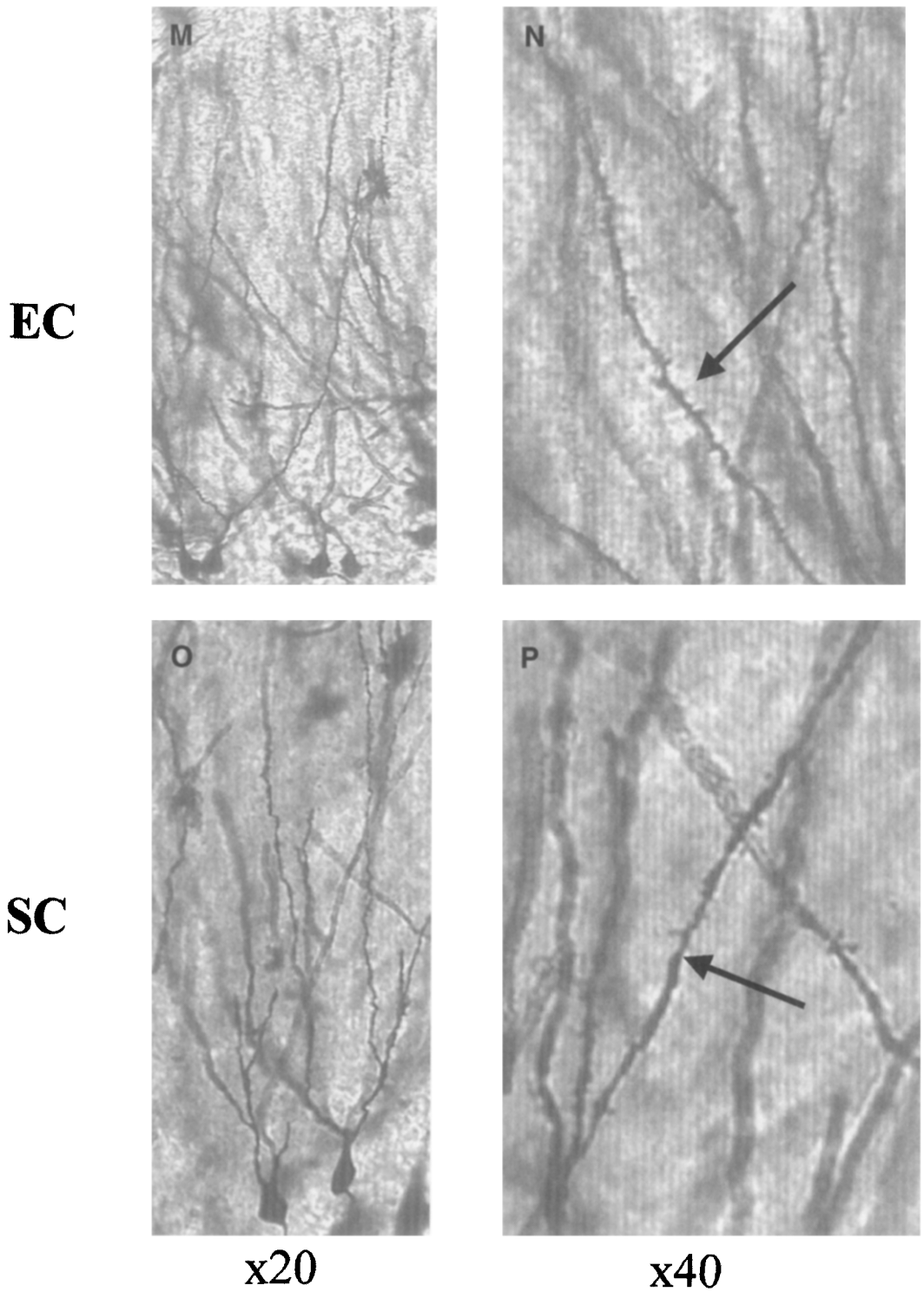

Fig. 5. (M–P) Photomicrographs of the granular cell layer in the dentate gyrus. Stained by Golgi–Cox in the aged rats (22 months old) housed for 1 month in enriched (A,B,E,F,I,G,M,N) or social (standard) environment (C,D,G,H,K,L,O,P). $n = 8$ per group. Photos were taken under lower and higher magnification (×20, ×40, respectively). The photos clearly show the difference in dendritic spine densities in all cortical regions between the two groups of rats (arrows indicate the position of dendritic spines).

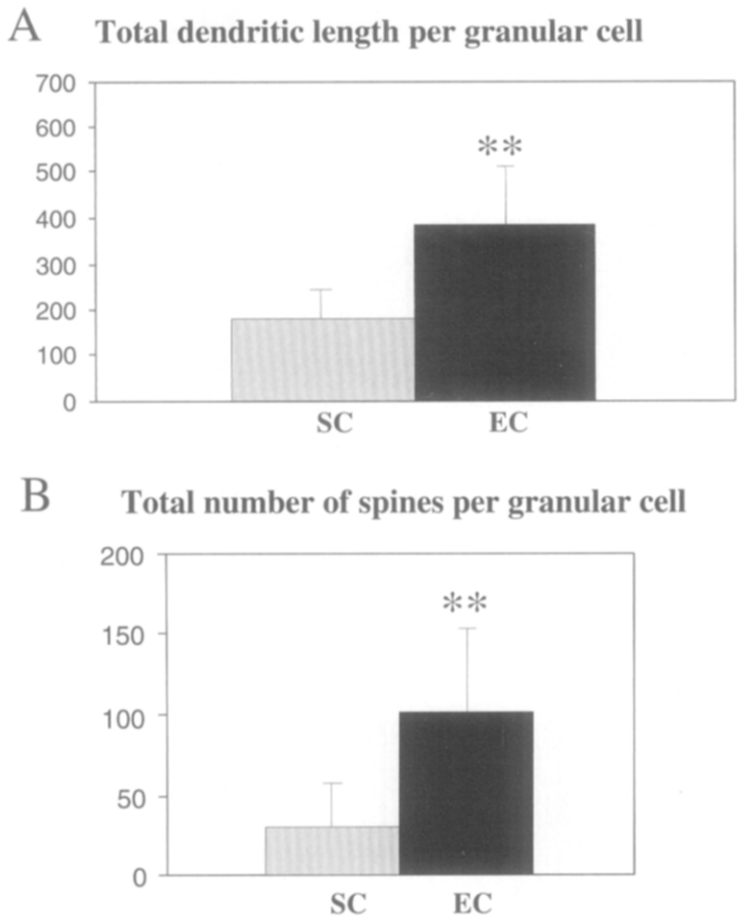

Fig. 6. Graphical presentation of (A) total dendritic length per granular cell, and (B) total number of spines per granular cell in the dentate gyrus of aged rats (22 months old) housed for 1 month in enriched environment or social (standard) environment. Results are presented as mean ± S.E.M. $n = 8$. $^{**}P < 0.01$ (Fischer PLSD test following one-way ANOVA).

to the SC rats. Fig. 6 shows graphically the results of total dendritic length per granular cell, and total number of spines per granular cell.

An important line of research into the EC influences deals with the possible therapeutic effects of environmental enrichment in experimental animals suffering from various nervous system dysfunctions induced by mechanical or neurotoxic lesions, hypothyroidism, malnutrition or genetic lesions. The potential therapeutic influence of EC can be deduced from findings that EC reduces apoptotic cell death in the hippocampus and prevents the development of motor seizures after injection with kainic acid (Young et al., 1999). Converging evidence indicates that enrichment can enhance the spared cognitive abilities of these disadvantaged animals. In an early study addressing this issue Smith (1959) found an interaction effect of cortical lesion size and placement with rearing environment whereby the EC rats were, in direct contrast to the IC rats, little affected by large posterior cortical lesions, but were highly affected by small anterior lesions.

In another early study, the influence of enrichment on rats sustaining neonatal bilateral cortical lesions was examined (Schwartz, 1964). The experimental animals and their sham operated controls were reared in EC from postnatal day 5 for a period of 3 months. Enrichment improved performance of

the lesioned rats in the Hebb–Williams maze. Subsequent studies did report some degree of improvement after brain damage in animals housed in enriched environment. Of interest were the observations that in many of these beneficial effects of EC the lesioned animals' performances in the behavioural tasks were even higher than that of the control animals. However, there were also some studies that did not report any beneficial effects of enrichment. The beneficial influence of enrichment appears to be dependent on a number of factors, among which are the nature of the task, the size and location of the lesion and the age of the animal. For example, rats sustaining unilateral or bilateral cortical lesions were tested in a large battery of tests after being housed in EC for 90 days. While enrichment attenuated deficits induced by the lesions, such as beam traversing and claw cutting, other lesion deficits like food hoarding and grooming were not affected (Kolb and Gibb, 1991). Relatively short periods of enrichment (2 h/day) were efficacious in promoting recovery of function in brain lesioned rats (Will et al., 1977). The beneficial effects of enrichment in rats with different lesions of the hippocampus, subiculum or entorhinal cortex were examined. It was shown that only rats with lesions of the hippocampus benefitted from enrichment as assessed in the Morris water maze test, the Hebb–Williams test and in exploration tests (Galani et al., 1997). There is also data indicating that postoperative enrichment can be therapeutic after certain kinds of brain damage, such as hippocampal lesions, but not after other lesions such as those affecting the afferent–efferent system of the hippocampus.

Rats with bilateral lesions of the fimbria-fornix show improvement in spatial learning following enrichment (Van Rijzingen et al., 1997). Age-dependent beneficial effects of enrichment have also been observed. EC improved performance in the water maze if rats received hemidecortication in adulthood, while no such effects were observed in rats that were hemidecorticated when 1 day old (Whishaw et al., 1984). Likewise, enrichment markedly attenuated the behavioural and morphological effects of lesions in rats given at 5 days of age, but not if the lesion was inflicted at 1 day of age (Kolb and Elliott, 1987).

A variety of insults to the nervous system can be counteracted by environmental enrichment. These include hormonally induced disturbances in brain function and behaviour. Neonatal hypothyroid rats are characterised by retarded nervous system development and deficits in learning ability. Environmental enrichment results in improvement of the learning capacity of neonatally hypothyroid (cretinous) rats (Davenport et al., 1976). Similarly enrichment reduces neurological and behavioural disturbances following neonatal anosmia (Iuvone et al., 1996), lead-induced neurotoxicity (Schneider et al., 2001), and malnutrition (Carughi et al., 1989, 1990). In the experiments by Carughi et al., pregnant rats were given protein-rich (17%) and protein-poor (8%) diets. The pups born under protein poor conditions were 50% lighter in body weight and also the fourth-, fifth-, and sixth-order dendrites were greatly reduced in cerebral cortical samples. There was no significant increase in dendritic arborisation with enrichment. Only after a combination of enriching the diets and experiential enrichment could dendritic growth be seen.

A growing area of interest is the influence of environment in facilitating recovery in transplanted animals. Grafting which had a minimal effect in lesioned rats led to significant improvement of function in these animals when combined with environmental enrichment (Kelche et al., 1988). Animals in which the middle cerebral artery (MCA) was ligated received fetal neocortical tissue transplant combined with environmental enrichment showed significant improvement of motor function (Grabowski et al., 1995). The beneficial effects of enrichment have been noted in rats sustaining a traumatic brain injury in which it was seen that injured animals recovering in an enriched environment for 11–14 days performed better in the Morris water maze than injured standard housed animals, and the lesion volume was smaller in enriched animals (Passineau et al., 2001). Similarly, a combination of physical training with enriched environment improved forelimb motor function in rats with ischaemic injury, and resulted in increased arborisation of dendrites in layer V pyramidal neurones in the undamaged motor cortex (Biernaskie and Corbett, 2001).

Obviously, genetic factors contribute to the animals' response to EC (Henderson, 1972, 1976). Different mouse strains display subtle differences in their diversity of exploration with different stimulus objects in the enriched cages (N. Henderson, per-

sonal communication). In a study of interaction of genetic background with undernutrition and differential environmental housing, it was found that the C57BL/6J and the DBA/2J strains responded differently in open-field tests after differential housing (Blizard and Randt, 1974). Environmental manipulation can also normalise behaviour of animals with genetic defects. The mouse staggerer is characterised by cerebellar mutation with loss of Purkinje cells resulting in motor disturbances and impaired reproductive and maternal behaviour. Manipulation of the environment could modify the impaired maternal behaviour (Guastavino, 1984a), and improve the gait of the cerebellar mutant mice (Guastavino, 1984b). Dwarf mice show deficits in T-maze spontaneous exploration, a deficit which could be modified by environmental enrichment (Bouchon and Will, 1982). Deficits in mutant mice with selective lesions of NMDA receptors in the CA1 hippocampal region could also be reversed by raising the mutant mice in an enriched environment (Rampon et al., 2000b). And as we have illustrated above, mice whose BDNF gene has been deleted respond to EC with some increase in dentate gyrus dendritic spines compared to the non-enriched mutant mice.

Conclusion: experience induced plasticity — from flies to philosophers

First shown in rodents, the EC induced brain changes have now been documented in a wide variety of species. In the fruitfly *Drosophila melanogaster*, the mushroom bodies lying in the dorsal anterior part of the brain are the main integrative centre of the brain. They contain about 5000 neurones and are known to be importantly involved in olfactory learning (Roman and Davis, 2001). These clusters of neurones send dendrites to the area of the fly brain known as the calyx. The number of fibres in the mushroom bodies are decreased by social isolation (Technau, 1984), and the volume of the calyx and other brain parts such as the central brain and medulla are increased by environmental stimulation and reduced by isolation (Heisenberg et al., 1995). Mushroom body neurogenesis during adulthood is increased in crickets exposed to environmental enrichment (Lomassese et al., 2000). In the African jewel fish, social experience affects dendritic spines and branches in tectal interneurones (Coss and Globus, 1979) and crayfish placed during adulthood in EC environment, compared to those placed in IC, show increased cell proliferation in the brain (Sandeman and Sandeman, 2000). Gerbils, squirrels, cats, monkeys and bears have all been found to respond with changes in brain and/or behaviour as a result of EC. In a recent study, 100 children were experimentally assigned to a 2-year enriched nursery school environment at ages 3–5 years and compared with hundred control subjects who received normal education and who were matched at the age of 3 years for psychophysiological measures, gender and ethnicity. Early educational and health enrichment led to long-term increases in psychophysiological orienting and arousal (Raine et al., 2001). Speculation that experiential factors can have an impact on brain structures have been entertained across the centuries going back to ancient Greece (Renner and Rosenzweig, 1987; Diamond, 2001). It was shown earlier that EC increases the number of glial cells in the rat cortex (Altman and Das, 1964; Diamond et al., 1966). In an effort to extrapolate this observation to humans, viz., the finding that 'mental exercise' increases glial cell numbers, Diamond et al. performed cell counts in the association cortical areas of a unique individual — Albert Einstein — and compared those with cell counts in brains of 11 male individuals ranging in age from 45–81 years. Because the number of glial cells is known to increase with age it was important to compare Einstein's brain with those of similar aged individuals. The results clearly indicated an increase in the number of glial cells per neurone in Einstein's brain (Diamond et al., 1985b). Fig. 7 represents a photomicrograph of a section of Einstein's brain showing the large number of glial cells surrounding the neurones in area 39 of the association cortex.

The findings of environmentally induced changes in the brains of aged organisms are compatible with the notion of 'use it or lose it', propounded by neuroscientists in the 80s and 90s (Diamond, 1988; Swaab, 1991). It was postulated that in organs other than the brain, cell activation seems to increase 'wear and tear', e.g. by increased free-radical formation, and so to cause an increased rate of aging. However, activation of nerve cells within the physiological range seems to lead to maintenance of neurones during aging, possibly by preferentially stimulating the ac-

Fig. 7. Photomicrograph of a section through the left Brodmann area 39 of Einstein's brain showing nerve cells and glial cells of different sizes. Kluver–Barrera staining was used to visualise the neurones and glial cells. Arrowheads indicate large and small pyramidal neurones. Arrows indicate increased density of oligodendroglial cells, especially around pyramidal cells ('satelitosis'). Open arrows indicate astroglial cells.

tion of protective mechanisms such as DNA repair. This 'use it or lose it' notion implies that neuronal activation might provide a means of prolonging its optimal function for the full life span. Amongst the significant players in neuronal activation are the neurotrophins. The vulnerability of the cholinergic basal forebrain neurones to age-associated loss may be checked by increased release of neurotrophins like NGF. An environment enriched in intellectual and physical activities can counteract many of the adverse effects of aging on the brain in part through the actions of neurotrophins. It has been proposed that the salutary effects of dietary restriction and environmental stimulation on aging involve stimulation of the expression of neurotrophic factors and 'stress proteins' which may protect neurones by suppressing oxyradical production (Mattson et al., 2001).

Neurotrophins are important in maintaining the integrity of populations of neurones that may be especially vulnerable to age and stress-associated loss and in neurodegenerative diseases (Sapolsky, 1992). In the case of Alzheimer's disease, the cholinergic neurones of the basal forebrain are particularly vulnerable and die. This could in part be due to reduction of neurotrophins such as NGF, which is known to support these cells (Mufson et al., 1999). Environmental stimulation can sustain the neurotrophin levels in this and other brain regions and help to maintain function by increasing neural reserve in the aged individual. The impact of environmental enrichment on the brain appears to be a universal phenomenon having being observed in many different species — from flies to philosophers. While it is impossible to single out the main factors mediat-

ing the EC-induced brain changes, this experimental paradigm continues to generate findings of interest and relevance to a broad spectrum of human endeavour, such as education, animal welfare and successful aging.

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