Chapter 1

How Does an Enriched Environment Impact Hippocampus Brain Plasticity?

Hadi Zarif, Sarah Nicolas, Agnès Petit-Paitel, Joëlle Chabry and Alice Guyon

Additional information is available at the end of the chapter

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

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

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, button 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-1β, IL-6, and TNF-α) 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].

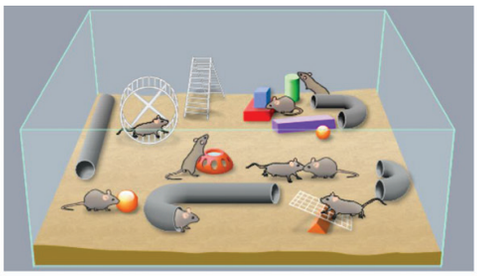
3.4. Immune system

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



Enriched environment
- Sensory stimulations
- Physical activity
- Exploration, learning
- Social interactions

Endocrine systems
Hormones (corticosterone, NA)

Adipose tissue
Adipokines (leptin, adiponectin)

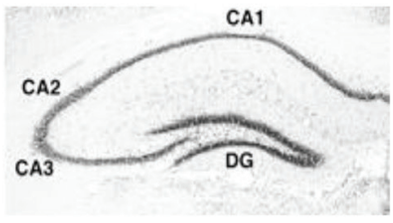
Afferent nerve endings upon muscle stimulation
Endorphins

Fluid circulation
Nutriment intake, Elimination of toxic metabolites

Immune systems
T cells…, cytokines, chemokines

Blood Brain Barrier
Choroid Plexus Barrier

Cerebral activity
Neurotrophic factors (BDNF, IGF1, VEGFα, NGF)



Hippocampus plasticity
- Neurogenesis in DG
- Synaptogenesis
- Synaptic plasticity
- Glia plasticity:

Oligodendrocytes (myelination)
Anti-inflammatory actions
(astrocytes and microglial cells)

- Angiogenesis

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.

Author details

Hadi Zarif, Sarah Nicolas, Agnès Petit-Paitel, Joëlle Chabry and Alice Guyon*

*Address all correspondence to: alice.guyon@ipmc.cnrs.fr

UMR 7275, CNRS, University of Nice-Sophia Antipolis, Institute of Molecular and Cellular Pharmacology, Côte d'Azur University, Valbonne-Sophia Antipolis, France

References

[1] Salleh MR. Life event, stress and illness. Malaysian Journal of Medical Sciences. 2008;**15**(4): 9-18

[2] Hensch TK. Critical period plasticity in local cortical circuits. Nature Reviews Neuroscience. 2005;**6**(11):877-888

[3] Videbech P, Ravnkilde B. Hippocampal volume and depression: A meta-analysis of MRI studies. The American Journal of Psychiatry. 2004;**161**(11):1957-1966

[4] Maguire EA et al. Navigation-related structural change in the hippocampi of taxi drivers. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(8):4398-4403

[5] Sale A, Berardi N, Maffei L. Enrich the environment to empower the brain. Trends in Neurosciences. 2009;**32**(4):233-239

[6] Redolat R, Mesa-Gresa P. Potential benefits and limitations of enriched environments and cognitive activity on age-related behavioural decline. Current Topics in Behavioral Neurosciences. 2012;**10**:293-316

[7] Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997;**386**(6624):493-495

[8] Garthe A, Roeder I, Kempermann G. Mice in an enriched environment learn more flexibly because of adult hippocampal neurogenesis. Hippocampus. 2016;**26**(2):261-271

[9] Leggio MG et al. Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. Behavioural Brain Research. 2005;**163**(1):78-90

[10] Paylor R et al. Brief exposure to an enriched environment improves performance on the Morris water task and increases hippocampal cytosolic protein kinase C activity in young rats. Behavioural Brain Research. 1992;**52**(1):49-59

[11] van Praag H et al. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**(23):13427-13431

[12] Benaroya-Milshtein N et al. Environmental enrichment in mice decreases anxiety, attenuates stress responses and enhances natural killer cell activity. The European Journal of Neuroscience. 2004;**20**(5):1341-1347

[13] Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nature Reviews. Neuroscience. 2006;**7**(9):697-709

[14] Huttenrauch M, Salinas G, Wirths O. Effects of long-term environmental enrichment on anxiety, memory, hippocampal plasticity and overall brain gene expression in C57BL6 mice. Frontiers in Molecular Neuroscience. 2016;**9**:62

[15] Connor JR, Wang EC, Diamond MC. Increased length of terminal dendritic segments in old adult rats' somatosensory cortex: An environmentally induced response. Experimental Neurology. 1982;**78**(2):466-470

[16] Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Experimental Neurology. 1973;**40**(2):491-504

[17] Yang S et al. Enriched environment increases myelinated fiber volume and length in brain white matter of 18-month female rats. Neuroscience Letters. 2015;**593**:66-71

[18] Volkmar FR, Greenough WT. Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science. 1972;**176**(4042):1445-1447

[19] Kempermann G, Brandon EP, Gage FH. Environmental stimulation of 129/SvJ mice causes increased cell proliferation and neurogenesis in the adult dentate gyrus. Current Biology. 1998;**8**(16):939-942

[20] Hosseiny S et al. Differential neuronal plasticity in mouse hippocampus associated with various periods of enriched environment during postnatal development. Brain Structure & Function. 2014

[21] Globus A et al. Effects of differential experience on dendritic spine counts in rat cerebral cortex. Journal of Comparative and Physiological Psychology. 1973;**82**(2):175-181

[22] Kleim JA et al. Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. The Journal of Neuroscience. 1996;**16**(14):4529-4535

[23] Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature. 1999;**399**(6731):66-70

[24] Maletic-Savatic M, Malinow R, Svoboda K. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. Science. 1999;**283**(5409):1923-1927

[25] Matsuzaki M et al. Structural basis of long-term potentiation in single dendritic spines. Nature. 2004;**429**(6993):761-766

[26] Zito K et al. Rapid functional maturation of nascent dendritic spines. Neuron. 2009;**61**(2): 247-258

[27] Bednarek E, Caroni P. Beta-Adducin is required for stable assembly of new synapses and improved memory upon environmental enrichment. Neuron. 2011;**69**(6):1132-1146

[28] Matsuzaki M et al. Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. Nature Neuroscience. 2001;**4**(11):1086-1092

[29] Murthy VN et al. Inactivity produces increases in neurotransmitter release and synapse size. Neuron. 2001;**32**(4):673-682

[30] Nusser Z et al. Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus. Neuron. 1998;**21**(3):545-559

[31] Takumi Y et al. Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nature Neuroscience. 1999;**2**(7):618-624

[32] Moser MB, Trommald M, Andersen P. An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. Proceedings of the National Academy of Sciences of the United States of America. 1994;**91**(26):12673-12675

[33] Rampon C et al. Effects of environmental enrichment on gene expression in the brain. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(23):12880-12884

[34] Siddoway B, Hou H, Xia H. Molecular mechanisms of homeostatic synaptic downscaling. Neuropharmacology. 2014;**78**:38-44

[35] Sale A et al. GABAergic inhibition in visual cortical plasticity. Frontiers in Cellular Neuroscience. 2010;**4**:10

[36] Voronin LL, Cherubini E. 'Deaf, mute and whispering' silent synapses: Their role in synaptic plasticity. The Journal of Physiology. 2004;**557**(Pt 1):3-12

[37] Keck T, Hubener M, Bonhoeffer T. Interactions between synaptic homeostatic mechanisms: An attempt to reconcile BCM theory, synaptic scaling, and changing excitation/inhibition balance. Current Opinion in Neurobiology. 2017;**43**:87-93

[38] Tang AC, Zou B. Neonatal exposure to novelty enhances long-term potentiation in CA1 of the rat hippocampus. Hippocampus. 2002;**12**(3):398-404

[39] Artola A et al. Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment. The European Journal of Neuroscience. 2006;**23**(1):261-272

[40] Malik R, Chattarji S. Enhanced intrinsic excitability and EPSP-spike coupling accompany enriched environment-induced facilitation of LTP in hippocampal CA1 pyramidal neurons. Journal of Neurophysiology. 2012;**107**(5):1366-1378

[41] Foster TC, Dumas TC. Mechanism for increased hippocampal synaptic strength following differential experience. Journal of Neurophysiology. 2001;**85**(4):1377-1383

[42] Eckert MJ, Abraham WC. Physiological effects of enriched environment exposure and LTP induction in the hippocampus in vivo do not transfer faithfully to in vitro slices. Learning & Memory. 2010;**17**(10):480-484

[43] Bouet V et al. Continuous enriched environment improves learning and memory in adult NMRI mice through theta burst-related-LTP independent mechanisms but is not efficient in advanced aged animals. Mechanisms of Ageing and Development. 2011;**132**(5):240-248

[44] Waters NS, Klintsova AY, Foster TC. Insensitivity of the hippocampus to environmental stimulation during postnatal development. The Journal of Neuroscience. 1997;**17**(20):7967-7973

[45] Foster TC. Regulation of synaptic plasticity in memory and memory decline with aging. Progress in Brain Research. 2002;**138**:283-303

[46] Leger M et al. Environmental enrichment improves recent but not remote memory in association with a modified brain metabolic activation profile in adult mice. Behavioural Brain Research. 2012;**228**(1):22-29

[47] Naka F et al. Modification of AMPA receptor properties following environmental enrichment. Brain Dev. 2005;**27**(4):275-278

[48] Grilli M et al. Exposure to an enriched environment selectively increases the functional response of the pre-synaptic NMDA receptors which modulate noradrenaline release in mouse hippocampus. Journal of Neurochemistry. 2009;**110**(5):1598-1606

[49] Frick KM, Fernandez SM. Enrichment enhances spatial memory and increases synaptophysin levels in aged female mice. Neurobiology of Aging. 2003;**24**(4):615-626

[50] Nithianantharajah J, Levis H, Murphy M. Environmental enrichment results in cortical and subcortical changes in levels of synaptophysin and PSD-95 proteins. Neurobiology of Learning and Memory. 2004;**81**(3):200-210

[51] Paolicelli RC et al. Synaptic pruning by microglia is necessary for normal brain development. Science. 2011;**333**(6048):1456-1458

[52] Costello DA et al. Long term potentiation is impaired in membrane glycoprotein CD200-deficient mice: A role for toll-like receptor activation. The Journal of Biological Chemistry. 2011;**286**(40):34722-34732

[53] Ransohoff RM, Stevens B. Neuroscience. How many cell types does it take to wire a brain? Science. 2011;**333**(6048):1391-1392

[54] Cardona AE et al. Isolation of murine microglial cells for RNA analysis or flow cytometry. Nature Protocols. 2006;**1**(4):1947-1951

[55] Hoek RM et al. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). Science. 2000;**290**(5497):1768-1771

[56] Maggi L et al. CX(3)CR1 deficiency alters hippocampal-dependent plasticity phenomena blunting the effects of enriched environment. Frontiers in Cellular Neuroscience. 2011;**5**:22

[57] Majde JA. Neuroinflammation resulting from covert brain invasion by common viruses: A potential role in local and global neurodegeneration. Medical Hypotheses. 2010;**75**(2): 204-213

[58] Jurgens HA, Amancherla K, Johnson RW. Influenza infection induces neuroinflammation, alters hippocampal neuron morphology, and impairs cognition in adult mice. The Journal of Neuroscience. 2012;**32**(12):3958-3968

[59] Jurgens HA, Johnson RW. Environmental enrichment attenuates hippocampal neuroinflammation and improves cognitive function during influenza infection. Brain, Behavior, and Immunity. 2012;**26**(6):1006-1016

[60] Briones TL, Woods J, Rogozinska M. Decreased neuroinflammation and increased brain energy homeostasis following environmental enrichment after mild traumatic brain injury is associated with improvement in cognitive function. Acta Neuropathologica Communications. 2013;**1**:57

[61] Brod S et al. The impact of environmental enrichment on the murine inflammatory immune response. JCI Insight. 2017;**2**(7):e90723

[62] Diamond MC et al. Increases in cortical depth and glia numbers in rats subjected to enriched environment. The Journal of Comparative Neurology. 1966;**128**(1):117-126

[63] Isaacs KR et al. Exercise and the brain: Angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. Journal of Cerebral Blood Flow and Metabolism. 1992;**12**(1):110-119

[64] van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nature Reviews. Neuroscience. 2000;**1**(3):191-198

[65] Cao L et al. VEGF links hippocampal activity with neurogenesis, learning and memory. Nature Genetics. 2004;**36**(8):827-835

[66] Falkenberg T et al. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. Neuroscience Letters. 1992;**138**(1):153-156

[67] Aberg MA et al. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. Molecular and Cellular Neurosciences. 2003;**24**(1):23-40

[68] Torasdotter M et al. Environmental enrichment results in higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus. Behavioural Brain Research. 1998;**93**(1-2):83-90

[69] Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science. 1995;**267**(5204):1658-1662

[70] Scotece M et al. Adiponectin and leptin: New targets in inflammation. Basic & Clinical Pharmacology & Toxicology. 2014;**114**(1):97-102

[71] Cao L et al. Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. Cell. 2010;**142**(1):52-64

[72] Nicolas S et al. Neurogenesis-independent antidepressant-like effects of enriched environment is dependent on adiponectin. Psychoneuroendocrinology. 2015;**57**:72-83

[73] Chabry J et al. Enriched environment decreases microglia and brain macrophages inflammatory phenotypes through adiponectin-dependent mechanisms: Relevance to depressive-like behavior. Brain, Behavior, and Immunity. 2015;**50**:275-287

[74] Heyman E et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression. Psychoneuroendocrinology. 2012;**37**(6):844-851

[75] Goldfarb AH, Jamurtas AZ. Beta-endorphin response to exercise an update. Sports medicine. 1997;**24**(1):8-16

[76] Kipnis J et al. T cell deficiency leads to cognitive dysfunction: Implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(21):8180-8185

[77] Schwartz M, Kipnis J. A conceptual revolution in the relationships between the brain and immunity. Brain, Behavior, and Immunity. 2011;**25**(5):817-819

[78] Brynskikh A et al. Adaptive immunity affects learning behavior in mice. Brain, Behavior, and Immunity. 2008;**22**(6):861-869

[79] Ellwardt E et al. Understanding the role of T cells in CNS homeostasis. Trends in Immunology. 2016;**37**(2):154-165

[80] Kipnis J, Gadani S, Derecki NC. Pro-cognitive properties of T cells. Nature Reviews. Immunology. 2012;**12**(9):663-669

[81] Marin I, Kipnis J. Learning and memory … and the immune system. Learning & Memory. 2013;**20**(10):601-606

[82] Ziv Y et al. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nature Neuroscience. 2006;**9**(2):268-275

[83] Garofalo S et al. Enriched environment reduces glioma growth through immune and non-immune mechanisms in mice. Nature Communications. 2015;**6**:6623

[84] Chimen M et al. Homeostatic regulation of T cell trafficking by a B cell-derived peptide is impaired in autoimmune and chronic inflammatory disease. Nature Medicine. 2015;**21**(5):467-475

[85] Wohleb ES et al. Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain. Biological Psychiatry. 2014;**75**(12):970-981

IntechOpen