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# How Does an Enriched Environment Impact Hippocampus Brain Plasticity?

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<http://dx.doi.org/10.5772/intechopen.71426>

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## Abstract

Brain plasticity is profoundly impacted by one's living environment. The hippocampus, involved in learning and memory, is highly susceptible to plasticity. Raising rodents in an "enriched environment" (EE) increases learning and memorization aptitudes and decreases the anxiety of the animals. EE consists of a combination of running wheels for voluntary physical exercise, complex inanimate toys, nests, mazes, etc. all of which favor sensory stimulations and social enrichment. EE housing concomitantly increases proliferation and survival of neurons and glia in the dentate gyrus of the hippocampus, induces changes in neuronal morphology, modifies synaptic plasticity, and favors angiogenesis. The mechanisms underlying the effects of EE on plasticity, which have recently been investigated are reviewed here, including the role of glia, the involvement of molecular factors including neurotransmitters (glutamate), neurotrophic factors (BDNF), adipokines (leptin and adiponectin), chemokines, cytokines, and hormones (corticosteroid and thyroid hormones), and at a higher level, the various systems involved (neural networks and hormonal systems). We emphasize recent findings that demonstrate the major role of the immune system in modulating EE-induced changes to hippocampal plasticity. This process involves a variety of immune cells (including macrophages, microglia, natural killer, B-cells, and T-cells), although the mechanisms are yet to be fully elucidated.

**Keywords:** hippocampus plasticity, enriched environment, neurogenesis, synaptogenesis, synaptic plasticity, neurotrophic factors, cytokines, chemokines, hormones

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## 1. Introduction

One's living environment has a profound impact on both health and brain plasticity. Indeed, an increasing number of studies show that exposure to prolonged stress can increase the risk

of not only cardiovascular diseases and cancers but also neuropsychiatric and neurodegenerative diseases [1]. In contrast, a stimulating environment can contribute to improve health and behavioral performances by optimizing brain plasticity. Neuroplasticity, also known as brain plasticity or neural plasticity, induces lasting change to the brain throughout an individual's life course. Neuroplasticity can be observed at multiple scales, from microscopic changes in individual neurons to larger scale changes, such as cortical remapping in response to injury. Although neuroplasticity is more efficient during development and in youth, it persists in adulthood [2]. Neuroplastic change through activity-dependent plasticity has significant implications for healthy development, behavior, learning, memory, and recovery from brain damage and can be elicited by thoughts, emotions, and environmental stimuli.

The hippocampus is involved in emotion and mood regulation, as well as learning and memory. This cerebral structure is very susceptible to plasticity. Hippocampal plasticity is a general term that describes many different phenomena at different levels. For instance, at the macroscopic level, a decrease in hippocampal volume has been observed in depressed patients [3]. Conversely, a stimulating environment, such as high-level spatial orientation training, leads to an increase in hippocampal volume [4]. At the cellular level, the number of new neurons that appears in the dentate gyrus of the hippocampus and their survival is linked to their insertion in the local hippocampal network. This response can also vary depending on the experience and enrichment of the living environment. Similarly, synaptic connections can be remodeled by experience, which can be measured both at the functional level (neurotransmitter release and electrophysiological recordings of spontaneous activity) and at the morphological level (number and shape of contacts between neurons). Finally, these changes can be accompanied by variations in the shape, number, and function of the other cells that surround the neurons, including glia, endothelial cells, and resident immune cells such as microglia and perivascular circulating macrophages.

Chronic stress and related pathologies, such as depression, induce “deleterious” effects on hippocampus plasticity and have been widely documented. However, the “positive” effects on brain plasticity, in response to an enriched and stimulating environment, have only been investigated more recently. An enriched environment (EE) can be modeled in rodents by housing mice in larger cages equipped with toys and nesting material to promote sensory stimulation and running wheels to promote voluntary physical activity. In addition, mice can be housed in large groups (10–12) to favor social interactions and the establishment of a hierarchy [5]. Depending on the studies, characteristics of EE housing can vary [6]. These variations include different strains, genotypes, or ages of mice and rats. The duration of EE, the type of enrichment objects, and the frequency of object changes also differ from one study to the other. Finally, standard “nonenriched” conditions (standard environment, SE which is used as control in comparison on the EE) vary, as some studies use isolated mice while others house up to five mice in a cage. A more standardized EE protocol would improve consistency between studies, and yet, in most cases, EE is shown to induce large benefits, including prevention or reduced incidence of a large number of diseases in both nonpathological and pathological conditions; depending on the duration, exposure to an EE can improve performance in a variety of hippocampus-dependent behaviors in rodent models, even in adulthood [7]. Enrichment has been shown to enhance memory function in various learning tasks [8]. Compared to mice housed in standard conditions, EE-housed animals perform better in

learning and memorization tests, such as the Morris Water Maze and the Barnes Maze which involve both working [9] and spatial memory [10, 11]. EE reduces the cognitive decline associated with aging [5] and decreases anxiety in mice [12]. EE also has remarkable beneficial effects on the behavior of animals with neurological disorders, as demonstrated in several models of neurodegenerative diseases or different types of brain lesions [13]. The aim of the present chapter is to review the increasing volume of data that report EE-induced changes in plasticity and to describe the proposed mechanisms of action underlying these changes.

## 2. Effect of EE on hippocampal plasticity

At the neuroanatomical level, EE increases the hippocampus volume [14]. This can be explained by an increase in the density of dendritic arborization [15, 16], the length and the volume of myelinated fibers [17], and the number of dendritic spines in hippocampus [18].

At the cellular level, EE has been shown to increase neurogenesis in the hippocampus dentate gyrus (DG) as measured by injections of BrdU, which labels dividing cells and can be detected using immunocytochemistry techniques days or weeks later to measure proliferation and survival [7, 19]. The extent of this increase in neurogenesis is dependent on the age of the mouse and the duration of EE housing. Indeed, the effects of EE are more pronounced for housing durations of 4–6 weeks, compared to 8 weeks, as well as in younger animals [20].

Synaptogenesis has also been shown to increase in response to EE housing [21, 22]. The establishment of new synapses can be evaluated from a morphological point of view (for instance by labeling the post-synaptic neurons and counting the spines using confocal microscopy) or from a functional point of view (using electrophysiology). It is now well established that functional activity-dependent changes parallel structural modifications [23–25], although a distinction between anatomical and functional synaptic structure has been observed [26, 27]. In the hippocampus, the majority of synapses that connect pyramidal neurons are located on dendritic spines, and synapse size is related to synapse strength [28–31]. Indeed, mice raised in EE present changes in synapse density, bouton morphology [32, 33], and hippocampal neuronal activity compared to mice raised in a SE; however, these changes can vary depending on the time spent in the housing environment and the age of the mouse (juvenile versus adult) [20]. Four weeks in EE increased the number of excitatory inputs received by pyramidal neurons in CA1 as measured by whole-cell patch clamp in acute hippocampus slices, in accordance with the observed increase in spinogenesis. However, for longer EE housing periods (6–8 weeks), despite maintenance of the increased number of spines, the number of excitatory inputs received by pyramidal neurons in CA1 returns to a lower level suggesting that synapses become silent by a homeostatic process of synaptic scaling [34]. Alternatively, the development of inhibitory synapses subsequent to habituation and the reduced attraction of the animals to their environment cannot be ruled out [35]. Overall, this suggests a distinction between anatomical spines and functional synaptic structures. Extra-spines could be maintained following enrichment periods even when they do not establish functional synapses. These silent structures could constitute a pool of synapses ready to be activated upon stimulation and might play a major role in learning, allowing EE mice to learn faster than their matched controls raised in standard conditions [36, 37].

EE also induces changes in long-term potentiation (LTP) as observed in field potentials recorded in the CA1 region after high-frequency stimulation of the Shaffer collaterals *in vitro* in acute hippocampal slices. However, these changes are complex and again depend on the protocol used. For example, EE has been shown to enhance [38–40], impair, or even have no effect on LTP at the CA3–CA1 synapse [41–44]. Because LTP induction and expression is age dependent [43, 45, 46], EE might have different consequences on plasticity of these synapses depending on the duration of enrichment and the postnatal developmental stage of the mice. This was demonstrated in an accurate kinetic analysis, where increases in LTP were found in adult mice after 4 weeks in EE, but decreases in LTP were observed after 4 weeks EE in juvenile mice, likely because CA3–CA1 excitatory synapses were already potentiated in these conditions, which induced a ceiling effect [20].

In accordance with EE regulation of morphology and function of excitatory synapses, EE can also regulate glutamatergic AMPA [47] and NMDA receptor subunit expression [48]. Similarly, in glutamatergic neurons, the expression of synaptic proteins such as PSD95, a post-synaptic scaffold protein, is also increased by EE housing [49, 50].

Immunomodulatory factors have recently been shown to play a key role in EE hippocampal plasticity effects [51–53]. Among them, two important players are CD200, which is a membrane glycoprotein expressed by various cell types (including B cells, a subset of T cells, thymocytes, endothelial cells, and neurons) and CX3CL1, also known as fractalkine, a chemokine which plays an important role in the neuronal control of microglia recruitment and activation [54, 55]. CX3CL1 was recently found to impact synaptic development and integrity. Indeed, CX3CR1 deficiency increases hippocampal plasticity and spatial memory, blunting the potentiating effect of EE [56] and thus showing that CX3CL1/CX3CR1 signaling is necessary for EE-dependent hippocampal plasticity processes.

In pathological conditions such as influenza infection, neuroinflammation alters hippocampal plasticity [57, 58]. This central inflammation is characterized by an increase in the hippocampal expression of proinflammatory cytokines (including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) and a decrease in the expression of neurotrophic (BDNF and NGF) and neuromodulatory factors. EE attenuates hippocampal neuroinflammation and therefore prevents the plasticity alteration [59–61].

Finally, EE also stimulates gliogenesis [62] and favors angiogenesis [63–65], consequently improving nutrient availability for neurons and the elimination of toxic waste from brain.

### 3. Cellular and molecular mechanisms

#### 3.1. Neurotrophic factors

At the molecular level, EE increases the expression of neurotrophic factors in the hippocampus. These factors include BDNF [66], IGF-1 [67], and NGF [68] and may affect hippocampal neurogenesis and synaptic plasticity [69].

It is not yet clear which cells produce these factors. They could be produced by neurons following increased neuronal activity upon stimulation, by glial or by endothelial cells.



However, the neurotrophic factors that are increased by EE conditions can act in various cell types, including neurons (promoting both neurogenesis in the DG and synaptogenesis), astrocytes (regulating metabolism, recycling and elimination of metabolites), microglia (regulating synaptic pruning), oligodendrocytes (promoting myelination), and endothelial cells (promoting angiogenesis). Mice raised in EE thus benefit from this virtuous circle; increased neuronal activity will increase neurotrophic factor release, which in turn will increase neurogenesis and synaptogenesis, thus promoting more neuronal activity.

### 3.2. Adipokines

EE also induces changes in levels of adipokines, cytokines that are produced by the white adipose tissue [70]. Examples include adiponectin (the concentration of which is increased by EE) either in plasma or CSF and leptin (decreased in EE), likely due to a decrease in fat mass in EE mice as a consequence of exercise [71, 72]. The variations in blood adipokines have consequences in the brain, including the hippocampus, as receptors of both adipokines are expressed within the central nervous system. For instance, it has been observed that in EE, microglia and perivascular circulating macrophages adopt an M2 anti-inflammatory profile *via* an adiponectin-dependent mechanism [73], likely contributing to the antidepressant effects of EE in a murine model of depression.

### 3.3. Hormones

Several hormonal systems are also regulated in EE. Indeed, EE has been shown to regulate levels of corticosterone and noradrenaline [71]. Muscular exercise could also increase the release in the blood of endogenous molecules such as endocannabinoids, BDNF, which may be released in response to cortisol [74] and beta-endorphins, which are released by muscle-afferent nerve endings upon exercise [75].

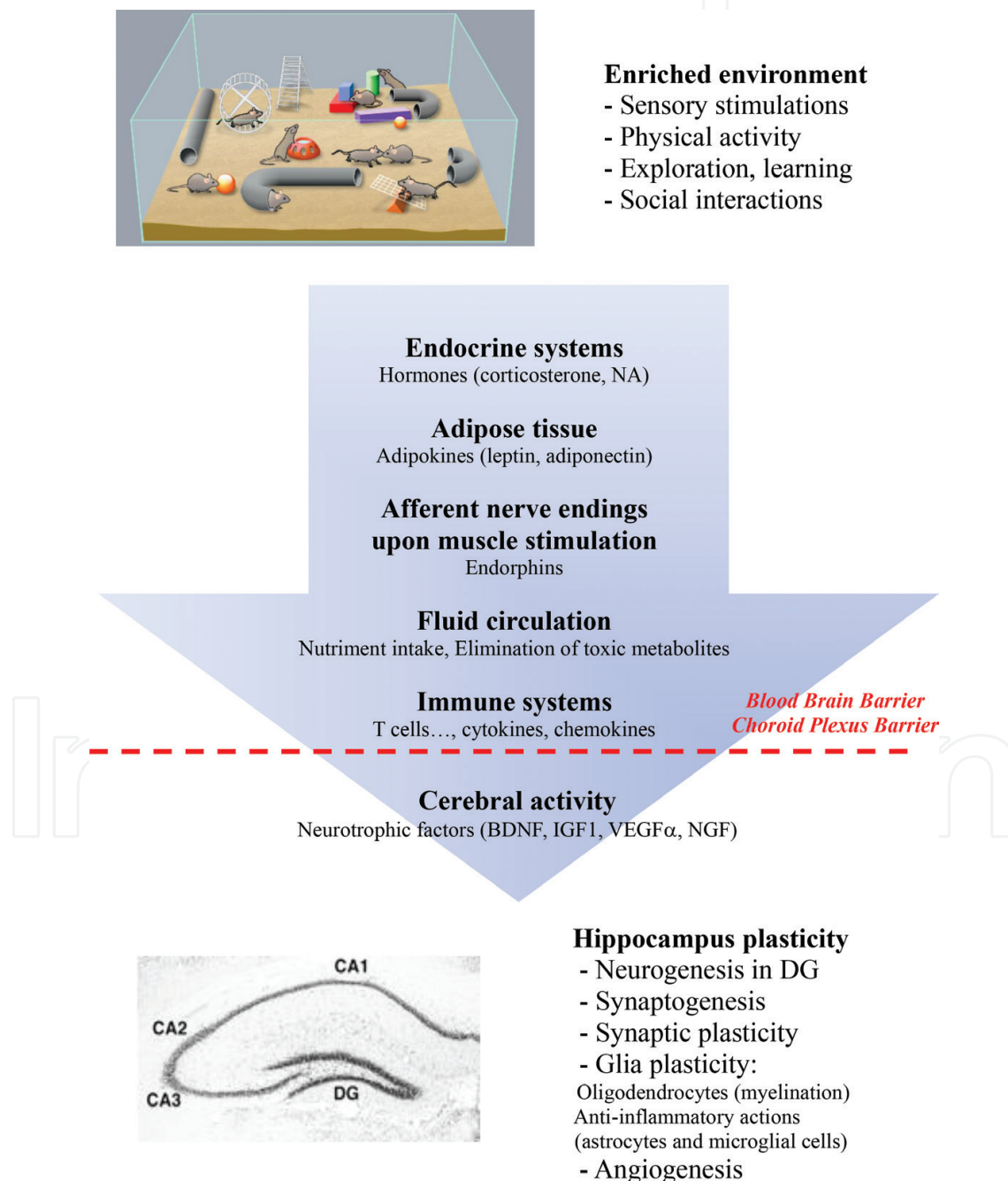
### 3.4. Immune system

The immune system is primarily involved in the surveillance of body tissues and in providing protection from infectious agents and various forms of injury. The idea that the immune system could be involved in normal neurobehavioral processes was suggested more than a decade ago, although initially, it did not receive much attention. Subsequent findings by Drs. M. Schwartz, J. Kipnis, and their colleagues showed that circulating T cells play a general supportive role in brain functioning, including cognitive abilities and hippocampus neurogenesis [76–81]. Additional work has shown that EE-induced neurogenesis is depressed in immunodeficient (SCID) mice, suggesting a putative role of T cells in EE-related effects on hippocampus plasticity [82]. The mechanisms by which T cells can influence hippocampal plasticity are still unknown. T cells do not enter the brain parenchyma in nonpathological conditions, but a small number of T cells are present in the brain blood vessels, in the choroid plexus, and in the meninges. T cells are thought to act at distance by releasing factors such as cytokines or chemokines in the blood or CSF or by interacting directly with endothelial or epithelial cells of the choroid plexus. Alternatively, T cells could act from the periphery by modulating the hormonal systems that regulate brain plasticity.

These innovative studies paved the way for future investigations of other immune cells, including but not limited to natural killer cells [83], B cells [84], macrophages [73] and monocytes [85], and their putative roles in modulating the effects of EE on hippocampal plasticity.

## 4. Conclusion

The effects of EE on the hippocampus are numerous and complex (**Figure 1**). They simultaneously involve multiple cell types and their interactions, both locally at the level of the



**Figure 1.** Enriched environment can modulate hippocampus plasticity through multiple pathways.

hippocampus and throughout the whole body, including muscles, bones, adipose tissue, endocrine, immune, and circulatory systems. Dysfunction in any of these components could subsequently reduce or impair the beneficial effects of EE. However, the pleiotropic effects of EE contribute to the prevention of vascular and neurodegenerative brain diseases. How does one define an EE for humans? It probably includes activities associated with spatial learning and motor coordination, such as sport, artistic and creative activities (for example, music or dance), learning new skills, training memory, playing games, and the presence of a developed social life, whereas life as a recluse, a prisoner, in temporary or permanent isolation could undermine the cognitive and learning abilities of the hippocampus. Elderly citizens are at particular risk of such decline. Conversely, a stimulating environment, such as that associated with a balanced lifestyle, should favor hippocampus activity, leading to enhanced learning aptitudes and improved adaptability to new situations.

## Acknowledgements

Our thanks to the UCA Office of International Scientific Visibility for comments on the English version of the manuscript. Hadi Zarif was financed by a Labex ICST (Ion Channel Science and Therapeutics) fellowship. This work was partly supported by Fondation de l'Avenir AP-rm.-16-011-chabry.

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