

NEURAL CONSEQUENCES OF ENVIRONMENTAL ENRICHMENT

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Neuronal plasticity is a central theme of modern neurobiology, from cellular and molecular mechanisms of synapse formation in *Drosophila* to behavioural recovery from strokes in elderly humans. Although the methods used to measure plastic responses differ, the stimuli required to elicit plasticity are thought to be activity-dependent. In this article, we focus on the neuronal changes that occur in response to complex stimulation by an enriched environment. We emphasize the behavioural and neurobiological consequences of specific elements of enrichment, especially exercise and learning.

Over the past two centuries, there have been several accounts of, and claims for, the positive effects of environmental stimulation and enrichment on the brain and brain function^{1,2}. A modern conceptual framework for neuronal plasticity in the adult brain was formulated by Hebb, who postulated in 1949 that, when one cell excites another repeatedly, a change takes place in one or both cells such that one cell becomes more efficient at firing the other³. Hebb's view has since been extended to include the plasticity of many definable anatomical substrates, such as synapses, neurites or entire neurons. Obviously, changes on these levels are, in turn, based on changes at the biochemical and molecular levels.

In the late 1940s, Hebb was also the first to propose the 'enriched environment' as an experimental concept. He reported anecdotally that rats that he took home as pets showed behavioural improvements over their litter mates kept at the laboratory⁴. In the early 1960s, two experimental approaches were initiated to investigate the effects of experience on the brain. Hubel and Wiesel established a programme to examine the effects of selective visual deprivation during development on the anatomy and physiology of the visual cortex^{5,6}, and Rosenzweig and colleagues introduced enriched environments as a testable scientific concept⁷⁻⁹. In the initial studies, the effects of environmental stimuli on parameters such as 'total brain weight', 'total DNA or RNA content' or 'total brain protein' were measured¹⁰⁻¹². Subsequently, many

studies have shown that environmental stimulation elicits various plastic responses in the adult brain, ranging from biochemical parameters to dendritic arborization, gliogenesis, neurogenesis and improved learning¹³⁻²⁴.

What is enrichment?

In an experimental setting, an enriched environment is 'enriched' in relation to standard laboratory housing conditions (FIG. 1). Some have argued that experimental enrichment is merely a step up from standard laboratory impoverishment (BOX 1). In general, the 'enriched' animals are kept in larger cages and in larger groups with the opportunity for more complex social interaction. The environment is complex and is varied over the period of the experiments: tunnels, nesting material, toys and (often) food locations are changed frequently. In addition, animals are often given the opportunity for voluntary physical activity on running wheels.

The standard definition of an enriched environment is "a combination of complex inanimate and social stimulation"²⁵. This definition implies that the relevance of single contributing factors cannot be easily isolated but there are good reasons to assume that it is the interaction of factors that is an essential element of an enriched environment, not any single element that is hidden in the complexity. Controls for the importance of single variables on the effects of enriched environment have been tested, particularly

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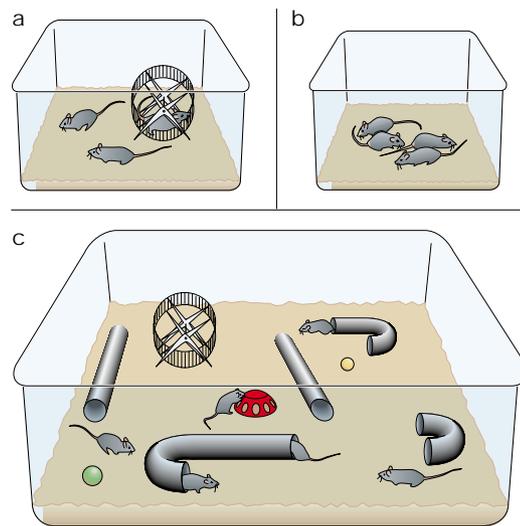


Figure 1 | Living conditions in different experimental groups. **a** | A cage containing a running wheel for voluntary physical exercise (48 × 26 cm). **b** | A standard housing cage (30 × 18 cm). **c** | Cage for an enriched environment (86 × 76 cm). Enrichment consisted of social interaction (14 mice in the cage), stimulation of exploratory behaviour with objects such as toys and a set of tunnels, and a running wheel for exercise.

for the effects of socialization and general activity^{25,26}. In general, the results have revealed that no single variable can account for the consequences of enrichment. For example, it has been shown that neither observing an enriched environment without being allowed active participation ('TV rat')²⁷ nor social interaction alone can elicit the effects of enriched environments²⁵.

Box 1 | Enriched, impoverished and naturalistic environments

One of the most remarkable features of the enrichment studies discussed in this article is that the changes in the brain can be detected even when the enriched experience is provided to an adult or aged animal. This finding underscores the possibility that experimental enrichment is a reversal of the impoverishment generally found in the laboratory setting rather than an enrichment over a natural setting. The potential contributions of isolation on the one hand and overcrowding on the other have been described as follows: "taken together, the isolation and overcrowding studies suggest that normal brain and behavior development depends upon an optimal, rather than a maximal level of environmental stimulation. The degree to which deviations from this optimum affect the organism through stress and through diminished sensorimotor stimulation (and indeed the degree to which these are independent) has not been determined"¹⁹.

One of the best examples of an attempt to address this issue were studies of birds captured from the wild and pulse-labelled with ³H-thymidine. Some were housed in an aviary and the rest returned to the wild^{109,110}. Some of the freed birds were recaptured and the recruitment of new neurons in the avian equivalent of the hippocampus in these birds was compared with that in the laboratory birds. More of the neurons that were born during the brief captivity period survived in the animals recaptured after six weeks from the wild than in those in the aviary. So, either the wild environment is enriched or the laboratory environment is relatively impoverished and stressful for the captured birds, which showed a decrease in new neurons. It is now clear that changes in the environment of an adult individual animal and the ways in which that individual animal reacts to those changes can have profound and robust effects on the brain and the behaviour of that animal.

Numerous cognitive theories about how environmental enrichment affects the brain have been proposed. Among them are the arousal hypothesis²⁸, which emphasizes the so-called 'arousal response' of animals when confronted with novelty and environmental complexity, and the 'learning and memory' hypothesis⁹, in which the mediator of the morphological changes is seen in the cellular mechanisms underlying learning processes. Although the learning-and-memory hypothesis is favoured by many investigators, it is difficult to prove that the neural consequences of the enriched environment are related to learning rather than to increased voluntary motor behaviour.

Completely separating different behaviours in a complex environment is difficult and can depend on the measure used to assess the changes in the brain. This was shown by trying to separate activity from learning as factors that might mediate an increase in the survival of newborn neurons in the dentate gyrus of adult rodents raised in an enriched environment^{24,29}. Some workers^{29,30} have found no effect on the total number of new neurons in the dentate with repeated exposure to a hippocampus-dependent learning task. However, others³¹ have found that all cells born just before a brief and selective hippocampal training experience would survive and differentiate into new neurons within two weeks. It has been suggested³² that the difference could be due to different bromo-deoxyuridine- (BrdU) labelling methods. In the studies that found no effect, the tests were carried out during and after the labelling period, whereas the BrdU label was administered before training (focusing on cell survival) in the study that found an effect. A recent study³³ found that, when BrdU was given during training, there was an increase in cell proliferation, a result that neither of the previous studies^{29,31} had found.

By contrast to the inconsistent results of the learning models, voluntary exercise in a running wheel in the home cage increased both cell proliferation and recruitment of new neurons into the dentate gyrus²⁹. So different, isolated elements of the enriched environment can have marked effects on specific components of brain plasticity, and it is reasonable to consider that what seem to be different experiences might result in similar anatomical and physiological changes. This process might reflect common final pathways of cellular and molecular events underlying the different experiences or might reveal our limited knowledge of the neurobiology of behaviour. In any event, we cannot at this point exclude the possibility that an increase in voluntary exercise is the feature common to all, or most, neural changes that result from exposure to enriched environments. Essentially, all measures affected by an enriched environment depend on, and have not been dissociated from, an increase in voluntary motor behaviour or exercise.

Consequences of enrichment in the intact brain As stated above, voluntary exercise and environmental enrichment produce notably similar effects on the brain. In a recent study, mice were assigned to groups

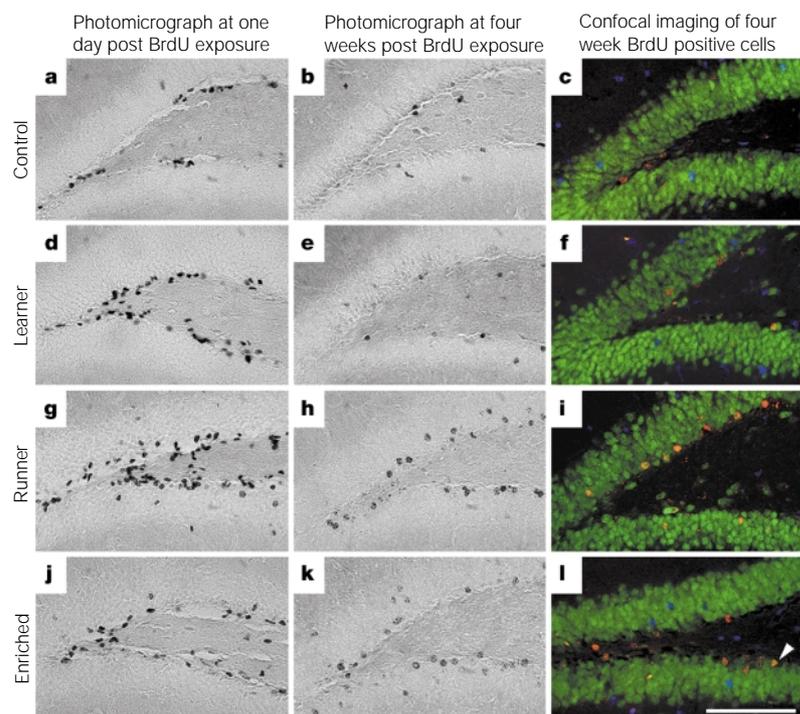


Figure 2 | Effects of elements of enrichment, such as learning and exercise, on cell proliferation (one day post BrdU exposure) and neurogenesis (four weeks post BrdU exposure) in the dentate gyrus. Both enrichment (k,l) and voluntary exercise (h,i) enhance the survival of newborn neurons. Learning did not affect cell survival (e,f), similar to controls (b,c). Confocal images of sections triple labelled for BrdU (red), NeuN (green, neuronal phenotype) and s100 β (blue, selective for glia), show that relatively more cells become neurons in the running and enriched groups. The arrow in (l) shows a BrdU-labelled neuron (orange=red + green). Scale bar is 100 μ m.

with a learning task, wheel running, enrichment or standard housing. Voluntary exercise in a running wheel enhanced the survival of newborn neurons in the dentate gyrus, which is similar to the effects of environmental enrichment, whereas none of the other conditions had any effect on cell genesis²⁹ (FIG. 2). This finding led to a comparison of the effects of enrichment and exercise on behavioural, morphological and molecular changes in the brain.

Improved learning and memory. Enrichment has been shown to enhance memory function in various learning tasks². Enriched mice also did better on the water-maze task (a test of spatial memory) than controls in standard housing did^{124,34–36}. Similarly, voluntary wheel running and treadmill training have been shown to enhance spatial learning^{37–39}. In the exercise studies, differences between sedentary and active animals were best observed when tasks were made more challenging^{38,39}. In addition, when tested on a different spatial memory task (a T-maze), enriched rats did better than isolated rats with a running wheel²⁶. So, the degree of learning improvement might be greater following enrichment that includes exercise than exercise alone. However, direct comparisons on several memory tasks between running and enriched groups are needed to draw definite conclusions.

SHOLL RING ANALYSIS

A clear overlay with concentric rings at 20 μ m intervals is centered over the cell body and the number of times the dendrites intersect the rings are counted.

Anatomical changes. The debate about whether environmental enrichment has any influence on cell number in the adult brain began early in this field. In 1964, Altman (the first researcher to describe adult neurogenesis in the hippocampus⁴⁰) investigated whether enrichment could affect the production of neurons but found only enhanced gliogenesis²³. In this study, the focus of the analysis was on cortex rather than hippocampus, which might be why no new neurons were observed. Subsequent studies reported that the increase in glia was attributable to oligodendrocytes⁴¹, as well as more modest increase in astrocytes^{21,24} in enriched animals.

Both enrichment and exercise enhance the number of new neurons in the dentate gyrus. However, the mechanisms by which new cells are generated might differ between the two conditions. Enriched living only affected cell survival and not cell proliferation. By contrast, running increased cell division and net neuronal survival in C57BL/6 mice²⁹. Cell proliferation and survival might therefore be regulated differently by different behavioural or environmental manipulations within a constant genetic background^{42,43}. One of the questions that remains open is whether the effects of running and enrichment are additive. For example, would mice housed with a running wheel to elicit proliferation and then moved to an enriched environment to enhance cell survival have a greater number of new cells than either condition alone?

Apart from their effects on the production of new neurons in the dentate gyrus of the hippocampus, both enrichment and exercise result in further morphological changes. Indeed, the functional changes associated with enrichment might be due not only to enhanced neurogenesis but also to increases in gliogenesis, synaptogenesis and angiogenesis, as suggested by W. Greenough and colleagues^{19,46,55}. Enriched living rodents have been observed to have increased brain weight and size^{10,16,44} as well as enhanced perikaryonal and nuclear sizes in the cortex⁴⁵. Early experiments also showed that enrichment enhances gliogenesis, neurite branching and synapse formation in the cortex^{15,16,18,20,23}. Specifically, dendrite branching in occipital cortex pyramidal neurons was quantified using SHOLL RING ANALYSIS. Upon bifurcation in the first dendrite, a second order dendrite is created, and subsequent bifurcation results in higher order dendrite branches. It was found that enriched rats have more higher order dendritic branches than controls. The length of the branches at a given order did not differ between the groups^{18,19,46}.

Synaptogenesis has also been reported to be increased in enriched animals. Initial research showed an increase in dendritic spines, possibly indicating enhanced synaptic contacts⁴⁷. Subsequent studies found that enrichment reduced neuronal density but increased synapse-to-neuron ratios, synaptic disc diameter and sub-synaptic-plate perforations^{20,48,49}. Within the hippocampus, similar morphological changes have been observed for dentate granule neurons as well as for pyramidal cells in areas CA1 and CA3 (REFS 17, 21, 22, 50–52). In particular, enriched female rats had more dendrites per neuron in the dentate gyrus than controls did⁵⁰. In the CA3 subfield, an

increase in total area of synaptic contacts was found⁵¹. Recently, a larger number of dendritic spines and an enhanced density of non-perforated synapses have been found in area CA1 after enrichment⁵².

It is not known whether voluntary exercise results in comparable changes in the hippocampus. Motor skill learning has been shown to increase cortical thickness and synaptogenesis⁵³ as well as the number of synapses per neuron in the cerebellum^{54,55}. Exercise alone has been reported to enhance capillary density or angiogenesis in the cerebellum but not synaptogenesis⁵⁴, although activity was not voluntary wheel running in these studies but was rather matched to a skill-learning task.

Electrophysiological changes. Few studies have addressed the possible relationship between enriched living and electrophysiological changes. In hippocampus slices taken from enriched or individually housed rats, excitatory postsynaptic potential (EPSP) slopes in the dentate gyrus were greater in the slices from enriched rats^{56,57}. Similarly, exposing rodents to a new, complex environment enhanced hippocampal field potentials⁵⁸. There is, however, extensive research documenting the relationship between physical and neuronal activity. For example, locomotion is correlated with the hippocampal THETA RHYTHM⁵⁹. In addition, the discharge frequencies of hippocampal pyramidal cells and interneurons have been shown to increase with increased wheel running velocity in rats⁶⁰. In a recent study, EPSP amplitudes and long-term potentiation (LTP), a physiological model of certain forms of learning and memory⁶¹, were compared in hippocampal slices from running and control mice. EPSPs were unchanged in both groups but LTP amplitude was selectively enhanced over the controls in the dentate gyrus in slices from running mice³⁹. So, electrophysiologically measurable changes occurred in the same region in which neurogenesis was stimulated by running, indicating that the newborn cells might have a functional role, possibly associated with learning and memory. It would be interesting to study synaptic plasticity after enrichment as well, comparing the dentate gyrus and area CA1.

Although the new cells are a small proportion of the granule cell layer, they might have greater plasticity than mature cells do. Indeed, the dentate gyrus LTP lasts longer in immature rats than in adults⁶². To test this hypothesis, recordings from individual newborn cells are necessary. In a recent paper, the electrophysiological properties of granule cells from the inner and outer layer of the dentate gyrus were compared. Inner layer cells were considered to be young cells and the outer layer old cells. Putative young cells had a lower threshold for LTP and were unaffected by GABA_A inhibition, indicating enhanced plasticity in the young cells⁶³. The problem with such a study is that the definition of young cells is ambiguous: we have found new neurons throughout the granule cell layer, although they do seem to arise initially from the subgranular layer²⁴. The only way to be sure that a recording is made from a newborn neuron would be to label it with a mitogenic marker that can be visualized in live tissue.

Effects of growth factors. During development, growth factors provide important extracellular signals regulating proliferation and differentiation of stem and progenitor cells in the central nervous system⁶⁴. Several investigations have been made into the role of these factors in the adult brain. Researchers have found that, in the mature organism, these factors might function in synaptic plasticity, learning, enrichment, exercise and neurogenesis. In particular, intracerebroventricular infusion of insulin-like growth factor (IGF)⁶⁵ but not epidermal growth factor (EGF) or fibroblast growth factor 2 (FGF-2)^{66,67} increased neurogenesis in the dentate gyrus in rats.

In song birds, seasonal regulation of adult neurogenesis depends on testosterone levels that mediate their effect through brain-derived neurotrophic factor (BDNF) (REF. 68). Exposure to an enriched environment increased the gene expression of nerve growth factor (NGF)^{69,70}, BDNF (REF. 71) and glial-cell-derived neurotrophic factor (GDNF)⁷². Physical activity elevated expression of IGF-1 (REF. 73), FGF-2 (REFS 74,75) and BDNF (REFS 76,77). Several of these factors have also been suggested to function in learning and synaptic plasticity, in particular NGF and BDNF (REFS 78–80). So, there seems to be some overlap in the expression of these factors in enrichment, running, learning and neurogenesis. The mechanism of action and the cause and effect relationship between these factors remain to be determined.

The role of neurotransmitters. The early studies of enriched environments reported an increase in neurotransmitters such as acetylcholine^{10,11,81}. Enrichment has also been shown selectively to enhance expression of the gene for the serotonin1A receptor⁸². Previous research showed that there was no increase in acetylcholinesterase enzymatic activity in rats housed with a running wheel^{83,84}. More recent work, however, reports that physical activity can change the activity of several neurotransmitter systems in the brain. Exercise influences cholinergic parameters, affecting choline uptake in hippocampus and cortex⁸⁵. In addition, the activity of opioid systems is enhanced⁸⁶. Furthermore, monoamines such as noradrenaline and serotonin are activated by running or physical activity^{87,88}. All of these transmitters have been reported to influence learning and synaptic plasticity in the adult brain, and the monoamines have also been suggested to function in neurogenesis. Prolonged administration of antidepressants, therapeutic agents acting on noradrenaline and dopamine receptors, and electroconvulsive shock increase the number of BrdU-positive cells in rats^{89–91}. In addition, grafting fetal raphe neurons also stimulated granule cell proliferation⁹², whereas depletion of serotonin reduced stem cell proliferation in the dentate gyrus⁹³.

In summary, exercise and enrichment seem to have many elements in common. Both enhance learning, neurogenesis, growth factors, neurotransmitters and possibly synaptic plasticity in a similar manner. It remains to be determined whether these findings indicate that exercise

THETA RHYTHM
Neural activity with a frequency
of 4–8 Hz.

Table 1 | Effects of enriched environment

Condition	Behaviour	Neuroanatomy	Cellular/molecular	References
Brain injury or trauma	Improves memory and motor skills	Increases brain weight and dendritic branching	No data available	34,94–96, 120,121
Stroke/ischaemia	Improves motor skills		Increases NGF A and glucocorticoid receptor mRNA levels; decreases BDNF mRNA levels	97,100, 122,123
Epilepsy	Prevents seizures	Inhibits apoptosis	Enhances growth factor gene expression	72
Ageing	Improves memory	Increases neurogenesis; decreases gliogenesis and prevents decrease in synaptic density	Increases RNA content; increases NGF	14,36,69, 124–126
Stress	No effect			127
Huntington's disease mouse model	Enhances exploration and motor skills, and prevents seizures	Increases peristriatal cerebral volume	Delays disease onset	101
CA1 <i>NMDAR1</i> knockout mice	Improves memory	Increases hippocampal synaptic and spine density	No data available	52
Prenatal alcohol	Improves memory		Improves cortical synaptic plasticity	35,128
Learning-impaired 129/SvJ mice	Improves memory	Enhances cell proliferation and neurogenesis	No data available	43

is the critical component of enrichment or whether enriched living has other unique features. Specific comparisons between exercise and enrichment conditions will help to answer this question.

Consequences for damaged or diseased brains
The effects of exposure to an enriched environment on pathological conditions, stress and ageing have been studied by several laboratories. In general, the effects of enrichment on conditions such as stroke, epilepsy and ageing seem to be beneficial (TABLE 1). A recent paper reported that three weeks of enrichment reduced apoptotic cell death in the hippocampus by 45% and also prevented the development of motor seizures after injection with kainic acid⁷². Previous studies showed that recovery from brain lesions was facilitated by pre- and postoperative enrichment^{94,95} or wheel running⁹⁶. Even a short enrichment can be effective. In particular, rats with lesions of the occipital cortex and part of the hippocampus that were housed in an enriched environment for 2 h each day improved performance on the HEBB–WILLIAMS MAZE as much as rats that were exposed to the enriched environment continuously⁹⁴.

In addition, enrichment can facilitate recovery when applied after a delay. For example, rats that were transferred to an enriched cage 15 days after middle cerebral artery ligation showed notable improvement in postural reflexes and limb placement compared with rats in standard housing when tested 7 weeks later⁹⁷. Interestingly, voluntary wheel running has also been shown to provide protection against ischaemia. In gerbils housed preoperatively with running wheels and then subjected to global cerebral ischaemia for 15–20 min, mortality was reduced from 55% to 10%. In addition, hippocampal cell damage was attenuated^{98,99}. Others, however, reported that, in spontaneously hypertensive rats, housing with running wheels after the insult did not enhance recovery after ligation of the middle cerebral artery¹⁰⁰.

Apart from effects in the above-mentioned pathologies, enrichment might have beneficial effects on genetic conditions. Deficits in nonspatial memory associated with disruption of the hippocampal *N*-methyl-D-aspartate (NMDA) receptor 1 subunit could be rescued by enrichment for three hours daily for two months. In addition, synaptic and spine density in area CA1 was increased by enrichment in the knockout animals⁵². In mice carrying the Huntington's disease transgene, enrichment delays the onset of behavioural deficits such as loss of motor coordination, even though neural symptoms such as the formation of striatal inclusion bodies were not changed¹⁰¹. Furthermore, enrichment has been shown to affect memory function and neurogenesis in mouse strains that are known as poor learners. There are differences in the amount of cell proliferation and neurogenesis between C57BL/6, BALB/c, CD1 (ICR) and 129/SvJ mice⁴²: the 129/SvJ mice are known to do poorly on learning tasks¹⁰² and produced more astrocytes and fewer neurons than other strains⁴². Exposure to an enriched environment stimulated neurogenesis and improved learning in these mice⁴³. Taken together, the findings indicate that an enriched environment may override some genetic constraints (TABLE 1).

Although the overall effects of enrichment seem to be beneficial, it is not clear how long these effects last, nor what happens when enrichment is discontinued. Initial studies showed that changes in neural anatomy and chemistry are reversed when animals are removed from the enriched environment^{56,103}. In addition, a recent study used mice that had lived in an enriched environment for 68 days and were then returned to standard housing, and also mice that lived in an enriched environment for the full six months. The first group did not differ from controls on spatial learning tests in the water maze three months later. There was also no difference in neurogenesis between the groups, although cell proliferation was increased in the animals that experienced withdrawal from enrichment¹⁰⁴. This

HEBB–WILLIAMS MAZE

A rectangular field with a start box and a goal box placed at opposite ends of the apparatus. Different configurations are obtained by placing barriers at different points of the field.

Box 2 | Neonatal handling and maternal deprivation

It is well known that adult rats that are handled briefly (15 min each day) for the first three weeks of life show markedly reduced responses to various stressful stimuli^{111,112}. Postnatal handling has been shown to increase glucocorticoid receptor expression in rat hippocampus, altering regulation of hypothalamic synthesis of corticotropin-releasing hormone and the hypothalamic–pituitary–adrenal response to stress¹¹². Apart from beneficial effects on stress and anxiety, hippocampal neuron cell loss and cognitive impairments associated with ageing are attenuated after early handling^{112,113}.

Recent findings indicate that mother–offspring interactions may be crucial in the development of behavioural and endocrine responses to stress¹¹⁴. In addition, maternal behaviour seems to be crucial for cognitive development. High levels of maternal licking and grooming during the first 10 days after birth correlate with increased gene expression of *N*-methyl-D-aspartate receptor subunits NR2A and NRB in the hippocampus. Hippocampal brain-derived neurotrophic factor (BDNF) mRNA and cholinergic innervation of the hippocampus were increased. Moreover, spatial learning in the water maze was improved. Cross-fostering of offspring from mothers with low levels of licking and grooming to mothers with high levels, and vice versa, showed that these effects were directly attributable to maternal behaviour¹¹⁵.

In contrast to the beneficial effects of enhanced maternal care, maternal deprivation is detrimental in many ways. Interruption of mother–infant interaction in rats for one hour or more caused a decrease in serum growth hormone¹¹⁶. In addition, two hours of daily maternal separation during the first two weeks after birth resulted in increased corticosterone levels during stress¹¹⁷. Adult cognitive deficits¹¹⁸ and an increased susceptibility to disease¹¹⁹ have also been associated with maternal deprivation.

study suggests that neither withdrawal nor long-term enrichment enhance function.

However, others have reported that long-term housing in an enriched environment increased NGF protein and receptor density as well as spatial learning in rats⁷⁰. In this study, exposure to enrichment was one year, twice as long as in the mouse study, and rats were trained in the water maze with four trials per day, compared with two trials daily for the mice^{70,104}. Moreover, brain changes induced by 80 days of enrichment were more persistent than those induced by 30 days of enrichment¹⁰³. So, although the beneficial effects of enrichment seem to depend on chronic exposure to the enriched environment, further research is needed.

Consequences for environmental manipulations
Two areas of neurobiological research that might benefit from the use of environmental enrichment are mouse genetics and studies of recovery of function following brain and spinal injury or disease. The results of many of the studies using transgenic animals vary depending on the conditions under which the animals are tested, and some of the effects that are seen in transgenic animals might be a result of the stress of impoverished housing. An excellent example of this type of study is the demonstration that many of the behavioural and electrophysiological deficits observed in mice with selective genetic ablation of NMDA receptors in the CA1 region of the hippocampus can be reversed or prevented by raising the mutant mice in an enriched environment⁵². This finding raises the question of whether the deficits in the mutant mice in standard housing conditions imply that the NMDA receptors in the CA1 are only important under impoverished conditions. Similar questions can be raised in response to a mouse model of

Huntington's disease¹⁰¹. An alternative and optimistic interpretation is that environmental enrichment can be considered to be therapeutic for various mutations. The converse should also be considered: that we might be missing some important functional consequences of gene mutations in animals by not testing animals in enriched as well as standard conditions.

New strategies are being developed to identify drugs, cells or genes to induce recovery of function following damage to the central nervous system. These potential therapies can result in structural changes, such as axonal growth or synaptic reorganization in the brain or spinal cord, with expected functional recovery. The structural reorganization or repair will have a greater probability of functional recovery if the newly forming synapses are provided with adequate training. Several examples of this approach have been reported⁹⁴. There is convincing evidence that behavioural training can enhance the survival and functional consequences of fetal tissue implants¹⁰⁵, and that training can result in very clear and profound effects on the spinal central pattern generator and motor response in spine-injured animals and patients^{106,107}. Clearly, just as experience strengthens appropriate connections during development (BOX 2) and learning, so will the newly forming synapses in the regenerating adult brain¹⁰⁸.

Conclusions

Despite the relatively long and successful history of environmental enrichment research, there are many questions that remain unanswered. As we look closer at molecular and behavioural mechanisms that are affected by the environment and that, in turn, can contribute to critical components of the environment, new questions emerge. How important are motivation and voluntary interaction with the environment? Are there negative consequences of environmental enrichment? How long do the consequences of environmental enrichment last? Is there a critical period in the adult and is enrichment more beneficial at certain ages than others? Are there unique consequences of the complexity of enrichment compared with, for example, exercise or learning? Do specific elements of the environment have specific effects on certain brain areas and behaviour? Is it really environmental enrichment that is important for positive outcomes or is changing the environment enough? Is deprivation the opposite of enrichment?

The daunting task of understanding the complexity of gene functions and interactions in the post-genomic era requires bioinformatics to handle these large data sets. It is likely that just this sort of computational tool will also be needed to handle and define the even more complex, but now approachable, issues that are intrinsic to the interactions between genetics and environment, or nature and nurture.

 Links

DATABASE LINKS [FGF-2](#) | [BDNF](#) | [IGF-1](#) | [serotonin 1A receptor](#)

1. Rosenzweig, M. R. in *Development and Evolution of Brain Size* 263–293 (Academic Press, 1979).
2. Renner, M. J. & Rosenzweig, M. R. *Enriched and Impoverished Environments: Effects on Brain and Behaviour* (Springer, New York, 1987).
- A comprehensive review of the early literature (1970–80s) on the neuroanatomical, neurochemical and behavioural consequences of enrichment. It also includes the history of enrichment dating back to Charles Darwin. In addition, the generalizability of effects of enrichment across species is reviewed. The authors identify learning as a critical component of the enriched environment.**
3. Hebb, D. O. *The Organization of Behaviour* (Wiley, New York, 1949).
4. Hebb, D. O. The effects of early experience on problem-solving at maturity. *Am. Psychol.* **2**, 306–307 (1947).
5. Wiesel, T. N. & Hubel, D. N. Extent of recovery from the effects of visual deprivation in kittens. *J. Neurophysiol.* **28**, 1060–1072 (1965).
6. Hubel, D. N. & Wiesel, T. N. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* **206**, 419–436 (1970).
7. Rosenzweig, M. R. Environmental complexity, cerebral change, and behavior. *Am. Psychol.* **21**, 321–332 (1966).
8. Rosenzweig, M. R., Krech, D., Bennett, E. L. & Diamond, M. C. Effects of environmental complexity and training on brain chemistry and anatomy. *J. Comp. Physiol. Psychol.* **55**, 429–437 (1962).
9. Rosenzweig, M. R. & Bennett, E. L. Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav. Brain Res.* **78**, 57–65 (1996).
10. Rosenzweig, M. R. & Bennett, E. L. Effects of differential environments on brain weights and enzyme activities in gerbils, rats, and mice. *Dev. Psychobiol.* **2**, 87–95 (1969).
11. Rosenzweig, M. R., Bennett, E. L. & Diamond, M. C. in *Psychopathology of Mental Development*. (eds Zubin, J. & Jervis, G.) 45–56 (Grune & Stratton, New York, 1967).
12. Bennett, E. L., Rosenzweig, M. R. & Diamond, M. C. Rat brain: effects of environmental enrichment on wet and dry weights. *Science* **164**, 825–826 (1969).
13. Bennett, E. L. in *Neural Mechanisms of Learning and Memory* (eds Rosenzweig, M. R. & Bennett, E. L.) 279–287 (MIT Press, Cambridge, Massachusetts, 1976).
14. Cummins, R. A., Walsh, R., Budtz-Olsen, O. E., Konstantinos, T. & Horsfall, C. R. Environmentally-induced changes in the brains of elderly rats. *Nature* **243**, 516–518 (1973).
15. Holloway, R. L. Dendritic branching: some preliminary results of training and complexity in rat visual cortex. *Brain Res.* **2**, 393–396 (1966).
16. Diamond, M. C. *et al.* Increases in cortical depth and glia numbers in rats subjected to enriched environment. *J. Comp. Neurol.* **128**, 117–126 (1966).
17. Diamond, M. C., Ingham, C. C., Johnson, R. E., Bennett, E. L. & Rosenzweig, M. R. Effects of environment on morphology of rat cerebral cortex and hippocampus. *J. Neurobiol.* **7**, 75–85 (1976).
18. Greenough, W. T. & Volkmar, F. R. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp. Neurol.* **40**, 491–504 (1973).
19. Greenough, W. T. *Neural Mechanisms of Learning and Memory* (eds Rosenzweig, M. R. & Bennett, E. L.) 255–278 (MIT Press, Cambridge, Massachusetts, 1976).
- Discusses similarities between enrichment and learning on brain and behaviour. In addition, changes in synaptic size and dendritic branching in response to enrichment are reviewed in detail.**
20. Greenough, W. T., West, R. W. & DeVogd, T. J. Postsynaptic plate perforations: changes with age and experience in the rat. *Science* **202**, 1096–1098 (1978).
21. Walsh, R. N., Budtz-Olsen, O. E., Penny, J. E. & Cummins, R. A. The effects of environmental complexity on the histology of the rat hippocampus. *J. Comp. Neurol.* **137**, 361–366 (1969).
22. Walsh, R. N. & Cummins, R. A. Changes in hippocampal neuronal nuclei in response to environmental stimulation. *Int. J. Neurosci.* **9**, 209–212 (1979).
23. Altman, J. & Das, G. D. Autoradiographic examination of the effects of enriched environment on the rate of glial multiplication in the adult rat brain. *Nature* **204**, 1161–1163 (1964).
- Investigated whether enrichment could add new neurons to the adult brain. The focus of the paper was on cortex rather than hippocampus and no new neurons were observed in response to**
- environmental changes. Subsequent studies focused on structural changes in existing cells in response to enrichment.**
24. Kempermann, G., Kuhn, H. G. & Gage, F. H. More hippocampal neurons in adult mice living in an enriched environment. *Nature* **386**, 493–495 (1997).
- The first paper to show that enrichment increases the survival of newborn cells in the dentate gyrus of the hippocampus in adult mice. Enriched mice had 57% more BrdU-positive cells per dentate gyrus than controls. Cell proliferation, however, was not affected.**
25. Rosenzweig, M. R., Bennett, E. L., Hebert, M. & Morimoto, H. Social grouping cannot account for cerebral effects of enriched environments. *Brain Res.* **153**, 563–576 (1978).
26. Bernstein, L. A study of some enriching variables in a free-environment for rats. *J. Psychosomatic Res.* **17**, 85–88, (1973).
27. Ferchmin, P. A. & Bennett, E. L. Direct contact with enriched environment is required to alter cerebral weights in rats. *J. Comp. Physiol. Psychol.* **88**, 360–367 (1975).
28. Walsh, R. N. & Cummins, R. A. Mechanisms mediating the production of environmentally induced brain changes. *Psychol. Bull.* **82**, 986–1000 (1975).
29. Van Praag, H., Kempermann, G. & Gage, F. H. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neurosci.* **2**, 266–270 (1999).
- Studied the effects of components of the enriched environment such as learning and motor activity on neurogenesis. No effect of learning was observed. However, this is the first study to show that voluntary activity on a wheel increases cell proliferation and survival in the dentate gyrus.**
30. Ambrogini, P. *et al.* Spatial learning affects immature granule cell survival in adult rat dentate gyrus. *Neurosci. Lett.* **286**, 21–24 (2000).
31. Gould, E. *et al.* Learning enhances adult neurogenesis in the hippocampal formation. *Nature Neurosci.* **2**, 260–265 (1999).
32. Greenough, W. T., Cohen, N. J. & Juraska, J. M. New neurons in old brains: learning to survive? *Nature Neurosci.* **2**, 203–205 (1999).
33. Lemaire, V., Koehl, M., Le Moal, M. & Abrous, D. N. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc. Natl Acad. Sci. USA* **97**, 11032–11037 (2000).
34. Pacteau, C., Eilon, D. & Sinden, J. Early rearing environment and dorsal hippocampal ibotenic acid lesions: long-term influences on spatial learning and alternation in the rat. *Behav. Brain Res.* **34**, 79–96 (1989).
35. Wainwright, P. E. *et al.* Effects of environmental enrichment on cortical depth and Morris-maze performance in B6D2F2 mice exposed prenatally to ethanol. *Neurotoxicol. Teratol.* **15**, 11–20 (1993).
36. Kempermann, G., Kuhn, H. G. & Gage, F. H. Experience-induced neurogenesis in the senescent dentate gyrus. *J. Neurosci.* **18**, 3206–3212 (1998).
37. Fordyce, D. E. & Farrar, R. P. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behav. Brain Res.* **46**, 123–133 (1991).
38. Fordyce, D. E. & Wehner, J. M. Physical activity enhances spatial learning performance with an associated alteration in hippocampal protein kinase C activity in C57BL/6 and DBA/2 mice. *Brain Res.* **619**, 111–119 (1993).
39. Van Praag, H., Christie, B. R., Sejnowski, T. J. & Gage, F. H. Running enhances neurogenesis, learning and long-term potentiation in mice. *Proc. Natl Acad. Sci. USA* **96**, 13427–13431 (1999).
40. Altman, J. Are new neurons formed in the brains of adult mammals? *Science* **135**, 1127–1128 (1962).
41. Szeligo, F. & Leblond, C. P. Response of three main types of glial cells of cortex and corpus callosum in rats handled during suckling or exposed to enriched, control, or impoverished environments following weaning. *J. Comp. Neurol.* **172**, 247–264 (1977).
42. Kempermann, G., Kuhn, H. G. & Gage, F. H. Genetic influence on neurogenesis in the dentate gyrus of adult mice. *Proc. Natl Acad. Sci. USA* **94**, 10409–10414 (1997).
43. Kempermann, G., Brandon, E. P. & Gage, F. H. Environmental stimulation of 129/SvJ mice results in increased cell proliferation and neurogenesis in the adult dentate gyrus. *Curr. Biol.* **8**, 939–942 (1998).
44. Altman, J., Wallace, R. B., Anderson, W. J. & Das, G. D. Behaviorally induced changes in length of cerebrum in rat. *Dev. Psychobiol.* **1**, 112–117 (1968).
45. Diamond, M. C., Lindner, B. & Raymond, A. Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. *J. Comp. Neurol.* **131**, 357–364 (1967).
46. Volkmar, F. R. & Greenough, W. T. Rearing complexity affects branching of dendrites in the visual cortex of the rat. *Science* **176**, 1445–1447 (1972).
47. Globus, A., Rosenzweig, M. R., Bennett, E. L. & Diamond, M. C. Effects of differential environments on dendritic spine counts. *J. Comp. Phys. Psychol.* **84**, 598–604 (1973).
48. Bhide, P. G. & Bedi, K. S. The effects of a lengthy period of environmental diversity of well-fed and previously undernourished rats. II. Synapse to neurons ratios. *J. Comp. Neurol.* **227**, 305–310 (1984).
49. Beaulieu, C. & Colonnier, M. The effect of richness of the environment on cat visual cortex. *J. Comp. Neurol.* **266**, 478–494 (1987).
50. Juraska, J. M., Fitch, J. M., Henderson, C. & Rivers, N. Sex differences in the dendritic branching of dentate granule cells following differential experience. *Brain Res.* **333**, 73–80 (1985).
51. Altschuler, R. A. Morphometry of the effect of increased experience and training on synaptic density in area CA3 of the rat hippocampus. *J. Histochem. Cytochem.* **27**, 1548–1550 (1979).
52. Rampon, C. *et al.* Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nature Neurosci.* **3**, 205–206 (2000).
53. Kleim, J. A., Lussnig, E., Schwarz, E. R., Comery, T. A. & Greenough, W. T. Synaptogenesis and FOS expression in the motor cortex of the adult rat after motor skill learning. *J. Neurosci.* **16**, 4529–4535 (1996).
54. Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A. & Greenough, W. T. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc. Natl Acad. Sci. USA* **87**, 5568–5572 (1990).
55. Isaacs, K. R., Anderson, B. J., Alcantara, A. A., Black, J. E. & Greenough, W. T. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. *J. Cereb. Blood Flow Metab.* **12**, 110–119 (1992).
56. Green, E. J. & Greenough, W. T. Altered synaptic transmission in dentate gyrus of rats reared in complex environments: evidence from hippocampal slices maintained *in vitro*. *J. Neurophysiol.* **55**, 739–750 (1986).
57. Foster, T. C., Fugger, H. N. & Cunningham, S. G. Receptor blockade reveals a correspondence between hippocampal-dependent behavior and experience-dependent synaptic enhancement. *Brain Res.* **871**, 39–43 (2000).
58. Sharp, P. E., McNaughton, B. L. & Barnes, C. A. Enhancement of hippocampal field potentials in rats exposed to a novel, complex environment. *Brain Res.* **339**, 361–365 (1985).
59. Vanderwolf, C. H. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* **26**, 407–418 (1969).
60. Czurko, A., Hirase, H., Csicsvari, J. & Buzsáki, G. Sustained activation of hippocampal pyramidal cells by ‘space clamping’ in a running wheel. *Eur. J. Neurosci.* **11**, 344–352 (1999).
61. Bliss, T. V. & Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31–39 (1993).
62. Bronzino, J. D. *et al.* Maturation of long-term potentiation in the hippocampal dentate gyrus of the freely moving rat. *Hippocampus* **4**, 439–446 (1994).
63. Wang, S., Scott, B. W. & Wojtowicz, J. M. Heterogenous properties of dentate granule neurons in adult rat. *J. Neurobiol.* **42**, 248–257 (2000).
64. Calof, A. L. Intrinsic and extrinsic factors regulating vertebrate neurogenesis. *Curr. Opin. Neurobiol.* **5**, 19–27 (1995).
65. Aberg, M. A. I. *et al.* Peripheral infusion of IGF-1 selectively induces neurogenesis in the adult rat hippocampus. *J. Neurosci.* **20**, 2896–2903 (2000).
66. Kuhn, H. G., Winkler, J., Kempermann, G., Thal, L. J. & Gage, F. H. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. *J. Neurosci.* **17**, 5820–5829 (1997).
67. Wagner, J. P., Black, I. B. & DiCicco-Bloom, E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J. Neurosci.* **19**, 6006–6016 (1999).
68. Rasika, S., Alvarez-Buylla, A. & Nottebohm, F. BDNF mediates the effects of testosterone on the survival of new neurons in an adult brain. *Neuron* **22**, 53–62 (1999).

69. Mohammed, A. H. *et al.* Environmental influences on the central nervous system and their implications for the aging rat. *J. Brain Res.* **57**, 183–191 (1993).
70. Pham, T. M. *et al.* Changes in brain nerve growth factor levels and nerve growth factor receptors in rats exposed to environmental enrichment for one year. *Neuroscience* **94**, 279–286 (1999).
71. Falkenberg, T. *et al.* Increased expression of brain-derived neurotrophic factor mRNA in rat is associated with improved spatial memory and enriched environment. *Neurosci. Lett.* **138**, 153–156 (1992).
72. Young, D. *et al.* Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nature Med.* **5**, 448–453 (1999).
73. Carro, E. *et al.* Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J. Neurosci.* **20**, 2926–2933 (2000).
74. Gomez-Pinilla, F., Dao, L. & Vannarath, S. Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.* **764**, 1–8 (1997).
75. Gomez-Pinilla, F., So, V. & Kesslak, J. P. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. *Neuroscience* **85**, 53–61 (1998).
76. Neeper, S. A., Gomez-Pinilla, F., Choi, J. & Cotman, C. Exercise and brain neurotrophins. *Nature* **373**, 109 (1995).
The first paper to indicate that growth factors may mediate the beneficial effects of exercise on the brain. Specifically, voluntary exercise in rats increased levels of BDNF mRNA in hippocampus and cortex.
77. Widenfalk, J., Olson, L. & Thoren, P. Deprived of habitual running, rats downregulate BDNF and TrkB messages in the brain. *Neurosci. Res.* **34**, 125–132 (1999).
78. Kang, H. & Schuman, E. M. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science* **267**, 1658–1662 (1995).
79. Figurov, A., Pozzo-Miller, L. D., Olafsson, P., Wang, T. & Lu, B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **381**, 706–709 (1996).
80. Fischer, W. *et al.* Amelioration of cholinergic neuron atrophy and spatial memory impairment in aged rats by nerve growth factor. *Nature* **329**, 65–68 (1987).
81. Por, S. B., Bennett, E. L. & Bondy, S. C. Environmental enrichment and neurotransmitter receptors. *Behav. Neural Biol.* **34**, 132–140 (1982).
82. Rasmuson, S. *et al.* Environmental enrichment selectively increases 5-HT_{1A} receptor mRNA expression and binding in the rat hippocampus. *Brain Res. Mol. Brain Res.* **53**, 285–290 (1998).
83. Krech, D., Rosenzweig, M. R. & Bennett, E. L. Effects of environmental complexity and training on brain chemistry. *J. Comp. Physiol. Psychol.* **53**, 509–515 (1960).
84. Zolman, J. & Morimoto, H. Cerebral changes related to duration of environmental complexity and locomotor activity. *J. Comp. Physiol. Psychol.* **60**, 382–387 (1965).
85. Fordyce, D. E. & Farrar, R. P. Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. *Behav. Brain Res.* **43**, 115–123 (1991).
86. Sforzo, G. A., Seeger, T. F., Pert, C. B., Pert, A. & Dotson, C. O. *In vivo* opioid receptor occupation in the rat brain following exercise. *Med. Sci. Sports Exerc.* **18**, 380–384 (1986).
87. Soares, J. *et al.* Brain noradrenergic responses to footshock after chronic activity-wheel running. *Behav. Neurosci.* **113**, 558–566 (1999).
88. Chaouloff, F. Physical exercise and brain monoamines: a review. *Acta Physiol. Scand.* **137**, 1–13 (1989).
89. Dawirs, R. R., Hildebrandt, K. & Teuchert-Noodt, G. Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. *J. Neural Transm.* **105**, 317–327 (1998).
90. Malberg, J. E. *et al.* Chronic antidepressant administration increases granule cell genesis in the hippocampus of the adult male rat. *J. Neurosci.* (in the press).
91. Madsen, T. M. *et al.* Increased neurogenesis in a model of electroconvulsive therapy. *Biol. Psychiatry* **47**, 1043–1049 (2000).
92. Brezun, J. M. & Daszuta, A. Serotonergic reinnervation reverses lesion-induced decreases in PSA-NCAM labeling and proliferation of hippocampal cells in adult rats. *Hippocampus* **10**, 37–46 (2000).
93. Brezun, J. M. & Daszuta, A. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. *Neuroscience* **89**, 999–1002 (1999).
94. Will, B. E., Rosenzweig, M. R., Bennett, E. L., Hebert, M. & Morimoto, H. A relatively brief environmental enrichment aids recovery of learning capacity and alters brain measures after postweaning brain lesions in rats. *J. Comp. Physiol. Psychol.* **91**, 33–50 (1977).
An important study of the effects of enrichment on recovery from brain lesions. Issues related to the age of the animal at time of injury and the amount of enrichment needed for therapeutic purposes were investigated. The authors found that enrichment of two hours a day was as beneficial as 24 hours a day.
95. Darymple-Alford, J. C. & Benton, D. Preoperative differential housing and dorsal hippocampal lesions in rats. *Behav. Neurosci.* **98**, 23–34 (1984).
96. Gentile, A. M. & Beheht, Z. Enrichment versus exercise effects on motor impairments following cortical removals in rats. *Behav. Neural Biol.* **47**, 321–332 (1987).
97. Johansson, B. B. Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia. *Stroke* **27**, 324–326 (1996).
98. Stummer, W., Weber, K., Tranmer, B., Baethmann, A. & Kempki, O. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. *Stroke* **25**, 1862–1869 (1994).
99. Stummer, W., Baethmann, A., Murr, R., Schurer, L. & Kempki, O. S. Cerebral protection against ischemia by locomotor activity in gerbils: underlying mechanisms. *Stroke* **26**, 1423–1430 (1995).
100. Johansson, B. B. & Ohlsson, A. Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Exp. Neurol.* **139**, 322–327 (1996).
101. van Dellen, A., Blakemore, C., Deacon, R., York, D. & Hannan, A. J. Delaying the onset of Huntington's in mice. *Nature* **404**, 721–722 (2000).
102. Gerlai, R. Gene-targeting studies of mammalian behavior: is it the mutation or the background genotype? *Trends Neurosci.* **19**, 177–181 (1996).
103. Bennet, E. L. *et al.* Effects of successive environments on brain measures. *Physiol. Behav.* **12**, 621–631 (1974).
104. Kempermann, G. & Gage, F. H. Experience-dependent regulation of adult hippocampal neurogenesis: effects of long-term stimulation and stimulus withdrawal. *Hippocampus* **9**, 321–332 (1999).
105. Brasted, P. J., Watts, C., Robbins, T. W. & Dunnett, S. B. Associative plasticity in striatal transplants. *Proc. Natl Acad. Sci. USA* **96**, 10524–10529 (1999).
106. Belanger, M., Drew, T., Provencher, J. & Rossilong, S. A comparison of locomotion in adult cats before and after spinal transection. *J. Neurophys.* **76**, 471–491 (1996).
107. de Leon, R. D., Hodgson, J. A., Roy, R. R. & Edgerton, V. R. Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training. *J. Neurophysiol.* **81**, 85–94 (1999).
108. Horner, P. J. & Gage, F. H. Regenerating the damaged nervous system. *Nature* **407**, 963–970 (2000).
109. Barnea, A. & Nottebohm, F. Seasonal recruitment of hippocampal neurons in adult free-ranging black-capped chickadees. *Proc. Natl Acad. Sci. USA* **91**, 11217–11221 (1994).
Suggests a correlation between neurogenesis and the formation of new memories in birds. Subsequent work in mammals has supported this hypothesis.
110. Barnea, A. & Nottebohm, F. Recruitment and replacement of hippocampal neurons in young and adult chickadees: an addition to the theory of hippocampal learning. *Proc. Natl Acad. Sci. USA* **93**, 714–718 (1996).
111. Levine, S. Infantile experience and resistance to physiological stress. *Science* **126**, 405–406 (1957).
112. Meaney, M. J., Aitken, D. H., van Berkel, C., Bhatnagar, S. & Sapolsky, R. M. Effect of neonatal handling on age-related impairments associated with the hippocampus. *Science* **239**, 766–768 (1988).
113. Meaney, M. J. *et al.* The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life. *Psychoneuroendocrinology* **16**, 85–103 (1991).
114. Francis, D. D. & Meaney, M. J. Maternal care and the development of stress responses. *Curr. Opin. Neurobiol.* **9**, 128–134 (1999).
115. Liu, D., Diorio, J., Day, J. C., Francis, D. D. & Meaney, M. J. Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neurosci.* **3**, 799–806 (2000).
116. Kuhn, C. M., Butler, S. R. & Schanberg, S. M. Selective depression of serum growth hormone during maternal deprivation in rat pups. *Science* **201**, 1034–1036 (1978).
117. Plotsky, P. M. & Meaney, M. J. Early postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in rats. *Mol. Brain Res.* **18**, 195–200 (1993).
118. Oitzl, M. S., Workel, J. O., Fluttert, M., Frosch, F. & DeKloet, E. R. Maternal deprivation affects behaviour from youth to senescence: amplification of individual differences in spatial learning and memory in senescent Brown Norway rats. *Eur. J. Neurosci.* **12**, 3771–3780 (2000).
119. Hofer, M. A. On the nature and consequences of early loss. *Psychosomatic Med.* **58**, 570–581 (1996).
120. Hamm, R. J., Temple, M. D., O'Dell, D. M., Pike, B. R. & Lyeth, B. G. Exposure to environmental complexity promotes recovery of cognitive function after traumatic brain injury. *J. Neurotrauma* **13**, 41–47 (1996).
121. Kolb, B. & Gibb, R. Environmental enrichment and cortical injury: behavioral and anatomical consequences of frontal cortex lesions. *Cereb. Cortex* **1**, 189–198 (1991).
122. Dahlqvist, P. *et al.* Environmental enrichment alters nerve growth factor-induced gene A and glucocorticoid receptor messenger RNA expression after middle cerebral artery occlusion in rats. *Neuroscience* **93**, 527–535 (1999).
123. Zhao, L. R., Mattsson, B. & Johansson, B. B. Environmental influence on brain-derived neurotrophic factor messenger RNA expression after middle cerebral artery occlusion in spontaneously hypertensive rats. *Neuroscience* **97**, 177–184 (2000).
124. Soffie, M., Hahn, K., Terao, E. & Eclancher, F. Behavioural and glial changes in old rats following environmental enrichment. *Behav. Brain Res.* **101**, 37–49 (1999).
125. Winocur, G. Environmental influences on cognitive decline in aged rats. *Neurobiol. Aging* **19**, 589–597 (1998).
126. Nakamura, H., Kobayashi, S., Ohashi, Y. & Ando, S. Age-changes of brain synapses and synaptic plasticity in response to an enriched environment. *J. Neurosci.* **56**, 307–315 (1999).
127. Widman, D. R., Abrahamsen, G. C. & Rosellini, R. A. Environmental enrichment: the influences of restricted daily exposure and subsequent exposure to uncontrollable stress. *Physiol. Behav.* **51**, 309–318 (1992).
128. Rema, V. & Ebner, F. F. Effect of enriched environment rearing on impairments in cortical excitability and plasticity after prenatal alcohol exposure. *J. Neurosci.* **19**, 10993–11006 (1999).
129. Warren, J. M., Zerweck, C. & Anthony, A. Effects of environmental enrichment on old mice. *Dev. Psychobiol.* **15**, 13–18 (1982).

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