Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990–2002)

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Abstract

In the 1960s, it was shown for the first time that enriched housing enhances functional recovery after brain damage. During the 1970s and 1980s, many findings similar to this initial one have been reported, enlarging greatly its generality. Over the last 13 years, many different kinds of brain damage were modelled in animals or even directly studied in humans. Overall, these recent studies corroborated earlier findings, although occasional exceptions were reported. Other critical data, obtained mainly in intact animals, showed that enriched housing increases neurogenesis in the adult hippocampus. Recent evidence that this neurogenesis is involved in hippocampal-dependent learning supports the original interpretation of the enrichment effects as being the result of an accumulation of informal learning experiences (e.g., [Rosenzweig et al., 1961. Heredity, environment, brain biochemistry, and learning. In: Current Trends in Psychological Theory. University of Pittsburgh Press, Pittsburgh, pp. 87–110; Rosenzweig et al., 1972. Brain changes in response to experience. Sci. Am. 226, 22–29]). Other components of enriched environment, such as physical exercise, may have additive effects with those of training. The comparison of the relative effectiveness of enriched experience, of physical exercise and of training on structural and/or functional assessments of recovery, shows that training/learning is generally more effective than physical exercise and that enriched experience is a more potent therapy than either of these two other treatments. The combination of enriched experience with some other neurosurgical and/or neuropharmacological treatments may further improve its therapeutic effectiveness. Finally, other recent reports emphasize that the treatment parameters may be changed in order to approximate clinical/rehabilitation conditions and, nevertheless, remain effective.

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Abbreviations: BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CA1, cornu ammonis 1; CA3, cornu ammonis 3; CNS, central nervous system; EC, enriched condition; FGF, fibroblast growth factor; FGF-2, basic fibroblast growth factor; GABA, gamma amino butyric acid; GDNF, glial-derived neurotrophic factor; IC, impoverished condition; IGF-I, insulin-like growth factor; MAM, methylnitrosemethanol; MCA, middle cerebral artery; mRNA, messenger ribonucleic acid; NBM, nucleus basalis magnocellularis; NGF, nerve growth factor; NT-3, neurotrophin-3; SC, standard condition; TBI, traumatic brain injury; T12–T13, thoracic level 12–13 of spinal cord; 5-HT, 5-hydroxytryptamine

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1. Introduction

Great progress has been achieved over the last decades showing that the brain displays plasticity (e.g., Kolb, 1999; Rosenzweig and Bennett, 1996), a term which refers to the capacity of a system to achieve new functions by transforming, on a long-term basis and under environmental constraint, either its constituting elements or its internal connectivity network (Paillard, 1976). It was also shown that both brain and spinal cord have a regenerative potential-connectivity network (Paillard, 1976). It was also shown that both brain and spinal cord have a regenerative potential, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998). A majority, especially in young but even, though to a lesser degree, in adult and senescent mammals (Will et al., 1998).

This review considers primarily the period of the last 13 years, roughly speaking the “decade of the brain”. For the preceding decades one may refer to previous reviews (e.g., Will, 1981; Will and Kelche, 1992). Since 1990, there were also some interesting reviews published on related topics (Edgerton et al., 2001; Feldman and Knudsen, 1998; Hall, 1998; Kolb and Gibb, 1991; Mohamed et al., 1993; Puurunen and Sivenius, 2002; Robbins et al., 1996; Rosenzweig and Bennett, 1996; Schrott, 1997; Taub et al., 2002; Van Praag et al., 2000; Weiler and Rijntjes, 1999), but the present review is the first to compare directly, in both functional and structural terms, the three main non-invasive therapeutic strategies used for achieving rehabilitation after brain damage, namely (1) environmental enrichment, (2) physical exercise, and (3) specific formal training (Fig. 1). The comparison between these strategies will be based mainly on animal studies that try to model some kind of brain damage observed in humans. The comparison will also be based on similar studies carried out in intact animals.

A first section will consider the behavioral effects of the three kinds of treatment and a second section will list their impact on the central nervous system (CNS). These latter effects may underlie their behavioral effects. The whole review will contribute to improve our understanding of the effectiveness of enriched experience, relative to physical exercise and to specific formal training. In focussing on our theme, we refrain from reviewing several related topics of current interest, including the following: (a) Do standard laboratory environments impair the utility of animals for behavioral and biomedical research (e.g., Knight, 2001; Wurzel, 2001)? (b) Do automated human-free environments provide superior housing for laboratory animals (Bohannon, 2002)? (c) How do stimulant drugs, in conjunction with enriched environment or training, enhance recovery from brain injury (e.g., Ferney, 1997; Johansson et al., 1997; Puurunen and Sivenius, 2002; Rosenzweig, 2002)?

2. Behavioral effects

An important question in terms of functional recovery is whether disruption of CNS structure by lesion or disruption of CNS development, secondary to either genetic or chromosomal anomalies, results in a profound deficiency of the plasticity required to respond to environmental enrichment, physical exercise or specific formal training. In other words, what is the generality of the previously reported behavioral data indicating recovery of function: are they limited or even invalidated by some kinds of brain or spinal cord damage, or by some other factors as well?

2.1. Environmental enrichment

2.1.1. Definition

The denominations enriched environment and enriched housing conditions were originally adapted from Hebb’s research (Hebb, 1947, 1949). They refer to environmental conditions (EC) which, in comparison to standard housing conditions (SC), provide enhanced possibilities of physical and social stimulation and/or interaction (see also Van Praag et al., 2000; Puurunen and Sivenius, 2002). In the early 1960s, Rosenzweig’s group carried out a series of experiments exploring the effects of an enriched environment on brain development and on cognitive abilities. These first findings provided the models for the standardized enriched...
Fig. 1. Photographs of typical conditions used to enhance recovery from brain damage in rodents: enriched housing conditions (A); exercise in a running wheel (B); three aspects of acrobatic training (C).
environmental conditions that are classically used today. In the standard housing conditions commonly used for rat housing in research laboratories, three to six rats are kept per cage without objects. In the enriched environmental condition, the rats are generally housed as groups of 8–12 per cage, providing opportunities for social interaction. Furthermore, the EC rats live in larger cages containing a variety of objects (e.g., boxes, chains, glass cups, ladders, etc.) that are changed daily, providing opportunities for sensory and physical interaction with non-social stimuli. In a third housing condition that, in comparison to the standard condition, is called impoverished (IC), rats are housed singly in smaller cages devoid of objects.

2.1.2. Generality of enrichment effects in brain-damaged animals

The earliest experimentation that presented an analysis of postoperative environmental effects in brain-damaged animals was that by Schwartz (1964). In order to take advantage of the greater plasticity of the neonatal brain, he subjected rats either to bilateral posterior cortical ablation or to sham operation at postnatal day 1 and raised them to early adulthood in environments that afforded either minimal or maximal opportunity for perceptual and motor experience. Early enriched experience offsets the effects of the lesions so efficiently that rats with cortical lesions from the EC made slightly fewer errors than non-lesioned controls reared in the SC.

Following the paper by Schwartz, a large number of reports indicated at least some degree of improvement after brain damage in animals subjected to environmental enrichment. Indeed, similar effects to those reported by Schwartz were found after various periods of differential rearing, in various behavioral testing situations, at different ages, in various strains of rats, in both sexes, and after various kinds of brain damage (see Will and Kelche, 1992).

During the last 13 years, the generality of the picture was further broadened. Many additional reports corroborated previous findings, mainly in rats, but also in mice which are quite interesting for an analysis of the interaction between the effects of the housing environment and the genetic background, and, to a smaller extent, in non-human primates, cats, gerbils, deer–mice, chickadees and some other species (Mohammed et al., 2002).

These effects were reported in animals that exhibited various kinds of CNS damage (Table 1). Whereas only one single article reported beneficial effects on locomotor function of environmental enrichment after moderately severe spinal cord contusion (Lankhorst et al., 2001), there are many reports on its effectiveness in brain-damaged animals. After brain damage, whatever was the origin of the damage, environmental enrichment had beneficial effects on the behavioral outcome of the injury or disease. In some studies, the damage was of genetic/developmental origin, as for instance in fragile X knockout mice (Grossman et al., 2001).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Beneficial effects of enriched environmental housing after various kinds of CNS damage (studies of the last 13 years; references in text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord contusion</td>
<td>Brain damage of genetic/developmental origin</td>
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<tr>
<td>Brain damage of genetic/developmental origin</td>
<td>Fragile X KO mice</td>
</tr>
<tr>
<td>Reticulum thalamus</td>
<td>Lurcher mice with cerebellar degeneration</td>
</tr>
<tr>
<td>NBM, fimbria–fornix, hippocampus</td>
<td>CA1-specific NMDA-R1 knockout mice</td>
</tr>
<tr>
<td>Pharmacological teratogenic origin</td>
<td>Huntington disease model</td>
</tr>
<tr>
<td>MAM-induced microcephaly</td>
<td>Focal or global ischemia</td>
</tr>
<tr>
<td>Prenatal alcohol</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Lead intoxication</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>α-2 agonists or β-blockers in pregnant females</td>
<td>Surgical lesions</td>
</tr>
<tr>
<td>Induced by inadequate life conditions</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>Low maternal care</td>
<td>Reticular thalamus</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Neonatal anoxia</td>
</tr>
</tbody>
</table>

in Ts65Dn partially trisomic mice (Martinez-Cue et al., 2002; Baamonde et al., 2001), in Lurcher mutant mice characterised by a massive degeneration of the cerebellar cortex (Caston et al., 1999), in CA1-specific NMDA receptor 1 subunit knockout mice which are profoundly impaired in object recognition, olfactory discrimination and contextual fear memories (Rampon et al., 2000b) and in transgenic mice that develop a neurodegenerative syndrome which closely models Huntington disease (Van Dellen et al., 2000). As shown by the latter report, exposure of these mice to a stimulating, enriched environment from an early age helps to prevent the loss of cerebral volume and delays the onset of motor disorders. As for Martinez-Cue and co-workers (Baamonde et al., 2001; Martinez-Cue et al., 2002), they found that, in Ts65Dn mice, the enrichment effect was gender-dependent.

Beneficial effects of enriched experience were also reported in animals that sustained either focal or global ischemic injury (e.g., Briones et al., 2000; Puurunen et al., 2001a). Biernaskie and Corbett (2001), for instance, found that enriched rehabilitation (a combination of enriched experience and skilled reach training) after middle cerebral artery (MCA) occlusion resulted in a dramatic improvement in skilled use of the impaired forelimb as measured by the reaching and beam-walking tasks. In addition, behavioral recovery was long lasting and occurred even though treatment started only 15 days after injury to both the cortex and striatum. Finally, ischemic animals exposed to enriched rehabilitation had significantly greater dendritic arborization...
Lesion specificity was al-

2.1.3.1. Lesion specificity.


observed a decrease in the number of newly generated gran-

ter 5,7-dihydroxytryptamine lesions of the dorsal and medial

5-HT innervation due to fimbria–fornix lesions. Indeed, af-

one possible explanation of such specificity of environmental

1985; Will, 1981; Will and Kelche, 1992 ). Data accumu-

ready documented during the 1970s and has been analysed

( Dalrymple-Alford and Kelche, 1987; Kelche et al., 1987,

lesions of the afferent-efferent systems of the hippocampus

hippocampal lesions, but not after certain others such as

produced traumatic cortical injury (TBI; Hamm et al., 1996;

Passineau et al., 2001), surgical lesions of the nucleus basalis magnocellularis (Sauro et al., 2001; Westhead et al.,

2000), reticular thalamic lesions (Sauro et al., 2001), medial

prefrontal cortex lesions (Widdell et al., 2000), hippocampal

formation lesions (Galani et al., 1997), section of the

fimbria–fornix fibre bundles (Van Rijzigen et al., 1997) or

unilateral lesions of the sensorimotor cortex (Christie and

Dalrymple-Alford, 1994).

Other cerebral and/or behavioral disorders that were

attenuated or abolished by an enriched experience were

those resulting from aging (Fernandez-Teruel et al., 1997;

Kobayashi et al., 2002) or from a pharmacological treat-

ment (prenatal exposure to alcohol, Rema and Ehner, 1999;

Wainwright et al., 1993; prenatal exposure to antia-
drenergic antihypertensive drugs, Ryan and Pappas, 1990;

methylazoxymethanol-induced microcephaly, Ueda et al.,

2000). Beneficial effects were also reported when disorders

were induced by environmental toxicants (lead intoxica-
tion during development, Lee et al., 2000; Schneider et al.,

2001) or by inadequate life conditions (low maternal care,

Bredy et al., 2001; social isolation, Hellemans et al., 2001;

neonatal anoxia, Iuvone et al., 1996).

2.1.3. Specificity of enrichment effects in brain-damaged

animals

If the generality of postoperative environmental effects

was expanded over the last years, one should, however, remember that its specificity has also been underlined in several reports. It appears that these effects may be lesion-
specific, task-specific and, as reviewed recently by Kolb

(1999), age-specific.

2.1.3.1. Lesion specificity. Lesion specificity was al-

ready documented during the 1970s and has been analysed

in our previous reviews (Dalrymple-Alford and Kelche,

1985; Will, 1981; Will and Kelche, 1992). Data accumu-
lated during the 1980s confirmed earlier findings showing that

postoperative enrichment may be an effective thera-
pptic tool after certain kinds of brain damage, such as

hippocampal lesions, but not after certain others such as

lesions of the afferent-efferent systems of the hippocampus

(Dalrymple-Alford and Kelche, 1987; Kelche et al., 1987,


As concerns, for instance, the septo-hippocampal system, one possible explanation of such specificity of environmental

effects may be linked to the drastic decrease of hippocampal

5-HT innervation due to fimbria–fornix lesions. Indeed, af-

ter 5,7-dihydroxytryptamine lesions of the dorsal and medial

raphe nuclei and as long as the hippocampal formation was

deprived of 5-HT innervation, Breun and Daszuta (2000)

observed a decrease in the number of newly generated gran-

ule cells labeled with bromodeoxyuridine. If some effects of

environmental enrichment are due to an enhanced survival

of newly generated cells in the dentate gyrus (Kempermann

et al., 1998a; see Section 3.1 ), then complete fimbria–fornix

lesions, but not partial and selective (non-serotonergic)

lesions of the hippocampal afferents, may thus prevent en-

riched environmental conditions from fulfilling their effects.

Aspirative or electrolytic lesions of the fimbria and fornix

pathways, by reducing the serotonergic innervation of the

hippocampus, may reduce cell proliferation in the dentate

 gyrus, and then environmental enrichment will not be able to

increase the survival of cells that are not produced. Such a

hypothesis may well be applicable only to the fimbria–fornix

pathways and not to other limbic systems (Galani et al.,

1997; Will et al., 1981). In addition, in the case of hippocam-

pal injury, the adult brain may respond to environmental

enrichment as though it were an immature brain (Kolb et al.,

1998). A careful analysis of such specificity is fundamen-
tally important and necessitates comparison, within the same

experiment, of animals with different lesions, but subjected to

the same differential housing conditions and to the same

functional (behavioral, neurological, etc.) assessments.

In order to study the effects of differential housing condi-
tions on recovery from damage to different components of

the hippocampal formation, Galani et al. (1997) assessed,

within a single experiment, the behavioral outcome of bi-

lateral lesions of the hippocampus, entorhinal cortex or

subiculum or of sham surgery in rats which were postop-

eratively housed for 1 month in either an enriched or an

impoveryished environment. Rats were subsequently tested

on a battery of behavioral tasks. Confirming and extending

previous findings in rats with various (but non-excitotoxic)

lesions of the hippocampus, a postoperative enriched ex-

perience had a beneficial effect on several of the deficits

observed in the tasks used (Fig. 2).

Further, only the rats with hippocampal lesions, and not

those with lesions of other components of the hippocampal

formation (i.e., subiculum or entorhinal cortex), benefited

from enriched housing (Galani et al., 1998). However, this

environmental-induced benefit was not observed in all be-

havioral tasks used; for instance, it was not seen in a task

measuring reaction to novelty.

Thus, after damage to different components of the

hippocampal formation, the beneficial effects induced by

enriched housing conditions were shown to be both

lesion-locus- and task-dependent.

2.1.3.2. Task specificity. As shown by Kolb and Gibb

(1991), environmental enrichment attenuated deficits in-

duced by frontal cortex lesions in several behavioral tasks,

such as beam traversing and claw cutting, but did not affect

other lesion-induced deficits such as food hoarding and

grooming.

In behavioral neuroscience, there are even some tasks

that seem to evaluate the same function, but in which ani-

mal performances are differently affected by postoperative

in the undamaged contralateral cortex when compared with

all other groups.

Other kinds of brain damage whose symptoms were al-

leviated by an enriched experience were fluid-percussion-

produced traumatic cortical injury (TBI; Hamm et al., 1996;

Passineau et al., 2001), surgical lesions of the nucleus basalis magnocellularis (Sauro et al., 2001; Westhead et al.,

2000), reticular thalamic lesions (Sauro et al., 2001), medial

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fimbria–fornix fibre bundles (Van Rijzigen et al., 1997) or

unilateral lesions of the sensorimotor cortex (Christie and

Dalrymple-Alford, 1994).
differential housing conditions (Will and Kelche, 1992). For instance Dalrymple-Alford et al. (1985) found that 10 days of postoperative differential housing was sufficient to induce significant effects in rats that sustained lesions of the dor- sal hippocampus. However, these effects were opposite in two behavioral tasks with quite similar functional demands, namely the Morris water-maze task and a “dry version” of this task. In the water maze, the lesion-induced reference memory deficit was much larger in enriched rats than in impoverished rats, while in the sawdust maze with food reinforcement enriched housing exerted beneficial effects in the same rats. It thus appears that the functional demands of these two tasks were not equivalent in all respects: while the spatial memory requirements to solve the tasks were virtually identical, the level of stress and other attributes (see Kessner, 1986)—sensory, motor, spatial, temporal, motivational—may have differed importantly in these tasks.

In this study, as in another one by Van Rijssen et al. (1996) on recovery of Morris water-maze performance after fimbria lesions in rats, a relative beneficial effect of impoverishment was found. Though not fully understood, the effects of impoverishment may rely on a difference in arousability or emotionality, a higher sensitivity to cues, an increased exploration and/or a better reaction to stressful situations. Clearly, more research is needed to explain this discrepancy.

Thus, though “environmental therapy” was shown to have various beneficial effects, it has some limitations. However, a better analysis and understanding of its effects may help to increase its efficacy. Impoverished and enriched conditions may be distinguished by several aspects or compo-

![Graph](image-url)

**Fig. 2.** Mean number (+ S.E.M.) of total errors committed throughout the 12 problems of the Hebb and Williams maze task in rats sustaining various hippocampal formation and housed postoperatively for 30 days either in enriched or impoverished condition. SHAM: sham-operated; HIPP: massive hippocampus damage; SUB: subiculum damage; ENT: entorhinal cortex damage; (*P < 0.05 IC compared to EC; (#) P < 0.01 lesion compared to sham.**

nents (e.g., Beaulieu and Cynader, 1990a,b; Chapillon et al., 1999; Varty et al., 2000; Woodcock and Richardson, 2000; Zimmermann et al., 2001), such as the amount of sensory stimulation, the possibilities of physical exercise and those of training or learning. As the role of sensory stimulation has been thoroughly analysed in previous reviews (e.g., Will and Kelche, 1992) and has not been specifically addressed during the last decade, we will concentrate on the two last components of differential housing: exercise and training. However, as will be illustrated later in this review (Section 3.4), the social component of EC housing is also a major factor to take into account.

2.2. Physical exercise

2.2.1. Definition

A component of enriched experience consists of increased physical exercise as the possibilities for motor, especially locomotor activity, are increased in the enriched condition in comparison to the other environmental conditions. This is particularly true when the enriched condition contains a running wheel that allows the rodent to run long distances, generally quite a few kilometers (Kleim et al., 2002b; Widenfalk et al., 1999).

2.2.2. Effects in intact animals

When exercise has been dissociated from enrichment treatment, it appeared that exercise per se, as for instance treadmill running, may induce both behavioral and cerebral modifications, although not in aged animals (Burnes et al., 1991). In intact animals, exercise was found to improve cognitive function (Radak et al., 2001), in particular to fa-
cilitate acquisition of hippocampal-related spatial learning tasks (e.g., Anderson et al., 2000). In this last study, rats could run freely in wheels attached to their home cage for 7 weeks prior to and throughout testing. In learning the radial-maze task, rats that exercised voluntarily took 30% fewer trials to reach criterion performance than sedentary, inactive controls.

2.2.3. Effects in brain-damaged animals

However, even if physical exercise was shown to have some efficacy, it was also reported, in a comparative study, that its efficacy remains more limited than that of environ-
mental enrichment or even of social grouping. This was shown by Johansson and Ohlsson (1996) who compared the recovery of various motor performances in rats after cere-
bral infarction (right MCA ligation). The main finding of this study was that IC rats (housed together in a large cage with no activity-stimulating facilities) improved their mo-
tor performances more than rats housed in individual cages with access to a running wheel. Furthermore, rats housed in an enriched environment improved their performances sig-
ificantly more than each of these two groups (Table 2).

Moreover, whereas exposure to an enriched environment was shown to promote recovery of cognitive function after
mals or humans may require some retraining/relearning for and corresponding plastic processes to occur. First 15 days following injury, may prevent this relearning non-impaired limb during this critical period, i.e. during the human) has to relearn coordinated locomotion. Casting the after injury during which the CNS-damaged animal (or animals having the impaired limb casted (Schallert and Jones, 1993). The authors showed that restricting use of after injury in rats. Though the exercise program in this study may not have been intense or long enough to produce cognitive or motor effects, it was sufficient, as we will see in Section 3, to elevate BDNF mRNA in specific regions of the hippocampus.

One kind of exercise that seems effective in humans with CNS injury is constraint-induced motor activity (e.g., Kunkel et al., 1999). This therapy involves constraining the limb that is less affected by CNS injury and, more importantly, "shaping" the affected limb movements for many hours a day for several consecutive weeks (Taub et al., 2002). Such a therapeutic strategy assumes that behavioral events are absolutely necessary for the neural changes to take place, especially and perhaps exclusively (see Schallert and Jones, 1993) after CNS damage. However, research in rats with unilateral injury to the forelimb includes that "learning and memory formation are taking place at a greater rate in the EC than in the SC or IC situations" (p. 208). They also provided strong arguments supporting the conclusion that EC–IC differences are the effect of only the differential opportunity to learn, and not of other variables such as handling, locomotion, stress, maturation effects or altered sensory input. In that chapter, they stress particularly the fact that direct interaction of the rats with the enriched environment is necessary to obtain the usual enrichment effects (see, for instance, Ferchmin et al., 1975).

In a recent review on use-dependent plasticity, Rosenzweig and Bennett (1996) came to the conclusion that the effects of an enriched experience are similar to those of formal training. This conclusion may suggest that, in a rehabilitation perspective formal training (with active interaction with the environment) may efficiently substitute for enriched experience. What is the evidence for this statement?

<table>
<thead>
<tr>
<th>Beam score</th>
<th>EC</th>
<th>SC</th>
<th>IC ± wheel</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>4.8 ± 0.8</td>
<td>3.8 ± 1.4</td>
<td>1.7 ± 1.3*</td>
</tr>
<tr>
<td>13 weeks</td>
<td>5.1 ± 0.4</td>
<td>3.4 ± 1.2</td>
<td>1.7 ± 1.1*</td>
</tr>
<tr>
<td>Rotating pole</td>
<td>5.4 ± 1.3</td>
<td>2.5 ± 1.9</td>
<td>0.7 ± 0.9*</td>
</tr>
<tr>
<td>13 weeks</td>
<td>5.8 ± 0.5</td>
<td>2.7 ± 2.6</td>
<td>1.3 ± 1.9*</td>
</tr>
</tbody>
</table>

Score 6: rat traverses beam or pole with no difficulty, score 0: rat falls down. Adapted from Johansson and Ohlsson (1996).

† Significantly different from enriched condition.

* Significantly different from standard condition.

TBI (Hamm et al., 1996) as already mentioned, 18 days of forced treadmill exercise was found by Hicks et al. (1998) to have no significant effect on spatial memory and motor performance following comparable fluid percussion brain injury in rats. Though the exercise program in this study may not have been intense or long enough to produce cognitive or motor effects, it was sufficient, as we will see in Section 3, to elevate BDNF mRNA in specific regions of the hippocampus.

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In many reports, "training" is loosely defined. Nevertheless, most people accept, at least implicitly, that "training" consists of carrying out a specific task that necessitates a learning process to occur. Thus, training consists, in some studies, of a cognitive task with a strong spatial component, but in most reported cases, of a more or less skilled motor task, sometimes called "acrobatic training". For instance, in the acrobatic condition, rats were given progressively longer and more difficult trials on an elevated path consisting of balance beams, see-saws, rope bridges, and other obstacles, until they reached five trials and seven obstacles each day after the first week (Black et al., 1999).

### 2.3.2. Effects in brain-damaged animals

Training was shown to attenuate motor deficits induced by motor cortex lesions, especially in the case of acrobatic training (Jones et al., 1999). Similar findings were reported after focal ischemia producing a cortical infarct, but in this case motor skill training was combined with enriched housing (Biernaskie and Corbett, 2001). Treadmill training was also reported to improve locomotor function, albeit only partially, after incomplete spinal cord injury in rats (Thota et al., 2001) and in humans with incomplete, chronic, thoracic spinal cord injuries (Protas et al., 2001). Similar training was even found to have enduring effects in cats with complete transaction of the spinal cord (at the T12–T13 junction; De Leon et al., 1999).

It should be noted that the time of starting the training program may be critical for functional recovery after focal brain ischemia. Indeed, whereas delayed training (i.e., starting only 7 days after ischemia) was shown to result in overall good performance, early training (starting 1 day after ischemia), with or without immobilization of the intact forelimb, exacerbated the effects of brain damage (Risedal et al., 1999). Although there are only few reports on the effects of training on functional recovery, these effects suggest that at least part of the EC effects may be due to the learning opportunities it provides.

Enriched housing and its components all appear as somewhat efficacious for promoting recovery from CNS damage. Learning to re-use the damaged CNS seems critical, but all that contributes to this achievement can be considered as positive: exercise, social grouping, enrichment of the social and physical environment, physical exercise and specific training. It is not astonishing that enriched housing which combines most of these characteristics appears often as a very potent therapeutic tool, and even, when compared with other treatments, as the most potent one.

However, one basic question remains: How can the effects on recovery be explained at the level of CNS structure and function? Answering this question may contribute to further improve the efficiency of environmental therapy and to better understand the neurobiology of learning and memory processes.

### 3. Effects on CNS

Recovery of behavioral function may be due to changes in non-damaged CNS areas and, it is worth, therefore, to take into account not only the effects of enrichment and of its major components on lesion-dependent plastic processes in damaged CNS areas, but also on those observed in intact CNS areas after injury as well as those observed in normal brains.

#### 3.1. Enrichment effects in intact and brain-damaged animals

Over the last half-century, experience-dependent cerebral modifications have been well documented in intact animals. Rats raised in EC develop heavier cerebral (particularly occipital) cortices, with more glial cells (especially oligodendrocytes), larger cell bodies, increased dendritic arborizations (Ip et al., 2002), larger synapses (for review, see Rosenzweig and Bennett, 1996), enhanced packing density of synaptic vesicles in synapses (Nakamura et al., 1999), and, depending on the age, increased or decreased spine density (Kolb et al., 1998). In cats, the richness of the environment was shown to reduce the numerical density of neurons in areas 17 and 18, an effect which might be due to an increase in the dendritic tree arborizations of neurons and in the number of glial cells leading to an increase of the dimensions of the occipital region of cerebral cortex (Beaulieu and Colonnier, 1989a,b). Early reports showed also that enriched housing affects brain neurochemistry, namely that of the cerebral cholinergic system (e.g., Kreek et al., 1960).

Over the last 13 years, enriched housing was shown to affect not only brain neurochemistry and neurophysiology, but also neurogenesis, even in the adult brain, by increasing the survival of newborn neuronal cells in both mice and rats (Kempermann and Gage, 1999; Kempermann et al., 1997, 1998a; Nilsson et al., 1999; Van Praag et al., 2000). Environmental enrichment does not seem to affect proliferation of progenitor cells, rather it appears to have a survival-promoting effect that is selective for neurons (Fig. 3). One should note that all these findings were obtained in intact animals and, as underlined by Rakic (2002), they might be different in animals with CNS damage, because "damaged or degenerating neurons can activate cyclins (cell-cycle-associated proteins) and initiate abortive DNA synthesis without mitosis" (Rakic, 2002, p. 67). One may also assume that the survival-promoting effect observed in intact animals is related to the accumulation of learning experiences in the EC and that it allows increased performances, especially in those depending on the integrity of the hippocampus (Shors et al., 2001).

In addition to those effects observed in intact animals, enriched housing was shown to have protective effects against the deleterious effects of aging (Coq and Xerri, 2001; Escorihuela et al., 1995; Fernandez-Teruel et al., 1997; Kempermann et al., 1998b; Mattson et al., 2001; Nakamura...
A single exception; Hicks et al., 2002) that EC enhances the last 13 years, it has been shown repeatedly (with only one cell death in the rat hippocampus (Young et al., 1999). Enriched housing was also shown to reduce by 45% spontaneous apoptotic enting could be detected between enriched animals and isolated animals. At 4 weeks after the last BrdU injections, the animals housed in the en-riched environment had a significantly higher density of BrdU-positive cells than did the isolated animals (** P < 0.01). From Nilsson et al., 1999, with permission.

Finally, in animals with brain damage, enriched housing was also repeatedly shown to foster plastic processes in some CNS areas that were not damaged. Kelche and Will (1982) carried out two experiments which both showed that dorsal hippocampal lesions decreased the branching and number of spines of basilar dendrites in layer V pyramidal cells of area 17. In rats with such lesions, they found that enriched housing increased the number of spines in this undamaged cortical area. However, such effects may be lesion-specific as was recently shown by Ip et al. (2002) in rats that sustained TBI.

Similarly, Johansson and Belichenko (2002) showed recently that contralateral to a cortical infarct produced by MCA occlusion in spontaneously hypertensive rats, pyramidal neurons in layers II/III, which have extensive intracortical connections that may play a role in cortical plasticity, had significantly more spines in rats housed for 3 weeks after surgery in an enriched environment than in SC control rats. This effect was more limited than in intact rats, but it may be sufficient to mediate compensatory processes underlying the EC effect on functional recovery following focal ischemia (Biernaskie and Corbett, 2001; Grabowski et al., 1995; Johansson, 1996; Johansson and Ohlsson, 1996; Ohlsson and Johansson, 1995). As shown by Puurunen et al. (2001b), rats housed in an enriched environment had an increased number of Fos-positive neurons in the granule cell layer of the dentate gyrus when assessed after a water-maze learning task. Moreover, this increase in the expression of transcription factor Fos was observed in sham-operated and, to some extent, in rats which underwent transient global ischemia.

3.2. The effects of physical exercise in intact animals

What may be stressed is that some of the components of EC, such as exercise, induce some of the cerebral changes just mentioned, however not necessarily all of them. For instance, voluntary exercise was reported to increase the thickness of the motor cortex (Anderson et al., 2002) and the expression of trophic factors in the brain such as BDNF, NGF and FGF (e.g., Berchtold et al., 2001; Gomez-Pinilla et al., 1997; Gomez-Pinilla et al., 2001; Neeper et al., 1995; Neeper et al., 1996; Widenfalk et al., 1999). Exercise was also shown to induce angiogenesis in both the cerebellar and motor cortices (Black et al., 1990; Kleim et al., 2002b) and to increase cholinergic and serotonergic neurotransmission (Bequet et al., 2001; Chauflolff, 1997; Chenmou et al., 2001; Fordyce and Farraz, 1991a; Fordyce et al., 1990; Gomez-Merino et al., 2001). Both acute and chronic vol-untary exercise affect the expression of hippocampal genes as revealed by microarray: an up-regulation is observed in many genes, especially in those related to the glutamater-gic system, while genes related to the GABA system are down-regulated (Molleni et al., 2002). As does enriched housing, voluntary exercise also enhances neurogenesis in the hippocampus of adult animals (Van Praag et al., 1999). It is likely that this exercise-induced increase of neurogenesis is related to the exercise-induced increase of IGF-I uptake (Carro et al., 2000; 2001). Indeed, cellular proliferation is blocked by IGF-I antisera (Trejo et al., 2001).

In contrast to enriched housing, which was shown in many studies to increase synapticogenesis, exercise was not reported to affect this process. The study by Black et al. (1990), for instance, showed that the size and the number of synapses per Purkinje cell are similar in the inactive and exercised
groups, whether exercise was voluntary (running wheel activity) or forced (treadmill walking).

Finally, also in contrast to enriched housing, exercise was not reported to promote neuroprotection. In outpatients with seizures, physical exercise was even reported to have a seizure-precipitant effect (Nakken, 1999).

3.3. The effects of training in intact animals

If the effects of enriched housing are mainly due to an accumulation of learning experiences, it is not astonishing to find strong similarities between the effects of enriched housing and those of formal, specific training.

Like enriched housing, formal training or learning was shown to increase gliogenesis (Gomez-Pinilla et al., 1998) and to affect gross anatomy, increasing for instance the thickness of the motor cortex, the volume of the cerebellar paramedian lobe in the case of motor skill training (Anderson et al., 2002; Klintsova et al., 2002, respectively) and the size of the posterior hippocampi in the case of spatial learning in humans (Maguire et al., 2000). However, in the latter case, that of London taxi drivers who certainly accumulated more spatial learning than control subjects, Maguire and co-workers have also reported a decrease of the size of the anterior hippocampus.

In contrast to physical exercise, training/learning was found in many studies to promote synaptogenesis and to be a prerequisite factor in driving representational plasticity (e.g., Plautz et al., 2000). Significant changes in synaptogenesis were observed in the hippocampus following spatial learning (Moser et al., 1994) and in the cerebellum or motor cortex after motor skill training (Anderson et al., 1996; Black et al., 1990; Diaz et al., 1994; Jones et al., 1999; Kleim et al., 1996, 1997a,b, 1998a,b, 2002a; Klintsova et al., 1997, 1998). Aerobic training, for instance, which involves some learning, increases the number of synapses per Purkinje cell.

Concerning angiogenesis, the findings of Isaacs et al. (1992) allowed to dissociate angiogenesis associated with increased neurite volume (as seen after motor learning) from angiogenesis associated with increased metabolic demands (as seen after exercise).

As concerns neurogenesis, which Shors et al. (2001) have suggested to be causally linked to hippocampal-dependent learning, there are two reports of seemingly incongruent data. Gould et al., 1999 found that the survival rate of labeled neurons was more than two times greater in rats that had learned a hippocampus-dependent task than in those learning a similar but hippocampal-independent task (“local cue” task or “delay” conditioning during which the conditioned stimulus and unconditioned stimulus overlap). Hippocampal-dependent tasks are “spatial” learning in a water maze or “trace” conditioning during which there is a temporal gap between the conditioned stimulus and the unconditioned stimulus requiring the animal to maintain or resurrect a memory “trace” of the conditioned stimulus to associate it with the unconditioned stimulus. In contrast, Van Praag et al. (1999) found that spatial learning in a water maze produced no effect on neurogenesis in the hippocampus. Greenough et al. (1999) analysed these data and suggested a way to reconcile them. The survival of newly generated neurons may depend on what happens during an initial postproliferative period of sensitivity during which the axons of these neurons emerge from the dentate gyrus and begin to contact target cells in the hippocampal CA3 area. Gould et al. (1999) administered water-maze training 1 week after labeling the neurons, i.e., during the period of supposed maximum sensitivity of the newborn neurons. In contrast, Van Praag et al. (1999) used a very rapid water-maze procedure so that learning was likely completed before labeling of the cells.

To test the hypothesis that neurogenesis in the hippocampus is required for trace conditioning, Shors et al. (2001) injected rats with an agent, methylazoxymethanol (MAM), that kills proliferating cells. The agent was injected over 2 weeks in a carefully controlled dose that killed about 80% of new neurons in the hippocampus and impaired trace conditioning but not delay conditioning and had no apparent effect on health. Although this experiment is an important step in testing the function(s) of newly generated neurons, the results are not conclusive. For one thing, as Macklis (2001) points out, trace conditioning is more difficult than delay conditioning, so a level of impairment that does not affect delay conditioning might nevertheless affect trace conditioning. Also, MAM kills proliferating glial cells as well as neurons, and this may play a role in the impairment of trace conditioning caused by the drug treatment.

The trophic factors involved in neuronal development, survival and plasticity are also affected by learning experiences. In particular, the expression of BDNF which plays an important role in the formation and also in the retention and/or recall of spatial memory is affected by such experience. Spatial learning in a water maze or in a radial maze increases BDNF mRNA in the hippocampus (Kesslak et al., 1998; Mizumo et al., 2000) and, in senescent rats, hippocampal BDNF expression is associated with memory performance (Schaf et al., 2001). Similarly, spatial learning in a water maze contributes to the induction of basic fibroblast growth factor (FGF-2) which was shown to have a critical trophic role in a variety of neuronal types and to promote proliferation or reactivity of astrocytes (Gomez-Pinilla et al., 1998).

Overall, the effects of training/learning on the intact CNS are qualitatively quite similar to those of enriched housing. They differ, however, by the fact that training, in contrast to enriched housing, was not reported to be neuroprotective after brain injury; in fact, if provided early after focal brain ischemia, training may even exacerbate brain damage (Risedal et al., 1999). The effects of training also differ from those of exercise mainly at the levels of synaptogenesis, gliogenesis and, to a more limited extent, at that of the survival of newly generated neurons.
3.4. Comparative studies

Finally, this conclusion may be refined by taking into consideration the few studies which directly compared enriched housing, physical exercise and training. Dahlgqvist et al. (2003) have shown that the social component of EC housing increases the expression of NGF mRNA in several cortical regions and in the hippocampal CA1 region, an effect which was not observed in isolated rats with or without exercise. Otherwise, as already mentioned, recovery of motor performance after right MCA occlusion was best in EC rats and worst in IC rats although IC rats in this experiment had free access to a running wheel (Johansson and Ohlsson, 1996). This result suggests that activities that require learning are better than repetitive exercise at enhancing motor performance (see also Gentile et al., 1987; Hicks et al., 1998).

However, it might be useful for comparing the efficacy of the different treatments to know how much experience (EC, exercise, training) is needed to produce the effects. As concerns the cerebral modifications induced by the treatments, most of the studies compare only exercise and training. With the exception of neurogenesis, all dependent variables considered are more strongly affected by a training/learning experience (e.g., Kelche et al., 1995; Mattsson et al., 1997 and 1999; this latter conclusion deserves, however, some qualification and may be better understood if one takes into account the temporal relationship between the learning experience and the cellular events. Both enriched housing and training have been shown to increase synaptogenesis, but it is plausible that they will do so in newly generated cells and thereby increase their survival only when their axons have sufficiently grown and reached their target cells. Testing this hypothesis will certainly contribute to the understanding of the neurobiology of learning and memory.

4. Conclusion

In most studies, it is not clear whether enriched experience, physical exercise or training promotes compensatory effects or genuine recovery. There are, however, some studies, in addition to those already mentioned (Biemanske and Corbett, 2001; Johansson and Belichenko, 2002; Kelche and Will, 1982), which demonstrate that compensatory effects are most probably the adequate explanation of the observed recovery, whether considering the behavioral level or the cerebral level (e.g., Ip et al., 2002; Klein et al., 1998a; Nudo and Mikkelsen, 1996; Nudo et al., 1996a,b). Indeed, recovery of function is often due to compensation of function. Animals with CNS injury learn to use alternative behavioral strategies for dealing with the lesion-induced deficit (e.g., Mikhyaeva et al., 1994; Whishaw, 2000). Even when they do not change their strategy, they may show recovery without a genuine return to normal function: using a behavioral task (two-way active avoidance) which is facilitated by the sustained (hippocampal) lesions and considering that genuine functional recovery can be interpreted as a return toward normal level of function, i.e., in this case, an impairment of performance, we have shown that an enriched postoperative or post-traumatic experience promotes a compensation of function rather than a genuine return to normal function (Will and Kelche, 1979).

Obviously, research on underlying processes should be expanded. Such research might help to understand some of the reported data, namely some of the previously mentioned specificities. It might also help to increase the efficacy of rehabilitative therapy or of combined treatments such as combined intracerebral grafting and postoperative enrichment (e.g., Kelche et al., 1995; Mattsson et al., 1997 and for a review, Dobroisy and Dunnett, 2001) or combined pharmacological and environmental therapies (e.g., Feeney, 1997; Johansson et al., 1997; Purrunen et al., 1997; Rosenzweig, 2002; Tees, 1999a,b; Walker-Batson, 2000; Winocur and Greenwood, 1999).

Overall, one may note that (1) information about both the generality and specificity of postoperative environmental effects have been expanded over the last 13 years, (2) under many circumstances, enriched experience constitutes a potentially powerful “therapeutic tool” which combines the effects of its components, and (3) in addition to its neuroprotective effects which may reduce secondary damage, enriched housing and its components may facilitate compensation, namely by reorganisation in intact parts of the CNS. The situation has not dramatically changed over the last 13 years, with perhaps the exception of the EC effect on neurogenesis (which was first reported by Beaulieu and Colonnier, 1989a,b, and by York et al., 1989). The specific efficacy of EC, as compared to exercise or training, may be induced not only by an additive effect of its components but also by the interaction of their effects. Moreover, the social component that is included in EC may increase the effects of both physical exercise and training.

On the basis of cumulative evidence, environmental enrichment appears now more and more as a potential therapeutic tool of high efficacy and low risk (e.g., Galani et al., 1997; Kelche et al., 1995; Baamonde et al., 2001; Martinez-Cue et al., 2002). However, therapeutic efficacy has to be determined by research of clinicians to specify what are enriched environments for rehabilitation of brain-damaged patients (e.g., Bach-y-Rita et al., 2002; Day et al., 2000; Rosenzweig, 2002).

An emerging trend in this area is the use of virtual reality displays for assessment and rehabilitation. An early paper on this topic pointed out that a basic justification for use of virtual environments in rehabilitation is firmly rooted in the neuroscience literature (e.g. Rose et al., 1998). “over the last half century there has been a wealth of published evidence
that enriching the environments of laboratory rats stimulates neuroplastic changes in the cerebral cortex, enhances learning and problem solving in normal rats and reduces cognitive impairment in brain damaged rats” (Rose et al., 1998, p. 233). To date, most of the publications in this area have been programmatic or pilot studies (e.g., Jack et al., 2001; Tarr and Warren, 2002).

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