

Psychobiology of plasticity: effects of training and experience on brain and behavior

Mark R. Rosenzweig * and Edward L. Bennett

Department of Psychology-1650, 3210 Tolman Hall, University of California, Berkeley, CA 94720-1650, USA

Received 17 March 1995; revised 9 June 1995; accepted 19 June 1995

Abstract

Supporting Hebb's 1949 hypothesis of use-induced plasticity of the nervous system, our group found in the 1960s that training or differential experience induced neurochemical changes in cerebral cortex of the rat and regional changes in weight of cortex. Further studies revealed changes in cortical thickness, size of synaptic contacts, number of dendritic spines, and dendritic branching. Similar effects were found whether rats were assigned to differential experience at weaning (25 days of age), as young adults (105 days) or as adults (285 days). Enriched early experience improved performance on several tests of learning. Cerebral results of experience in an enriched environment are similar to results of formal training. Enriched experience and training appear to evoke the same cascade of neurochemical events in causing plastic changes in brain. Sufficiently rich experience may be necessary for full growth of species-specific brain characteristics and behavioral potential. Clayton and Krebs found in 1994 that birds that normally store food have larger hippocampi than related species that do not store. This difference develops only in birds given the opportunity to store and recover food. Research on use-induced plasticity is being applied to promote child development, successful aging, and recovery from brain damage; it is also being applied to benefit animals in laboratories, zoos and farms.

Keywords: Brain plasticity; Enriched experience; Enriched environment; Long-term memory; Memory storage; Neural plasticity

It seems very appropriate that this symposium is keyed to the concept of use-dependent plasticity of the nervous system, proposed by Donald O. Hebb in his book of 1949 [36], and its importance for Alzheimer's disease. Hebb's concept has influenced several papers at this meeting and is enjoying a resurgence of interest. One of us was fortunate to learn about Hebb's ideas from him when he gave a graduate seminar at Harvard in the summer of 1947, using a mimeographed version of his still unpublished book as text, and benefitted from further exchanges with him over the years.

This paper will review several related topics: (1) research that first demonstrated use-dependent plasticity of the nervous system; (2) generalization of these findings over the entire life span and to several species; (3) extensions of this research; and (4) applications.

1. Differential experience produces changes in cerebral neurochemistry and anatomy

Ten years after Hebb's book was published, his postulate of use-dependent plasticity had still not been demon-

strated experimentally. It seemed to many that it would not be possible, with available techniques, to find changes in the brain induced by training or experience. Then in the early 1960s two experimental programs announced findings demonstrating that the brain can be altered by training or differential experience. First was the demonstration by our group at Berkeley that both formal training and informal experience in varied environments led to measurable changes in neurochemistry and neuroanatomy of the rodent brain. Soon after came the report of Hubel and Wiesel that occluding one eye early in development led to reduction in the number of cortical cells responding to that eye.

The original clues for our discovery came from data on rats given formal training in a variety of problems. The purpose of that study was to examine relations between individual differences in brain chemistry and problem-solving ability in laboratory rats. We found significant correlations between levels of the enzyme acetylcholinesterase (AChE) in the cerebral cortex and ability to solve spatial problems [43,60]. When we tested the generality of this finding over six different behavioral tests, we found a surprise: The AChE activity was higher in the cerebral cortex of groups that had

* Corresponding author. Fax: (1) (510) 642 5293, For messages: (1) (510) 642 5292; E-mail: memory@garnet.berkeley.edu.

been trained and tested on more difficult problems than in those given easier problems, and all the tested groups measured higher in cortical AChE activity than groups given no training and testing. It appeared that training was altering the AChE activity of the cortex! To test this, we then conducted an experiment in which littermates were either trained on a difficult problem or left untrained, and the trained rats developed significantly higher cortical AChE than their untrained littermates [61]. Instead of continuing to train rats in problem-solving tests, which is a time-consuming and expensive procedure, we decided to house the animals in different environments that would provide differential opportunities for informal learning. Measures made at the end of the experiment showed that informal enriched experience led to increased cortical AChE activity [44]. The discovery that differential experience caused changes in cortical chemistry was soon followed by the even more surprising finding that enriched experience increased the *weights* of regions of the neocortex [63]. As Bailey and Kandel noted in a recent review [3], “The initial reports by Rosenzweig, Bennett, Diamond and their colleagues provided the first evidence that enrichment of the environment could lead to structural changes in the brain” (p. 399).

Work by students of Hebb [28] provided the models for the environments we used in these experiments. Typically, we assigned littermates of the same sex by a random procedure to various laboratory environments, the three most common being the following: A large cage containing a group of 10 to 12 animals and a variety of stimulus objects, which were changed daily. This was called the enriched condition (EC) because it provided greater opportunities for informal learning than did the other conditions.

The standard colony (SC) situation with three animals in a standard laboratory cage provided with food and water.

SC-size cages housing single animals; this was called the impoverished condition or isolated condition (IC).

Our first reports of changes in the brain induced by experience were greeted with scepticism and incredulity. Hebb cautioned that the more important the claims, the more careful should be the tests. Over the next several years, replications and extensions by us [7] and then by others [1,29,32] gained acceptance for the idea that training or differential experience could produce measurable changes in the brain. Further studies revealed experience-induced increases in other measures, especially in occipital cortex, including cortical thickness [21], sizes of neuronal cell bodies and nuclei [20], size of synaptic contact areas [74], an increase of 10% in numbers of dendritic spines per unit of length of basal dendrites [31], an increase of 25% or more in extent and branching of dendrites [32], and a parallel increase

in numbers of synapses per neuron [72]. These effects suggest a substantial increase in processing capacity of the cortical region concerned.

The brain weight differences caused by differential experience were extremely reliable, although small in percentage terms. Moreover, these differences were not uniformly distributed throughout the cerebral cortex. They were almost invariably largest in occipital cortex and smallest in the adjacent somesthetic cortex; the rest of the brain outside the cerebral cortex tended to show very little effect [7,8]. Thus the experience caused changes in specific cortical regions and not undifferentiated growth of brain.

Soon after our early publications came another kind of evidence of cortical plasticity—the announcement by Hubel and Wiesel that depriving one eye of light in a young animal, starting at the age at which the eyes open, reduced the number of cortical cells responding to stimulation of that eye [37,75,76]. Depriving an eye of light is a rather severe and pathological condition. In contrast, giving animals different amounts of experience without depriving them of any sensory modality is a rather mild and natural treatment, yet it leads to measurable changes of neurochemistry and neuroanatomy, and it has significant effects on problem-solving ability.

1.1. Differential experience can produce cerebral changes throughout the life span; the effects occur rather rapidly

Further experiments revealed that significant cerebral effects of enriched vs. impoverished experience could be induced at any part of the life span and with relatively short periods of exposure. In contrast, Hubel and Wiesel reported that depriving an eye of light altered cortical responses only if the eye was occluded during a critical period early in life. Later, however, other investigators found that modifying sensory experience—especially in the cases of touch and hearing—could alter both receptive fields of cells and cortical maps, as reviewed by Kaas [38] and Weinberger [73].

In our initial experiments, supposing that cerebral plasticity might be restricted to the early part of the life span, we assigned animals to differential environments at weaning (25 days of age) and kept them there for 80 days. Later we found that we could obtain similar effects in rats assigned to the differential environments for 30 days as juveniles at 50 days of age [79] and as young adults at 105 days of age [7,62]. Riege [55] in our laboratory found that similar effects occurred in rats assigned to the differential environments at 285 days of age and kept there for periods of 30, 60 or 90 days. Two hours a day in the differential environments for a period of 30 or 54 days was found to produce similar cerebral effects to 24-h exposure [64]. Four days of differential

housing produced clear effects on cortical weights [10], and four 10-min daily sessions in EC significantly altered cortical RNA concentrations [22].

The fact that differential experience can cause cerebral changes throughout the life span, and relatively rapidly, was consistent with our interpretation of these effects as due to learning. Recall also that our original observation of differences in cortical neurochemistry came from experiments on formal training. Later Chang and Greenough [13] reported that formal visual training confined to one eye of rats caused increased dendritic branching in the visual cortex contralateral to the open eye. Recently single-trial peck-avoidance training in chicks has been found to result in changes in density of dendritic spines [45].

It should be noted that although the capacity for these plastic changes of the nervous system, and for learning, remain in older subjects, the cerebral effects of differential environmental experience develop somewhat more rapidly in younger than in older animals, and the magnitude of the effects is often larger in the younger animals. Also, continuing plasticity does not hold for all brain systems and types of experience. As we noted earlier, changes in responses of cortical cells to an occluded eye are normally restricted to early development [75]. But this restriction may itself be modifiable: Plasticity of the adult visual cortex could be restored by infusing acetylcholine and noradrenaline [5]. Thus, whether the adult brain remains plastic to a particular kind of experience depends on the brain region, the kind of experience and perhaps also on special circumstances that enhance or impair plasticity.

2. Enriched experience improves subsequent ability to learn and solve problems

Hebb [36] reported briefly that when he allowed some laboratory rats to explore his home for some weeks as pets of his children and then returned them to the laboratory, they showed better problem-solving ability than rats that had remained in the laboratory throughout. They maintained their superiority or even increased it during a series of tests. Hebb concluded that “*the richer experience of the pet group during development made them better able to profit by new experience at maturity—one of the characteristics of the ‘intelligent’ human being*” (pp. 298–299, italics in the original). Moreover, the results seemed to show a *permanent* effect of early experience on problem-solving at maturity.

We and others have found that experience in an enriched laboratory environment improves learning and problem-solving ability on a wide variety of tests, although such differences have not been found invariably. One general finding is that the more complex the

task, the more likely it is that animals with EC experience will perform better than animals from SC or IC groups. Several different explanations have been offered for this effect, as reviewed by Renner and Rosenzweig [54] (pp. 46–48).

One aspect of Hebb’s report that we were unable to replicate is that over a series of tests, EC rats maintain or increase their superiority over IC rats. On the contrary, we found that IC rats tend to catch up with EC rats over a series of trials; this occurred in each of three different tests, including the Hebb-Williams mazes [57] (p. 321). Thus we did not find that early deprivation of experience caused a permanent deficit, at least for rats tested on spatial problems. Also, decreases in cortical weights induced by 300 days in the IC (versus the EC) environment could be overcome by a few weeks of training and testing in the Hebb-Williams mazes [18]. Later we will see a similar effect in birds: Although preventing birds from storing and retrieving food decreased the weight of the hippocampus, allowing them this experience at a later age than usual led to hippocampal growth [14].

2.1. Similar effects of experience occur in other species

Experiments with several strains of rats showed similar effects of EC vs. IC experience on both brain values and problem-solving behavior [54] (pp. 53–54). Similar effects on brain measures have been found in several species of mammals—mice, gerbils, ground squirrels, cats and monkeys [54] (pp. 54–59). Effects on training and of experience on brain values of birds have also been found, as will be reported in two sections below. Thus the cerebral effects of experience that were surprising when first found in rats have now been generalized to several mammalian and avian species.

2.2. Experience may be necessary for full growth of brain and of behavioral potential

Sufficiently rich experience may be necessary for full growth of species-specific brain characteristics and behavioral potential. This is seen in recent research on differential experience conducted with different species of the crow family. Species that store food in a variety of locations for future use are found to have significantly larger hippocampal formations than related species that do not store food [42,68]. But the difference in hippocampal size is not found in young birds who are still in the nest; it appears only after food storing has started, a few weeks after the birds have left the nest [35]. Even more interesting is the fact that this species-typical difference in size of the hippocampus is dependent on experience; it does not appear in birds that have not had the opportunity to store food [14]. Different groups of hand-raised birds were given experience in storing

food at 3 different periods, either 35–59 days posthatch, 60–83 days or 115–138 days. Experience at each of these periods led to increased hippocampal size, much as we had found for cortical measures in the rat. Thus, both birds and rats appear to retain considerable potential for experience-induced brain growth if it does not occur at the usual early age.

2.3. Enriched experience and formal training appear to evoke the same cascade of neurochemical events that cause plastic changes in brain

By what processes do enriched experience or formal training lead to plastic changes in cerebral neurochemistry and neuroanatomy? We found early that enriched experience causes increased rates of protein synthesis and increased amounts of protein in the cortex [7]. Later, training (imprinting) was reported to increase the rates of incorporation of precursors into RNA and protein in the forebrain of the chick [34], and enriched experience was found to lead to increased amounts [6,23] and expression [33] of RNA in rat brain. Maze training led to increased ratios of RNA to DNA in rat cortex [11]. These findings were viewed in the light of the hypothesis, perhaps first enunciated by Katz and Halstead [39], that protein synthesis is required for memory storage.

Tests of the protein-synthesis hypothesis of memory formation were initiated by Flexner and associates [24,25] in the early 1960s, and much research followed their design: (1) giving animal subjects brief training that, without further treatment, would yield evidence of retention at a test a few days later; (2) administering to experimental subjects an inhibitor of protein synthesis at various times close to training, while control subjects received an inactive substance, and (3) comparing test performance of experimental and control subjects. By the early 1970s, considerable evidence indicated that protein synthesis during or soon after training was necessary for formation of long-term memory (LTM), but the interpretation of the findings was clouded by serious problems such as these: (1) The inhibitors of protein synthesis that were available for research were rather toxic, which impeded experiments and complicated interpretation. (2) It appeared that inhibition of protein synthesis could prevent memory formation after weak training but not after strong training (e.g., Barondes [4]).

The discovery by Bennett et al. [9] that anisomycin (ANI) is an effective amnestic agent in rodents opened the way to resolving the main challenges to the protein-synthesis hypothesis of formation of LTM. ANI has much lower toxicity than other protein synthesis inhibitors, and giving doses repeatedly at 2-h intervals can prolong the duration of cerebral inhibition at amnestic levels. By varying the duration of inhibition in this way,

we found that the stronger the training, the longer protein synthesis had to be maintained to prevent formation of LTM [26,27]. We also found that protein must be synthesized in the cortex soon after training if long-term memory (LTM) is to be formed; short-term memory (STM) or intermediate-term memory (ITM) do not require protein synthesis [9,48,49]. Further studies were then designed to find the neurochemical processes that underlie formation of STM and ITM.

Much of our work on the neurochemistry of STM and ITM has been done with chicks, which have several advantages for this research, including the following: The chick system is convenient for study of the stages of memory formation because chicks can be trained rapidly in a one-trial peck-avoidance paradigm and can be tested within seconds after training, or hours or days later. Large numbers of chicks can be studied in a single run, so one can compare different agents, doses, and times of administration within the same batch of subjects. Unlike invertebrate preparations or tissue slices, the chick system can be used to study the roles of different vertebrate brain structures and to investigate questions of cerebral asymmetry in learning and memory. The chick system permits study of learning and memory in the intact animal. Further advantages have been stated elsewhere [59].

Using the chick system, we and others have traced a cascade of neurochemical events from initial stimulation to synthesis of protein and structural changes [30,51,56,59]. Without going into detail, we can note some of the stages here. At some if not all stages, parallel channels operate. At the outset, sensory stimulation activates receptor organs which stimulate afferent neurons by using various synaptic transmitter agents such as acetylcholine (ACh) and glutamate. Inhibitors of ACh synaptic activity, such as scopolamine and pirenzepine, can prevent STM. So can inhibitors of glutamate receptors, including both the NMDA and AMPA receptors. Alteration of regulation of ion channels in the neuronal membrane can inhibit STM formation, as seen in effects of lanthanum chloride on calcium channels and of ouabain on sodium and potassium channels. Inhibition of second messengers is also amnestic, for example inhibition of adenylate cyclase by forskolin or of diacylglycerol by bradykinin. Agents that inhibit calcium-calmodulin protein kinases prevent formation of ITM, whereas agents that do *not* inhibit calcium-calmodulin protein kinases but *do* inhibit protein kinase A or protein kinase C prevent formation of LTM [67]. One-trial training leads to increase of immediate early gene RNA in the chick forebrain [2] and to increase in the density of dendritic spines [45]. Many of these effects occur only in the left hemisphere of the chick, or are more prominent in the left than in the right hemisphere. Thus, with learning in the chick system, we can study many of

the steps that lead from sensory stimulation to formation of neuronal structures.

The neurochemical cascade involved in formation of memory in the chick is similar to the cascade involved in long-term potentiation in the mammalian brain [15] and in conditioning in *Drosophila* [19].

Many of the steps in formation of memory in the chick can also be modulated by opioids and other substances. Opioid agonists tend to impair, and opioid antagonists to enhance, memory formation. Different opioids modulate formation of different stages of memory [16,17,53,59].

3. Research on use-induced brain plasticity is being applied in a variety of ways

Research on effects of experience on brain plasticity and learning is being applied to promote child development, successful aging, and recovery from brain damage; it is also being applied to benefit animals in laboratories, zoos and farms. A few of these kinds of application are reviewed briefly below. Presenting these applications is not intended to claim that they all derive directly from laboratory research or that some may not have occurred independently, but laboratory research has clearly led to some applications and has supported others.

3.1. Applications to child development

The findings of effects of differential experience in animals have been applied to research on child development. Evidence for the importance of this approach comes from a major 1994 report, "Starting points: Meeting the needs of our youngest children" issued by the Carnegie Task Force on Meeting the Needs of Young Children [12]. The tenor of the findings is indicated by this quotation:

Beginning in the 1960s, scientists began to demonstrate that the quality and variety of the environment have direct impact on brain development. Today, researchers around the world are amassing evidence that the role of the environment is even more important than earlier studies had suggested. For example, histological and brain scan studies of animals show changes in brain structure and function as a result of variations in early experience.

These findings are consistent with research in child development that has shown the first 18 months of life to be an important period of development. Studies of children raised in poor environments—both in this country and elsewhere—show that they have cognitive deficits of substantial magnitude by 18 months of age and that full reversal of these deficits may not be possible. These studies are based on observational

and cognitive assessments; researchers say that neurobiologists using brain scan technologies are on the verge of confirming these findings.

In the meantime, more conventional studies of child development—using cognitive and observational measures—continue to show short- and long-term benefits of an enriched early environment (p. 8).

Several factors have complicated attempts to apply research on environmental enrichment to improve the cognitive status of children raised in poor environments. One is that some proponents have overestimated the potential effects of relatively short periods of enrichment and then have been disappointed that the effects were not larger. This has been one of the problems confronting the Head Start program in the United States [78]. Although this and related programs have proved to be beneficial and cost-effective, they were unable to bring participating children up to the scholastic levels of children living in better environments. Another problem is that the human programs involve a variety of aspects, so it is difficult to determine whether the positive effects are attributable to enriched experience and training or to other causes such as improved nutrition and health care.

But these problems should not overshadow the clear beneficial effects of programs to provide environmental enrichment to children in need of it. We believe that current programs need to be expanded to include more children and to retain them for a longer period of years.

3.2. Applications to 'successful aging'

At the latter ages of the life span, enriched experience also helps to ensure maintenance of ability into old age. Thus, although some kinds of learning and performance decline with age after middle adulthood, this is not true of other kinds of learning and memory. People who continue to learn actively can maintain high levels of performance. For example, professors in their 60s perform as well as professors in their 30s on many tests of learning and memory [69].

Beyond the age of retirement, stimulation and activity continue to contribute to health and mental status. This is borne out in a longitudinal study that has assessed mental abilities of more than 5000 adults and has followed some for as long as 35 years [66]. Among the eight variables that were found to reduce the risk of cognitive decline in old age, three are particularly relevant to our discussion:

Living in favorable environmental circumstances as would be the case for persons characterized by high socio-economic status. These circumstances include above-average education, histories of occupational pursuits that involve high complexity and low

routine, above-average income, and the maintenance of intact families.

Substantial involvement in activities typically available in complex and intellectually stimulating environments. Such activities include extensive reading habits, travel, attendance at cultural events, pursuit of continuing education activities, and participation in clubs and professional associations.

Being married to a spouse with high cognitive status. Our studies of cognitive similarity in married couples suggest that the lower functioning spouse at the beginning of marriage tends to maintain or increase his or her level vis à vis the higher functioning spouse [66] (p. 312).

Infantile handling or later enriched experience help prevent hippocampal damage caused by stress in rats. Meaney et al. [47], handled some neonatal rat pups each of their first 21 days and left other rats unhandled. They examined cognitive function of the rats at different ages from 3 months to 24 months and also measured basal and stress levels of glucocorticoids, numbers of hippocampal neurons and of glucocorticoid receptors. Chronic excess of glucocorticoids is toxic to neurons, particularly those of the hippocampus, and aged rats are particularly vulnerable [65]. Handling was found to improve spatial memory, to increase hippocampal corticoid receptors, and to lead to a more rapid return of corticosterone to basal levels after response to a stressful situation. In old age, the handled animals, as compared to the unhandled, had lower basal levels of corticosterone and less loss of hippocampal neurons.

Rats given EC or IC experience beginning at 50 days of age, like rats given infantile handling, showed higher expression of the gene encoding glucocorticoid receptors in the hippocampus, and they also showed induction of genes for nerve growth factors in the hippocampus [50,52]. The investigators suggest that enriched experience in adulthood, like infantile handling, may protect the aging hippocampus from glucocorticoid neurotoxicity.

Enriched experience may also cushion the brain and intellectual function against the effects of Alzheimer's disease. As Terry [71] has reviewed at this meeting, loss of synapses correlates strongly with the severity of symptoms in Alzheimer's disease. Enriched experience produces richer neural networks in the brains of all species that have been studied in this regard, as reported earlier in this paper. If similar effects occur in humans, as seems likely, this may set up reserves of connections that protect intellectual function from the signs of Alzheimer's disease.

3.3. *Applications to recovery from brain damage*

At all parts of the life span, training and enriched experience help in recovery from or compensation for

effects of brain damage. We showed this in experiments with rats in the 1970s [77] and research along this line continues. One of the major questions is the extent to which experience actually aids in recovery or only in compensation for the effects of brain injury. At a minimum, psychological applications aid the quality of life of people with injuries of the brain or of the spinal cord. Beyond this, there may be interaction between physiological and behavioral interventions.

In attempts to promote recovery from brain damage, some neuroscientists are transplanting fetal brain cells into the region of a brain lesion. Many psychologists along with other neuroscientists are taking parts in this research. Sometimes the neural transplants or implants are successful and help to restore function. But often the neural implants do not work, for reasons that are not yet fully understood.

A few years ago, investigators started to combine the two methods, by studying the separate and the combined effects of enriched environment and neural transplants [40,41]. Under some conditions, neither the enriched experience or the transplant alone had a beneficial effect, but the combination of the two treatments yielded significant improvement in learning. Further work indicates that formal training of rats may also promote the effects of brain cell grafts on learning. These results of animal research may find application in attempts to aid human patients. At present one sees quite varied reports about results of attempts to aid patients with Parkinson's disease by implanting brain cells. Perhaps the differences among clinics in success of cell grafts may reflect the kinds and amounts of training and stimulation given the patients; this may interact with the skill of the neurosurgeon. The combination of brain implants with training and stimulation may become an increasingly important area of interaction between research and application in the field of neural bases of learning and memory.

3.4. *Research on effects of enriched environments is being applied to benefit animals in laboratories, zoos and farms*

Animals not only contribute to research on effects of environmental enrichment, but they also benefit from such research, as we have described in more detail elsewhere [58]. Newer standards for housing animals in laboratories reflect findings that animals benefit from adequate space for exercise and for species-specific activities of running, investigating, and so forth. Zoos are also providing more natural settings and apparatus that permits animals to engage in species-specific activities. Two of our former students who worked with rats in enriched laboratory environments have since worked to improve settings for zoo animals. Some farms have found that animals thrive better in more natural settings and are providing them.

4. Conclusion

From this review, what conclusion can we draw in regard to Swaab's [70] query whether, in adulthood and old age, use of the nervous system is better characterized by the phrase 'wear and tear' or by the phrase 'use it or lose it'? It seems to us that the research reviewed here, and in the articles that commented on Swaab's paper, mainly supports the conclusion 'use it or lose it.' But we should add to that the fact that use and experience are especially effective early in life and they set the basis for later use and maintenance of the brain and of ability. So perhaps we need a formulation that includes both early experience and later sustained use:

It's a fortunate person whose brain
Is trained early, again and again,
And who continues to use it
To be sure not to lose it,
So the brain, in old age, may not wane.

Acknowledgement

The research of our laboratories was supported by grants from the National Science Foundation, the Department of Energy, the National Institute of Mental Health, and the National Institute on Drug Abuse.

References

- [1] Altman, J. and Das, G.D., Autoradiographic examination of the effects of enriched environment on the rate of glial multiplication in the adult rat brain. *Nature*, 204 (1964) 1161–1163.
- [2] Anokhin, K.V. and Rose, S.P.R., Learning-induced increase of early immediate gene messenger RNA in the chick forebrain. *Eur. J. Neurosci.*, 3 (1991) 162–167.
- [3] Bailey, C.H. and Kandel, E.R., Structural changes accompanying memory storage. *Annu. Rev. Physiol.*, 55 (1993) 397–426.
- [4] Baronides, S.H., Some critical variables in studies of the effect of inhibitors of protein synthesis on memory. In W.L. Byrne (Ed.), *Molecular Approaches to Learning and Memory*. Academic, New York, 1970, pp. 27–34.
- [5] Baer, M.F. and Singer, W., Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature*, 320 (1986) 172–176.
- [6] Bennett, E.L., Cerebral effects of differential experience and training. In M.R. Rosenzweig and E.L. Bennett (Eds.), *Neural Mechanisms of Learning and Memory*. MIT Press, Cambridge, 1976, pp. 279–287.
- [7] Bennett, E.L., Diamond, M.C., Krech, D. and Rosenzweig, M.R., Chemical and anatomical plasticity of brain. *Science*, 164 (1964) 610–619.
- [8] Bennett, E.L., Krech, D. and Rosenzweig, M.R., Reliability and regional specificity of cerebral effects of environmental complexity and training. *J. Comp. Physiol. Psychol.*, 57 (1964) 440–441.
- [9] Bennett, E.L., Orme, A.E. and Hebert, M., Cerebral protein synthesis inhibition and amnesia produced by scopolamine, cycloheximide, streptovitacin A, anisomycin, and emetine in rat. *Fed. Proc.*, 31 (1972) 838.
- [10] Bennett, E.L., Rosenzweig, M.R. and Diamond, M.C., Time courses of effects of differential experience on brain measures and behavior of rats. In E.L. Byrne (Ed.), *Molecular Approaches to Learning and Memory*. Academic Press, New York, 1970, pp. 55–89.
- [11] Bennett, E.L., Rosenzweig, M.R., Morimoto, H. and Hebert, M., Maze training alters brain weights and cortical RNA/DNA ratios. *Behav. Neural. Biol.*, 26 (1979) 1–22.
- [12] Carnegie Task Force on Meeting the Needs of Young Children. *Starting points: Meeting the Needs of Our Youngest Children*. Carnegie Corporation of New York, New York, 1994.
- [13] Chang, F.-L. and Greenough, W.T., Lateralized effects of monocular training on dendritic branching in adult split-brain rats. *Brain Res.*, 232 (1982) 283–292.
- [14] Clayton, N.S. and Krebs, J.R., Hippocampal growth and attrition in birds affected by experience. *Proc. Natl. Acad. Sci. USA*, 91 (1994) 7410–7414.
- [15] Colley, P.A. and Routtenberg, A., Long-term potentiation as synaptic dialogue. *Brain Res. Rev.*, 18 (1993) 115–122.
- [16] Colombo, P.J., Martinez, J.L., Bennett, E.L. and Rosenzweig, M.R., Kappa opioid receptor activity modulates memory for peck-avoidance training in the 2-day-old chick. *Psychopharmacology*, 108 (1992) 235–240.
- [17] Colombo, P.J., Thompson, K.R., Martinez, J.L., Bennett, E.L. and Rosenzweig, M.R., Dynorphin_(1–13) impairs memory formation for aversive and appetitive learning in chicks. *Peptides*, 14 (1993) 1165–1170.
- [18] Cummins, R.A., Walsh, R.N., Budtz-Olsen, O.E., Konstantinos, T. and Horsfall, C.R., Environmentally-induced changes in the brains of elderly rats. *Nature*, 243 (1973) 516–518.
- [19] DeZazzo, J. and Tully, T., Dissection of memory formation: From behavioral pharmacology to molecular genetics. *TINS*, 18 (1995) 212–218.
- [20] Diamond, M.C., Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. *J. Comp. Neurol.*, 131 (1967) 357–364.
- [21] Diamond, M.C., Krech, D. and Rosenzweig, M.R., The effects of an enriched environment on the histology of the rat cerebral cortex. *J. Comp. Neurol.*, 123 (1964) 111–119.
- [22] Ferchmin, P. and Eterovic, V., Forty minutes of experience increase the weight and RNA content of cerebral cortex in periadolescent rats. *Dev. Psychobiol.*, 19 (1986) 511–519.
- [23] Ferchmin, P., Eterovic, V. and Caputto, R., Studies of brain weight and RNA content after short periods of exposure to environmental complexity. *Brain Res.*, 20 (1970) 49–57.
- [24] Flexner, J.B., Flexner, L.B., Stellar, E., de la Haba, G. and Roberts, R.B., Inhibition of protein synthesis in brain and learning and memory following puromycin. *J. Neurochem.*, 9 (1962) 595–605.
- [25] Flexner, J.B., Flexner, L.B., de la Haba, G. and Roberts, R.B., Loss of memory as related to inhibition of cerebral protein synthesis. *J. Neurochem.*, 12 (1965) 535–541.
- [26] Flood, J.F., Bennett, E.L., Rosenzweig, M.R. and Orme, A.E., Influence of duration of protein synthesis inhibition on memory. *Physiol. Behav.*, 10 (1973) 555–562.
- [27] Flood, J.F., Bennett, E.L., Orme, A.E. and Rosenzweig, M.R., Relation of memory formation to controlled amounts of brain protein synthesis. *Physiol. Behav.*, 15 (1975) 97–102.
- [28] Forgays, D.G. and Forgays, J.W., The nature of the effect of free-environmental experience on the rat. *J. Comp. Physiol. Psychol.*, 45 (1952) 747–750.
- [29] Geller, E., Yuwiler, A. and Zolman, J.F., Effects of environmental complexity on constituents of brain and liver. *J. Neurochem.*, 12 (1965) 949–955.
- [30] Gibbs, M.E. and Ng, K.T., Psychobiology of memory: Towards a model of memory formation. *Biobehav. Rev.*, 1 (1977) 113–136.

- [31] Globus, A., Rosenzweig, M.R., Bennett, E.L. and Diamond, M.C., Effects of differential experience on dendritic spine counts in rat cerebral cortex. *J. Comp. Physiol. Psychol.*, 82 (1973) 1757–181.
- [32] Greenough, W.T. and Volkmar, F.R., Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp. Neurol.*, 40 (1973) 136–143.
- [33] Grouse, L.D., Schrier, B.K., Bennett, E.L., Rosenzweig, M.R. and Nelson, P.G., Sequence diversity studies of rat brain RNA: Effects of environmental complexity on rat brain RNA diversity. *J. Neurochem.*, 30 (1978) 191–203.
- [34] Haywood, J., Rose, S.P.R. and Bateson, P.P.G., Effects of an imprinting procedure on RNA polymerase activity in the chick brain. *Nature*, 288 (1970) 373–374.
- [35] Healy, S.D. and Krebs, J.R., Development of hippocampal specialisation in a food-storing bird. *Behav. Brain Res.*, 53 (1993) 127–130.
- [36] Hebb, D.O., *The Organization of Behavior: A Neuropsychological Theory*. Wiley, New York, 1949.
- [37] Hubel, D.H. and Wiesel, T.N., Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.*, 28 (1965) 1041–1059.
- [38] Kaas, J.H., Plasticity of sensory and motor maps in adult mammals. *Annu. Rev. Neurosci.*, 14 (1991) 137–67.
- [39] Katz, J.J. and Halstead, W.G., Protein organization and mental function. *Comp. Psychol. Monogr.*, 20 (1950) 1–38.
- [40] Kelche, C., Dalrymple-Alford, J.C. and Will, B., Housing conditions modulate the effects of intracerebral grafts in rats with brain lesions. *Behav. Brain Res.*, 53 (1988) 287–296.
- [41] Kelche, C., Roeser, C., Jeltsch, H., Cassel, J.C. and Will, B., Intra-hippocampal grafts, postoperative housing and training conditions, and recovery of function after septohippocampal damage. In W.J. Freed and J.M. Rosenstein (Eds.), Abstracts, IV International Symposium on Neural Transplantation. *Rest. Neurol. Neurosci.*, 4 (1992) 143.
- [42] Krebs, J.R., Sherry, D.F., Healy, S.D., Perry, V.H. and Vaccarino, A.L., Hippocampal specialisation of food-storing birds. *Proc. Natl. Acad. Sci. USA*, 86 (1989) 1388–1392.
- [43] Krech, D., Rosenzweig, M.R. and Bennett, E.L., Dimensions of discrimination and level of cholinesterase activity in the cerebral cortex of the rat. *J. Comp. Physiol. Psychol.*, 82 (1956) 261–268.
- [44] Krech, D., Rosenzweig, M.R. and Bennett, E.L., Effects of environmental complexity and training on brain chemistry. *J. Comp. Physiol. Psychol.*, 53 (1960) 509–519.
- [45] Lowndes, M. and Stewart, M.G., Dendritic spine density in the lobus parolfactorius of the domestic chick is increased 24 h after one-trial passive avoidance training. *Brain Res.*, 654 (1994) 129–136.
- [46] Meaney, M.J., Aitkin, D.H., Bhatnagar, S., Van Berkel, C. and Sapolsky, R.M., Postnatal handling attenuates neuroendocrine, anatomical, and cognitive impairments related to the aged hippocampus. *Science*, 238 (1988) 766–768.
- [47] Meaney, M.J., Mitchell, J.B., Aitkin, D.H., Bhatnagar, S., Bodnoff, S.R., Iny, L.J. and Sarrieu, A., 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 (1991) 85–103.
- [48] Mizumori, S.J.Y., Rosenzweig, M.R. and Bennett, E.L., Long-term working memory in the rat: Effects of hippocampally applied anisomycin. *Behav. Neurosci.*, 99 (1985) 220–232.
- [49] Mizumori, S.J.Y., Sakai, D.H., Rosenzweig, M.R., Bennett, E.L. and Wittreich, P., Investigations into the neuropharmacological basis of temporal stages of memory formation in mice trained in an active avoidance task. *Behav. Brain Res.*, 23 (1987) 239–250.
- [50] Mohammed, A., Henriksson, B.G., Soderstrom, S., Ebendal, T., Olsson, T. and Seckl, J.R., Environmental influences on the central nervous system and their implications for the aging rat. *Behav. Brain Res.*, 23 (1993) 182–191.
- [51] Ng, K.T. and Gibbs, M.E., Stages in memory formation: A review. In R.J. Andrew (Ed.), *Neural and Behavioural Plasticity: The Use of the Domestic Chick as a Model*. Oxford University Press, Oxford, UK, 1991, pp. 351–369.
- [52] Olsson T., Mohammed A.H., Donaldson L.F., Henriksson B.G. and Seckl J.R., Glucocorticoid receptor and NGFI-A gene expression are induced in the hippocampus after environmental enrichment in adult rats. *Mol. Brain Res.*, 23 (1994) 349–353.
- [53] Patterson, T.A., Schulteis, G., Alvarado, M.C., Martinez, J.L., Bennett, E.L., Rosenzweig, M.R. and Hruby, V.J., Influence of opioid peptides on learning and memory processes in the chick. *Behav. Neurosci.*, 103 (1989) 429–437.
- [54] Renner, M.J. and Rosenzweig, M.R., *Enriched and Impoverished Environments: Effects on Brain and Behavior*. Springer-Verlag, New York, 1987.
- [55] Riege, W.H., Environmental influences on brain and behavior of old rats. *Dev. Psychobiol.*, 4 (1971) 157–167.
- [56] Rose, S.P.R., On chicks and Rosetta stones. In L.R. Squire and N. Butters (Eds.), *Neuropsychology of Memory*, 2nd Edn., Guilford, New York, 1992, pp. 547–556.
- [57] Rosenzweig, M.R., Effects of environment on development of brain and behavior. In E. Tobach (Ed.), *Biopsychology of Development*, Academic, New York, 1971, pp. 303–342.
- [58] Rosenzweig, M.R., Experience, memory and the brain. *Am. Psychol.*, 39 (1984) 365–376.
- [59] Rosenzweig, M.R., Bennett, E.L., Martinez, J.L., Colombo, P.J., Lee, D.W. and Serrano, P.A., Studying stages of memory formation with chicks. In L.R. Squire and N. Butters (Eds.), *Neuropsychology of Memory*, 2nd Edn., Guilford, New York, 1992, pp. 533–546.
- [60] Rosenzweig, M.R., Krech, D. and Bennett, E.L., Brain chemistry and adaptive behavior. In H.F. Harlow and C.N. Woolsey (Eds.), *Biological and Biochemical Bases of Behavior*. Wisconsin University Press, Madison, WI, 1958, pp. 367–400.
- [61] Rosenzweig, M.R., Krech, D. and Bennett, E.L., Heredity, environment, brain biochemistry and learning. In *Current Trends in Psychological Theory*, University of Pittsburgh Press, Pittsburgh, 1961, pp. 87–110.
- [62] Rosenzweig, M.R., Krech, D. and Bennett, E.L., Effects of differential experience on brain AChE and ChE and brain anatomy in the rat, as a function of strain and age. *Am. Psychol.*, 18 (1963) 430.
- [63] Rosenzweig, M.R., Krech, D., Bennett, E.L. and Diamond, M.C., Effects of environmental complexity and training on brain chemistry and anatomy: A replication and extension. *J. Comp. Physiol. Psychol.*, 55 (1962) 429–437.
- [64] Rosenzweig, M.R., Love, W. and Bennett, E.L., Effects of a few hours a day of enriched experience on brain chemistry and brain weights. *Physiol. Behav.*, 3 (1968) 819–825.
- [65] Sapolsky, R.M., *Stress, The aging Brain and Mechanisms of Neuronal Death*. MIT Press, Cambridge, MA, 1992.
- [66] Schaie, K.W., The course of adult intellectual development. *Am. Psychol.*, 49 (1994) 304–313.
- [67] Serrano, P.A., Beniston, D.S., Oxonian, M.G., Rodriguez, W.A., Rosenzweig, M.R. and Bennett, E.L., Differential effects of protein kinase inhibitors and activators on memory formation in the 2-day-old chick. *Behav. Neural Biol.*, 61 (1994) 60–72.
- [68] Sherry, D.F., Vaccarino, A.L., Buckenham, K. and Herz, R.S., The hippocampal complex of food-storing birds. *Brain Behav. Evol.*, 34 (1989) 308–317.
- [69] Shimamura, A., Berry, J.M., Mangels, J.A., Rusting, C.L. and Jurica, P.J., Memory and cognitive abilities in university professors: Evidence for successful aging. *Psychol. Sci.*, 6 (1995) 271–277.
- [70] Swaab, D.F., Brain aging and Alzheimer's disease, 'wear and tear' versus 'use it or lose it.' *Neurobiol. Aging*, 12 (1991) 317–324.

- [71] Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Hansen, L.A. and Katzman, R., Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment, *Ann. Neurol.*, 30 (1991) 572–580.
- [72] Turner, A.M. and Greenough, W.T., Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron. *Brain Res.*, 329, (1985) 195–203.
- [73] Weinberger, N.M., Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annu. Rev. Neurosci.*, 18 (1995) 129–158.
- [74] West, R.W. and Greenough, W.T., Effects of environmental complexity on cortical synapses of rats: Preliminary results. *Behav. Biol.*, 7, (1972) 279–284.
- [75] Wiesel, T.N. and Hubel, D.H., Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.*, 26 (1963) 1003–1017.
- [76] Wiesel, T.N. and Hubel, D.H., Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J. Neurophysiol.*, 28 (1965) 1029–1040.
- [77] Will, B.E., Rosenzweig, M.R., Bennett, E.L., Hebert, M. and Morimoto, H., Relatively brief environmental enrichment aids recovery of learning capacity and alters brain measures after postweaning brain lesions in rats. *J. Comp. Physiol. Psychol.*, 91 (1977) 33–50.
- [78] Zigler, E. and Muenchow, S., *Head Start: The Inside Story of America's Most Successful Educational Experiment*. Basic Books, New York, 1994.
- [79] Zolman, J.F. and Morimoto, H., Effects of age of training on cholinesterase activity in the brains of maze-bright rats. *J. Comp. Physiol. Psychol.*, 55 (1962) 794–800.