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REVIEW ARTICLE

Environmental Enrichment as a Positive Behavioral Intervention Across the Lifespan

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Abstract: ***Background*:** In recent decades, the interest in behavioral interventions has been growing due to the higher prevalence of age-related cognitive impairments. Hence, behavioral interventions, such as cognitive stimulation and physical activity, and along with these, our lifestyle (education level, work position, frequency of cognitive and social activities) have shown important benefits during the cognitive impairment, dementia and even recovery after brain injury. This is due to the fact that this type of intervention and activities promote the formation of a cognitive and brain reserve that allows tolerating brain damage during a long period of time without the appearance of cognitive symptoms. With regard to this, animal models have proved very useful in providing information about the brain mechanisms involved in the development of these cognitive and brain reserves and how they interact with each other.

***Methods*:** We summarize several studies showing the positive effects of Environmental Enrichment (EE), understood as a housing condition in which animals benefit from the sensory, physical, cognitive and social stimulation provided, on brain and cognitive functions usually impaired during aging.

***Results*:** Most of studies have shown that EE is a successful protocol to improve cognitive functions and reduce anxiety-related behaviors across the lifespan, as well as in animal models of neurodegenerative diseases.

***Conclusion*:** Therefore, EE is a laboratory condition in which some aspects of an active lifestyle are reproduced.

Keywords: Aging, experience-dependent plasticity, animal model, environmental enrichment, neurodegenerative diseases.

INTRODUCTION

Developed nations are experiencing substantial increases in the elderly population. Thus, for those who live into older age, there is a higher risk of chronic diseases due to the physical and mental decline that occurs with aging.

Aging of the population is the highest risk factor of dementia (typically in the form of Alzheimer's disease) [1, 2]. Hence the current research is focused on investigating new approaches to improve and maintain healthy aging and independent living [3-6]. Fortunately, nowadays it has been proposed that an active lifestyle is a powerful way to delay the appearance of age-related deficits, promoting healthy aging of the brain. It is known that an aged brain retains considerable plasticity which depends on our lifestyles.

Taking this into account, in this review we will start explaining how behavioral treatments, such as cognitive stimulation or physical exercise, can promote more efficient aged brains with more capacity and compensatory mechanisms to solve the cognitive tasks with a better performance. However, even nowadays, little is known about the effect of these interventions on the brain's plasticity and therefore, research with animal models is very useful to understand the influence of an active lifestyle on cognitive deterioration related to aging, while it can also provide information on the brain mechanisms involved in the beneficial effect of living in a stimulating environment [7]. Studies on how the brain responds to stimulating experiences have frequently used the experimental paradigm of Environmental Enrichment (EE) and consequently a part of this review will show the benefits of this stimulation protocol, even in advanced ages.

ACTIVE LIFESTYLE AND SUCCESSFUL AGING

Current research about aging focuses on new avenues to delay cognitive and brain impairments, promoting, as much as possible, independence in our lives [4, 5].

The *cognitive reserve* concept has been proposed to account for the frequent discrepancy between the brain pathology and the cognitive performance of an individual [8, 9]. The reserve concept can be divided in *cognitive reserve* and *brain reserve* being both not exclusive and taking part in the protection against neurodegenerative diseases. The main difference between them is their active or passive role. The

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brain reserve is an example of a passive reserve in which individual differences in brain size, number of neurons, synapsis or dendritic branches allow us to cope better with brain damage [10, 11]. In contrast, the *cognitive reserve* has an active role, the functioning rather than the structure of the brain being more important. Hence, our brain copes with the injury activating compensatory mechanisms and using more efficient ways of processing [8]. However, current studies suggest a close relationship between both *reserves* and a higher *cognitive reserve,* promoted by an active lifestyle, would develop a higher *brain reserve,* which in turn would help us to tolerate brain damage [12] (Fig. **1**).

One example of a compensatory mechanism was proposed in the *scaffolding theory of aging and cognition* (STAC) [13]. Thus, *scaffolding is a process that results in changes in brain function through the strengthening of existing connections, formation of new connections and disuse of connections that have become weak or faulty* [13]. Another compensatory mechanism is the *hemispheric asymmetry reduction* (*HAROLD*) [14, 15] observed when old people perform a cognitive task. Regarding this, the bilateral activation of the prefrontal cortex in older age may reflect a compensatory mechanism to cope with the impairments resulting during the cognitive decline (deficient hippocampal activation or sensory problems). However, *HAROLD* might also reflect other mechanisms of functional reorganization of the aging brain helping to diminish the aged-related cognitive decline [14, 16]. Finally, older people with higher *reserve* also show a higher *efficiency*, so they use fewer neural resources to execute the task well [13, 17]. Therefore, individuals with a higher *reserve* can maintain greater network efficiency or capacity, can compensate in an advantageous way, or can avoid resorting to less advantageous alternate networks.

Similar to the *reserve* concept, the *brain maintenance* concept has also been proposed [18]. It is based on the evidence that there exists a group of old people who do not show cognitive impairment due to the absence of brain damage or due to compensatory mechanisms or some brain characteristics, as the *reserve* concept proposes [12, 19].

The development of these *reserves* depends on our life experiences, such as our formal education, emotional support, work position, leisure activities or the practice of aerobic exercise [20-22].

The education level is the most studied reserve factor [23, 24]. In general, the studies show a lower risk of developing dementia when the years of education are higher [25]. However, the benefits of education seem to be process specific, improving measures of crystallized intelligence related to abilities that we acquire during our life, rather than fluid intelligence more involved in reaction time and speed processing [26]. In addition to this, it has also been hypothesized that a demanding job, for example supervising

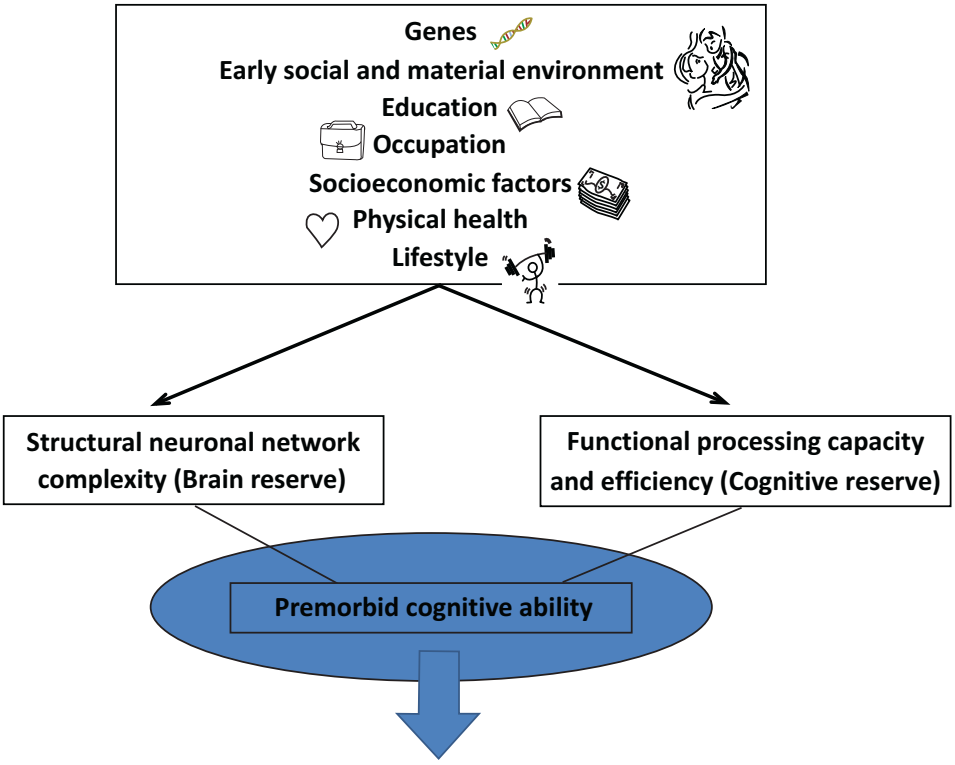

Fig. (1). The cognitive and brain reserves are built up over the course of our lives and therefore, our early environment, education level, work position, socioeconomic factors along with our state of health are important variables that determine our brain efficiency when damage appears.

and organizing groups, protects against dementia [27]. Moreover, supervisory experience reduces the hippocampal atrophy described in later life [28].

It is necessary to take into account that education and occupational characteristics can be affected by cognitive as well as social-economic status [29]. With regard to this, it can be argued that an early-life prerequisite for educational or occupational attainment is the childhood cognitive ability and may be a more valid measure of reserve capacity [30, 31]. Interestingly, the few studies that have analyzed this variable have reported an elevated risk of dementia in individuals with low childhood cognitive ability [31] and also, a higher school performance is protective of dementia risk even in the absence of later-life educational or occupational stimulation [30].

On the other hand, studies such as that carried out by Wilson *et al*. (2002) [32] show the importance of our leisure activities. They assessed the effect of the participation of elderly subjects in cognitively demanding activities as part of a project called Chicago Health and Aging Project. They focused on several measures: listening to the radio, reading newspapers, magazines or books, playing games such as cards or checkers and going to museums. Four years later, they found that the risk of developing Alzheimer´s disease (AD) was reduced by participation in these demanding activities. Related to this, in a recent study [33] have also found that daily stimulation, such as playing chess, cards, using a computer or attending lessons, plays an important role in cognitive functioning outside education or the type of profession performed. Overall, the results of this study show the importance of everyday activity as a protective mechanism against cognitive decline. However, these activities must be challenging, useful and significant to the old person, non-automatic or repetitive, and offer novel challenges in each session to be effective.

On the other hand, physical activity, diet, and social activity are additional factors linked to maintained cognition in aging that have been used as a basis for interventions to prevent cognitive decline. In the case of physical activity, it has been shown that it improves measures of fluid intelligence, such as speed processing as well as executive functions and sustained attention [6]. Respect to the diet, it has been demonstrated that some of the free fatty acids, both saturated and polyunsaturated fats and omega 3 fatty acids show neuroprotective effects against oxidative stress and preventing symptoms of several neurodegenerative diseases [34, 35]. With regard to social activity, several studies have found that the engagement with our social network is more important than the size of it [36].

Therefore, all these studies show the importance of our lifestyle in the promotion of successful aging, but a drawback of the *cognitive reserve* hypothesis is the lack of knowledge about its neural substrate, so animal research and the Environmental Enrichment (EE) paradigm provide us with information about the effect of different types of stimulation on the brain structure and function. Besides, the research with animal models allows us a better control of the different variables and also of longitudinal studies owing to their short lifespan.

WHAT IS THE ENVIRONMENTAL ENRICHMENT PARADIGM?

The term EE refers to an improvement of the conditions of confinement of laboratory animals in comparison with those housed in a standard way [37]. These conditions include larger cages that contain objects and different spaces that facilitate exercise, play, exploration, while allowing the animals greater control over their environment. In some experimental paradigms, EE can also increase the number of animals per cage, favoring constant and unpredictable interactions [38] (Fig. **2**). Some recent studies have even opted for the use of mirrors with the aim of simulating social stimulation, noting a positive effect on the levels of exploration and anxiety of the rodents [39].

In this way greater welfare is ensured for animals, mainly rodents, through the social, cognitive, motor, and sensory stimulation offered [40]. There is still no consensus about which paradigm of EE is the most beneficial since the protocols differ widely from laboratory to laboratory [41, 42]. Another important variable is the daily exposure time to EE that can also influence the results. In this regard, several studies have shown that even daily exposures for short periods (3h) have positive effects on cognition in old rats [43-45]. On the other hand, works such as that of Bennett *et al*. (2006) [46] observed that only exposures of 24 h to EE conditions were able to reduce the deficits of spatial memory in old rats. Regarding the duration of the EE protocol, although a brief exposure (a few weeks) has shown to be capable of reducing the deficits in learning and memory in old rodents [46, 47], others have found that lifetime exposure can have a more powerful effect [48]. In this respect it has been noted that 30 days exposure is sufficient to induce changes in cortical areas in young rodents and that prolonging the period of EE (80 days) does not provoke great changes, rather a longer duration of them, while old rodents require longer exposures to EE with frequent changes of stimuli.

There are also relative differences as to whether EE implies having or not access to wheels in which to perform

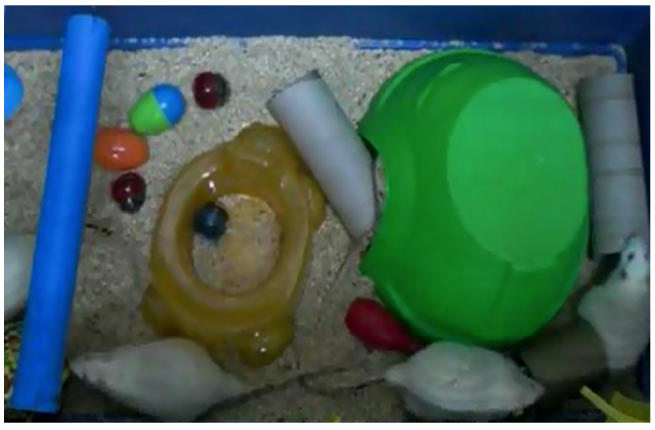

Fig. (2). Enriched environment with motor, sensory, cognitive and social stimulation is reflected in this figure. The objects must be changed frequently to ensure the novelty exposure and the complex environment.

voluntary exercise, since aerobic exercise in itself promotes the neurogenesis in the dentate gyrus (DG), the angiogenesis [49-51] as well as improvements in cognition [52].

Despite this variability of protocols, two of the key aspects of EE seem to be spatial complexity, and the exposure to novelty achieved through the changing of objects and of their position.

History of Environmental Enrichment

As indicated by Rosenzweig (1979) [53], the first research into EE was carried out by the Italian Malacarne (1744-1816). Malacarne found that birds who had received EE showed larger brains (a fact particularly evident in the cerebellum) than those not enriched, maintained in conditions of isolation and coming from the same clutch of eggs [54]. Later, Charles Darwin, in 1874 [55], also gave great importance to the role of environmental stimulation on brain size, pointing out that the brains of domestic rabbits were smaller than those of the wild, postulating that these differences could be attributed to the confinement and relative impoverishment imposed by domestic life. In the 20th century, Santiago Ramón y Cajal (1913) [56] suggested that brain stimulation could establish new and more numerous connections between neurons. Later, Hebb in 1947 [57] hypothesized that animals raised in enriched environments during infancy could develop permanent changes in the brain related to the increase in problem-solving capabilities. This was based on the fact that the rats used as pets, and which had experienced more stimulating living conditions, performed better in the execution of mazes than laboratory rats. However, it was not until the 1960s that EE began to be considered a scientific paradigm. It was then, in the Psychology Laboratory of Berkeley [58] that the initial studies were carried out where the first neuroanatomic effects of EE were clearly shown. In the tests, a group of 12 male rats of 25 days of age was placed in a large cage (64 x 64 x 46 cm) where there was a small wooden maze that could be used as a nest and in which wooden toys were introduced daily. In addition, the rats explored for 30 minutes a day a maze with different configurations which varied daily. At the same time, rats of the same litter and age as those exposed to EE were placed in a condition of impoverishment, in individual cages (28 x 20 x 20 cm) with food and water *ad libitum*. The histological analyses of the brains of these animals showed that these environmental manipulations caused neurochemical and brain weight changes. The most surprising result was the increase in weight of the visual cortex (8%) and somatosensory cortex (3%) in enriched animals in comparison with those kept in isolation.

After this pioneer work, different authors have shown other neuroanatomic and behavioral effects of EE in animals of different ages and during enrichment periods ranging from several days to weeks or months [59-61].

Cognitive and Behavioral Effects of EE

EE has proved capable of minimizing the changes that appear with age in various memory types. For example, in tests which evaluate the non-spatial memory, such as the test of recognition of objects or contextual conditioning to fear, the enriched animals perform better than those who were stabled under standard conditions [62-64]. In the case of spatial memory, EE significantly improved the performance of middle-aged rats and mice in a memory test of spatial reference in the Morris water maze (MWM) [65, 66] with similar results regarding learning in the Hebb-Williams labyrinth [48]. It is in this middle-aged period when it is considered that cognitive decline begins and the animals begin to have difficulties in solving spatial memory tests in which allocentric clues have to be used to find the platform [67-69]. In this way, stimulating experiences such as EE may have a highly positive effect on these ages when alterations related to the passing of the years are still not very severe. However, the results have sometimes been contradictory. For example, Freret *et al*. (2012) [70] showed that EE has to be carried out before middle-age to have a positive effect on cognition, while Kempermann *et al*. (1998) [71] observed that EE, even in this period, produces benefits in performance in the MWM. In contrast, a recent study of Mora-Gallegos *et al*. (2015) found that young rats benefited more from the social and physical stimulation provided by the EE than their mature adult counterparts [72].

Similarly, in aged rats and mice, it has also been noted that EE is able to improve the performance in a test of spatial reference in the MWM memory [65]. Some studies have suggested that this improvement is due to a rapid acquisition and a flexible use of spatial information [73], while others consider that EE can have a greater impact on the processes of consolidation, finding that enriched animals show a better maintenance of spatial information 24 h after finishing the training [74].

On the other hand, also during old age, EE causes improvement in tests of delayed matching to sample in which the capacity and functioning of the short-term memory is assessed (Soffie *et al*., 1999), in spontaneous alternation [75] and in incidental learning [76].

Effect on Anxiety-Related Behaviors and Exploration Levels

The evidence indicates that EE can counteract the negative effect of exposure to intense and uncontrollable stressors [77, 78]. With the exception of a single work, in which rodents were exposed to a special type of EE that consisted in a gradual increase in difficulty to find food [79], most of the studies have revealed that EE is capable of reducing the emotional reactivity with a decrease in the levels of freezing and defecation [80, 81]. Enriched animals are also more relaxed, easier to handle, less impulsive [82, 83] and with a greater tendency to play [84].

It is interesting to note that the anxiolytic effect of EE appears to be more notable when the test contexts are challenging for the animal [85]. For example, EE improved exploration only when 8 arms were available in the radial-arm maze (RAM), but not with only 4 [86]. This seems to suggest that EE produces anxiolytic effects solely when the level of stress associated with the new situation is relatively high as to cause pronounced anxiety. In contrast, the exposure to more ethological stressors, such as cat odor, did

not produce differences for behavior between enriched and non-enriched groups, although the CORT levels were lower in the enriched group [77].

Moreover, recent studies such as that of Goes *et al*. (2014) [87] and Ravenelle *et al*. (2014) [88] have shown that EE is able to reduce the levels of trait anxiety in adult rats, understood as those individual characteristics relatively stable in time, which make the subject more vulnerable to problems of anxiety [89].

Generally, it is assumed that exploratory behavior, such as the degree of locomotion or rearing, is a reflection of low levels of anxiety [90]. Thus, enriched animals tend to present a different exploration pattern, both quantitatively and qualitatively compared with unenriched rodents, and they invest more time in searching for unfamiliar stimuli [91, 92]. These superior levels of exploration seem to be greater during the first few minutes of behavior tests such as the open field test, while later activity tends to be reduced due to a faster habituation to the new environment [93, 94]. Some authors maintain that this rapid habituation to the novelty may be understood as a better capacity for learning and short-term memory, or perhaps a constant tendency towards the pursuit of novelty [95, 96].

Recently, Harris *et al*. (2009) [97] even suggested that the reduction of the levels of anxiety that EE causes when the rodents are in an evaluation situation, whether in the MWM or another type of maze, is key to understanding the better performance of these animals in tests of cognitive assessment.

Nevertheless, we must take into account that it is unknown if the positive effects of EE on anxiety-related behaviors are a consequence of this housing condition or a consequence of comparing these animals with others in an impoverished environment. Due to this issue, recent studies about animal models of neurodegenerative and psychiatric diseases have started to employ animals in enriched conditions as the control group.

What Happens in the Brain after EE?

All of these behavioral benefits are related to changes in the structure and functioning of the brain. Morphologically, the first studies on the subject described an increase in cortical volume and weight, primarily of the visual, somatosensory and frontal cortex [98]. Likewise, it was also seen that EE was able to increase the thickness of the occipital cortex [99], the volume of the hippocampus [100], and even that of some subcortical areas [101].

Moreover, the effects that have aroused the greatest interest during recent years are those relating to the impact of EE on neurogenesis. It has been shown that EE produces an increase of the survival of the new granular neurons which proliferate in the GD of the hippocampus of mice [94, 102] and adult and aged rats [61, 103]. Currently there are numerous studies which suggest that adult neurogenesis is involved in both cognitive and emotional functions dependent on the hippocampus [104]. In this way, the rodents which show greater neurogenic capacity also register a better performance in tests on spatial memory, revealing a relation between the level of learning reached and the number of new neurons [105]. Furthermore, according to Kempermann (2008) [104], training during adulthood builds a hippocampal neurogenic reserve for use in old age. He hypothesized that combining cognitive challenges with physical exercise will be most effective in maintaining a pool of new neurons in the dentate gyrus that can be recruited later in development to confront cognitive challenges. Extrapolating the animal data to the situation with humans, Kempermann (2008) [104] proposes that *broad ranges of activity early in life would not only help to build a highly optimized hippocampal network adapted to a complex life . . . [but] would also contribute to a neurogenic reserve by keeping precursor cells in cycle*.

On the other hand, EE not only produces changes in the number of neurons, but also in the morphology itself of nerve cells, increasing the number of branches and dendritic spines [60]. Given that the dendritic spines are where the synaptic connections are established, this rise is no more than an indirect indication of an increase in the synaptic activity of neurons, which may have functional consequences on the information processing capacity of enriched animals.

These changes in the number and morphology of neurons are better understood if the effects that EE has on gene expression and neurotrophic factors are taken into account. The increase of the expression of certain genes is possibly mediated by factors of transcription such as CREB (Camp response element-binding) whose levels increase after EE [106]. For example, enriched rodents show changes in the expression of genes related with the formation of new synapses and the reorganization and strengthening of those already existing [60]. In addition, EE also increases the expression of pre and postsynaptic proteins involved in the synaptogenesis process [65, 91, 107].

Other types of molecules that increase their expression as a result of EE are neurotrophic factors [108, 109] which are proteins that promote the survival, division, growth and also differentiation and morphological plasticity of the neurons, as well as being responsible for feeding these nerve cells during their lifespan (Fig. **3**).

In addition, EE induces alterations in the expression of the receptors forming part of the transmission of glutamatergic signals (N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)) [64, 110]. In this sense, in the study of Segovia *et al*. (2006) [103] an increase in the levels of glutamate was found in the CA3 in old rats, which would increase the excitatory synaptic potentials [108] and also the Long-term potentiation (LTP) [61]. Similarly, in the brains of enriched rodents an increase in the number of glial cells has also been described, a phenomenon known as gliogenesis [111, 112] as well as a change in their morphology. This morphological change is probably involved in mediating the interaction between the new dendritic spines and astrocytic ramifications [113, 114]. Recent evidence on the subject suggests that astrocytes play an active role in synaptic transmission, plasticity and neurotransmission [115, 116]. This has led some authors to formulate the concept of

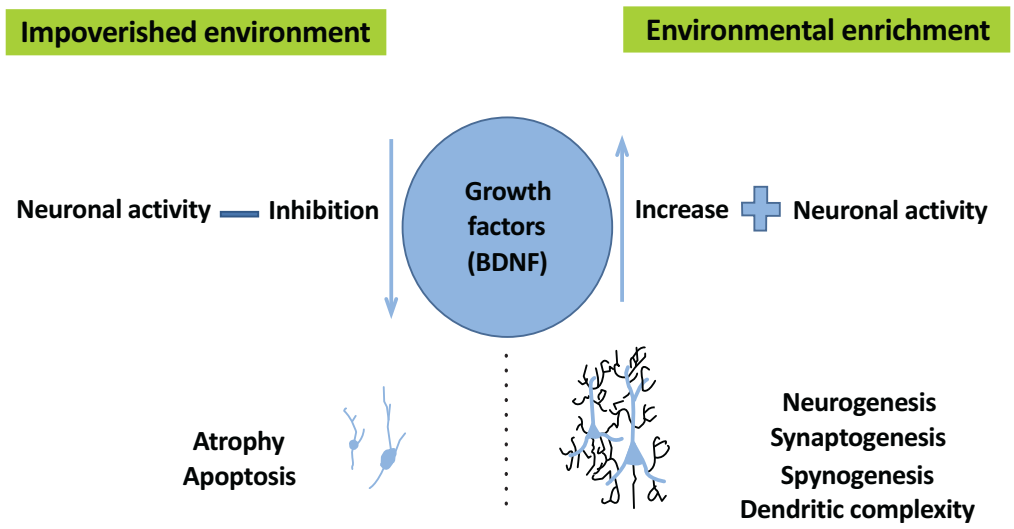

Fig. (3). The EE condition is known to increase the expression of neurotrophic factors, such as BDNF, NFG, GDNF, VEGF, which are involved in maintaining the neuronal homeostasis and also in promoting neurogenesis and the neuronal survival and maturation. These trophic factors are also implicated in increasing the dendritic branches and the number of spines. In contrast, an impoverished environment inhibits the neuronal activity and produces apoptosis.

tripartite synapses, understood as the set of pre and postsynaptic neurons and astrocytic processes that modulate neurotransmission *via* the release of gliotransmitters [117, 118]. On the other hand, a study by our group showed that a daily EE protocol (3h/day) carried out in 18 month-old rats was able to promote astrocytes with more complex morphology respect to rats in standard conditions [119]. It is possible that this higher complexity would allow the astrocytes to envelop the synaptic terminals and influence the synaptic transmission [120]. Besides, this study was carried out in aged animals, so it is probably that more complex astrocytes could compensate the possible age-related neuronal and synaptic impairments.

Finally, in relation to the reduction of anxious responses in enriched aged rodents, several studies have pointed out that, thanks to this protocol of stimulation, a reduction is achieved in the blood of hormone levels involved in the activation of the HPA axis, such as adenocorticotropin hormones, secreted by the paraventricular nucleus of the hypothalamus, and the GCs, secreted by the cortex of the adrenal glands, when animals are exposed to different stressors [121, 122]. EE also increases levels of GRs in the hippocampus, which facilitates the inhibition of the activity of the HPA axis and a restoration of the basal levels of GCs [80, 123]. Finally, the increase caused by EE in the expression of the growth factor BDNF in the aged brain has been linked to a greater capacity of resilience in these animals [124, 125] (Fig. **4**).

Effects of EE on Neurodegenerative Disorders

The first evidence that EE could be beneficial in a genetic model of a brain disorder was provided using Huntington´s disease transgenic mice [126]. Then, other studies were developed with animal models of AD and Parkinson´s disease [127]. Furthermore, EE has also been applied in animal models of other disorders, such as depression [128], epilepsy [129], stroke [130], multiple sclerosis [131], addiction [132], schizophrenia [133], autism spectrum disorders [134] and in neurodevelopmental disorders [135] showing important positive effects on the brain and behavior. Nevertheless, in animal models of amyotrophic lateral sclerosis (ALS), the EE program produced negative effects, only exacerbating the symptoms in female transgenic mice SOD1(G93A) [136].

In transgenic animal models of Huntington´s disease, wheel running or complex enrichment (exercise + enriched environment) have been shown to reduce abnormal motor behaviors, improve spatial memory, increase hippocampal and neocortical synaptophysin levels and even delay the onset of deficits in postsynaptic plasticity [137]. On the other hand, in a pharmacological model of Parkinson´s disease, enriched mice showed significantly less dopaminergic neuron loss in the substantia nigra, specifically only 40% compared with the 75% observed in control animals [138]. Also, enriched mice showed reduced dopamine transporter activity or levels, with an increase of striatal BDNF levels [139].

AD is a neurodegenerative disorder that mainly affects the neocortex and hippocampus. It is characterized by two pathological hallmarks, senile plaques and neurofibrillary tangles (NFTs) [140-142]. Nevertheless, recent studies have found that although these molecular alterations are a hallmark of AD, the neurogenesis impairment is present before the onset of cognitive deficits in AD animal models. This evidence suggests that behavioral interventions promoting survival of new neurons may protect us from this disease [143, 144]. Related to this, Kempermann and other authors [104] have proposed the *neurogenic reserve hypothesis*, suggesting that EE promotes neurogenesis and allows the aged hippocampus to cope better with environmental demands and damage.

Apart from other benefits of EE in AD models, it has been shown to increase cerebral angiogenesis, reduce cerebral oxidative stress and the apoptotic enzyme expression [145].

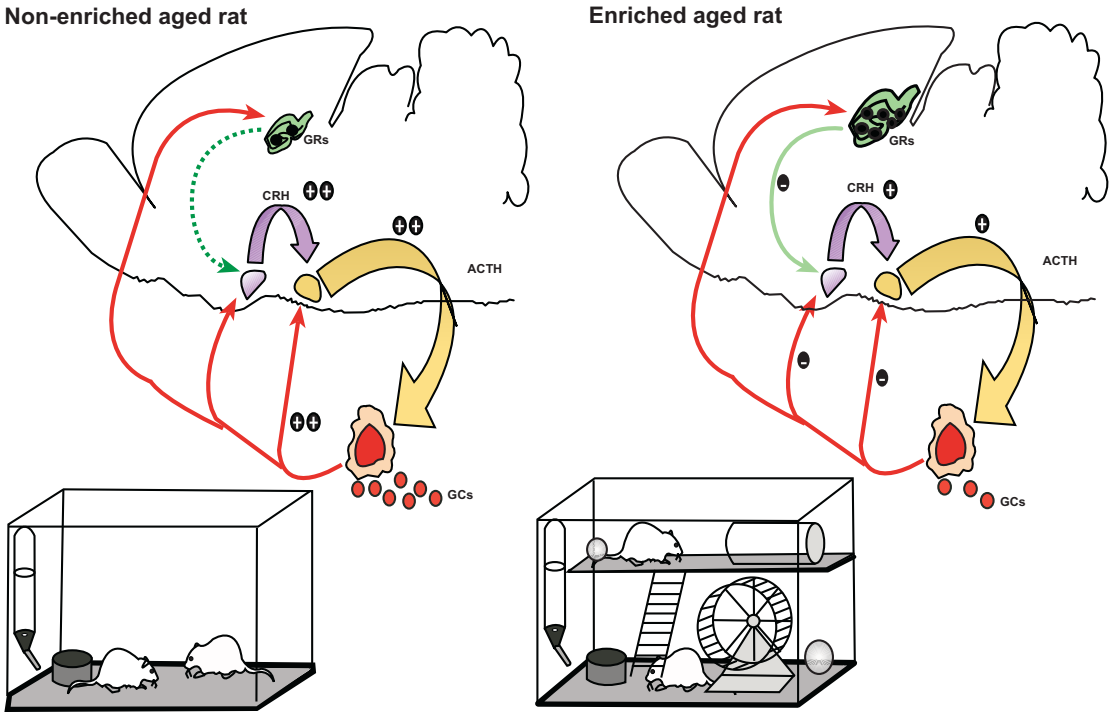

Fig. (4). The exposure to a stressor activates the release of glucocorticoids due to the activation of the HPA axis. These hormones, owing to their lipophilic nature, cross the hematoencephalic barrier and interact with their receptors widely distributed in different brain regions, such as the hippocampus. During aging, an impairment in the regulation of the HPA axis has been described which leads to a chronic, and therefore elevated, exposure to glucocorticoids which has been related with a higher vulnerability to psychological, metabolic and immune diseases. In contrast, EE has shown to reduce the activity of the HPA in aged enriched rats diminishing the secretion of hormones taking part in the HPA axis and in consequence, showing lower levels of anxiety-related behaviors.

Furthermore, EE also enhances the hippocampal neurogenesis, the synaptophysin immunoreactivity, the neurotrophin levels, the immediate early gene expression [146], and also increases the expression of the neprilysin protein involved in slowing the progression of AD [147]. Interestingly, previous studies have found that the effects of EE in Alzheimer´s animal models were observed after complex enrichment (enriched environment plus exercise) but not after exercise alone [125, 148]. However, a recent study [149] has found that voluntary exercise improved the memory performance in the APP/PSEN1 double-transgenic mouse model, although the amount of daily exercise was not correlated with spatial performance. As previously mentioned, EE is a stimulation protocol also involved in the recovery from different sorts of brain damage [150]. For example, rearing rats in enriched environments reduces the cognitive flexibility impairment induced by basal forebrain lesions [151] and improves spatial learning performance in rats with subicular lesion-induced neurodegeneration [152]. Also, in rats with cholinergic damage, EE increases the gene expression as well as the behavioral performance [153]. In addition, encouraging results have been found which show that EE combined with genetic factors could offer a non-invasive treatment in some types of cancer [154].

Finally, we must take into account that there are a variety of types of EE and each of them can produce different effects on the cognition and behavior of the animals. For example, apart from the novelty and the complex environment, EE can consist in putting food pellets at the bottom of the cage hidden with bedding, introducing different kinds of treats into toys, boxes or ice cubes, encouraging the animals to seek and work for food. This type of EE gives animals a certain control over their environment and essential resources [155]. However, not all types of EE are effective to improve the cognition and the welfare of the animals. For example, with certain mouse strains, it has been found that a lot of stimuli can increase aggressive behavior and anxiety levels [156].

CONCLUSION

All in all, the aging of our population and the higher rates of dependence in our society has led to an important interest in preventive strategies to promote a healthy and autonomous life, above all during aging. Related to this, behavioral treatments and an active lifestyle have shown encouraging benefits compared to pharmacological interventions, and even in aged people they are more convenient to avoid the overconsumption of medicine, characteristic of this age. However, there are many questions that are still to be answered about the effects of an active lifestyle on the brain, animal models being an alternative to study said effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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