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REVIEW ARTICLE

Coping with Stress During Aging: The Importance of a Resilient Brain

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Abstract: ***Background*:** Resilience is the ability to achieve a positive outcome when we are in the face of adversity. It supposes an *active resistance* to adversity by coping mechanisms in which genetic, molecular, neural and environmental factors are involved. Resilience has been usually studied in early ages and few is known about it during aging.

***Methods*:** In this review, we will address the age-related changes in the brain mechanisms involved in regulating the stress response. Furthermore, using the EE paradigm, we analyse the resilient potential of this intervention and its neurobiological basis. In this case, we will focus on identifying the characteristics of a resilient brain (modifications in HPA structure and function, neurogenesis, specific neuron types, glia, neurotrophic factors, nitric oxide synthase or microRNAs, among others).

***Results*:** The evidence suggests that a healthy lifestyle has a crucial role to promote a resilient brain during aging. Along with the behavioral changes described, a better regulation of HPA axis, enhanced levels of postmitotic type-3 cells or changes in GABAergic neurotransmission are some of the brain mechanisms involved in resilience.

***Conclusion*:** Future research should identify different biomarkers that increase the resistance to develop mood disorders and based on this knowledge, develop new potential therapeutic targets.

Keywords: Aging, stress, resilience, brain, healthy lifestyle, affective disorders.

1. INTRODUCTION

The research in the field of mental health has been dominated over the years by studies aimed at determining the risk and vulnerability to develope mental illness. However, for a number of years, there has been a shift in focus aimed at analyzing not so much the causes of mental illness, but the factors or mechanisms that make it possible for certain people to maintain their health conditions or to recover, when they have been exposed to severe adversities throughout life [1]. Regarding this, no one doubts today that the cause of affective disorders is not the traumatic event itself, rather than the way in which these events are processed psychologically by each individual [2]. This ability to successfully cope with and overcome the aftermath of a trauma is known as resilience [3].

Resilience is based on genetic, molecular, neural, but mainly environmental factors, so the importance of our experiences in its development has to be taken into account [4]. A current approach is based on developing programs to provide training in coping with adverse events. In these studies, groups of individuals are confronted with traumatic situations and they work on several skills, such as self-efficacy or the perception that one is able to manage and recover from stressful life events [5, 6]. In the case of animal models, the environmental enrichment (EE) paradigm has been frequently used in order to encourage patterns of resilient behavior. This paradigm consists of modifying the standard housing condition of the laboratory animals by another in which social, cognitive, physical and sensorial stimulation is given to the animals. This type of complex stimulation improves not only cognitive functions, such as memory or attention [7-12], but also reduces anxiety, impulsiveness and increases the tendency to play and explore new and potentially stressful situations [13-17].

Firstly, we address the age-related changes in the brain mechanisms involved in regulating the stress response. Secondly, using the EE paradigm, we analyse the resilient potential of this intervention and the underlying neurobiological bases in aged rodents.

2. THE RESPONSE TO STRESS: EFFECTS OF AGING

Aging is one of the most challenging public health issue that is faced by the developed countries nowadays. With the growth in aged population, there has been an expansion in

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initiatives and interventions to promote successful aging. Mental health is one of the most relevant factors related to quality of life among the elderly [18]. Some decades ago, neurodegenerative disorders and dementia were on the top of the most prevalent diseases in older adults, while epidemiological studies were pointing to anxiety, and also depression, as psychiatric disorders less common among this population [19, 20]. However, several authors have postulated that the occurrence of anxiety and depression is underestimated in old individuals, especially because these psychopathologies are qualitatively different from those experienced by younger persons, and the symptoms experienced by elders are commonly superposing disabilities generated by senescence, *i.e*. apathy, cognitive impairments and sleep disorders [19, 20]. It should be mentioned that subjective complaints of poor memory and concentration are also common among depressed older adults. The majority of individuals with subjective complaints never progress to significant cognitive decline, but some of them have a higher risk of progression to objective cognitive impairment than persons with no cognitive concerns [21]. In fact, literature supports that geriatric depression is more frequently associated with cognitive deficits and somatic complaints than depression in younger age [21]. Consequently, depressive and anxious symptoms in the elderly are often misinterpreted and not treated adequately.

A growing field of research has emerged on the concept of resilience among older adults and its role in successful aging. Successful aging has several components but is typically defined as *freedom from chronic disease and disability, as well as high physical and mental functioning* [22]. High resilience later in life has been associated with optimal outcomes, such as reduced depression and mortality risk [23-26] as well as better self-perception of successful aging [22, 26, 27], increased quality of life, and improved lifestyle behaviors. To understand resilience more fully, it is first necessary to establish how the hypothalamic-pituitary-adrenal (HPA) axis changes during aging.

The major neuroendocrine response to stress is *via* activation of the HPA axis, consisting of stimulation of parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) and consequent release of the neuropeptides, corticotrophin releasing hormone (CRH) and vasopressin (VP), which stimulate pituitary adrenocorticotropic hormone (ACTH) release. This leads to stimulation of glucocorticoid secretion by the adrenal cortex, which is essential for stress adaptation [28, 29]. Glucocorticoids (cortisol in humans, and corticosterone in rats and mice) act upon specific receptors present in most peripheral tissues and in the brain, initiating metabolic and neuromodulatory changes necessary for coping with the challenge [30]. It is clear that acute activation of the HPA axis during stress is necessary for stress adaptation [30]. On the other hand, excessive exposure to sustained elevated levels of stress hormones, including CRH and corticosterone (CORT), can be harmful and predispose to psychiatric, reproductive, immune, metabolic, and cardiovascular disorders [31]. Thus, appropriate termination of the stress response is essential to reduce the damaging effects of chronic elevations of CRH and glucocorticoids. During aging, excessive activation of the HPA axis and hypersecretion of glucocorticoids can lead to dendritic atrophy in neurons in the hippocampus, resulting in impairment in learning and memory functions. Damage or loss of hippocampal neurons would result in impaired feedback inhibition of the HPA axis and glucocorticoid secretion, leading to further damage caused by elevated glucocorticoid concentrations. This feed-forward effect on hippocampal neuronal loss is known as the *glucocorticoid cascade hypothesis* [32], and is proposed to contribute to reductions in hippocampal neuron number and cognitive impairment observed in some aged individuals. Interestingly, recent studies in humans and rodents have observed an increase of co-chaperone FKBP5 with aging, which acts as negative regulator of GR function [33]. Thus, it is possible that deficits in stress resistance in aging are in part due to this enhanced expression of this protein. At date, we do not know any study which has carried out an analysis about the impact of EE on FKBP5 expression.

Related to HPA axis functioning, a recent study has related the levels of diurnal cortisol with stress, resilience and well-being in older adults [34, 35]. Existing evidences suggest that diurnal cortisol increases with age, but it is not a closed topic. Also, a decreased GC sensitivity with age has been described which supposes a higher peak of cortisol levels and longer stress response [36].

The implications of stress and glucocorticoid effects on the hippocampus have led to the exploration of other brain regions involved in cognition, mood and behavioral self-regulation. The amygdala shows quite different responses to acute and chronic stress compared to the hippocampus. The amygdala responds to glucocorticoids in the formation of emotionally-charged memories [37], and acute stress causes a delayed formation of dendritic spines in basolateral amygdala neurons and an increase of anxiety after 10 days [38]. Chronic stress of the same type that impairs dentate gyrus neurogenesis and causes dendritic shrinkage and spine loss in Ammon's horn neurons, causes expansion of dendrites in the basolateral amygdala [39] while causing spine down-regulation in the medial amygdala [40]. The prefrontal cortex (PFC) is another, now well-studied, target of chronic stress [41]. In the same chronic stress models that lead to amygdala neuronal hypertrophy and shrinkage of dendrites in hippocampus, there is shrinkage of dendrites and loss of spines throughout the medial prefrontal cortex while dendrites expand in the orbitofrontal cortex (OFC) [42]. Along with this, a study has demonstrated an enhanced elevation of post-stress extracellular glutamate levels in the hippocampus and medial prefrontal cortex of aged rats compared to young rats [43]. Increased glutamate levels after stress, and perhaps other neurotoxic insults, might thus increase the vulnerability of the aging brain to neuronal damage. Unfortunately, these structural changes are largely reversible in healthy young animals after the termination of stress, but there is clearly loss of reversibility in aging [44].

The neurogenic cells of the hippocampus are commonly linked to psychiatric disorders, and neurogenesis is thought to be required for a therapeutic response to antidepressant treatment. Aging and stress reduce cell proliferation, survival, and neuronal differentiation of the newly formed neurons [45]. Either a reduction of neurogenesis by decreased stem cell activity or a reduction of neuronal survival can be observed. Further, abnormal stem cell maturation could lead

to aberrant integration into hippocampal circuits. Nevertheless, the functional implications of decreased neurogenesis in psychiatric disease, as well as the therapeutic implications of rescuing neurogenesis with interventions, remain unclear. The emerging links between neurogenesis and mental health disorders support the idea that neurogenic therapies may one day enhance less effective treatments for patients suffering from major depression, schizophrenia, cognitive decline, and neurodegeneration [46].

On the other hand, stress responses are also mediated by various neurotransmitters and neuropeptides, including serotonin, which is closely related to the regulation of physiological and psychological functions, such as anxiety and stress responses in the brain [47, 48]. Serotonergic neurons directly project to corticotropin-releasing factor CRH-containing neurons in the paraventricular hypothalamic nucleus and control HPA function [49]. In the dorsal raphe nucleus, which is a major region of serotonin production in the midbrain and is composed of several subdivisions [50, 51], innocuous stressors enhance neuronal activation in young male rats [51, 52]. In addition, the administration of a serotonin 1A receptor antagonist decreases the acute restraint stress-induced CORT response and neuronal activation in the paraventricular hypothalamic nucleus in adult rats [53]. The function of the serotonergic system changes with age [54, 55], and it has been proposed that such dysfunction of the serotonergic system is heavily involved in mood disorders including depression [50, 56]. Therefore, it is highly possible that age-dependent changes in the serotonergic system contribute to the vulnerability to stress in old age. Related to this, brain-derived neurotrophic factor (BDNF) has shown to be involved in the differentiation and survival of serotonergic neurons [57, 58]. Aging itself appears to be associated with decreased BDNF signaling in the brain and depressed patients are also characterised by low blood BDNF levels [59-61]. In rodents, chronic stress decreases the expression of this neurotrophin, which can lead to neuronal atrophy in the hippocampus and other brain structures [62], while direct hippocampal infusion of BDNF produces anxiolytic and antidepressant effects [63, 64]. In addition, a very recent study reports that knocking-down BDNF in specific rat's brain sites precipitates behaviours associated with depression such as low preference for a sucrose solution [65-68].

γ-Aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the brain, progressively decreases during aging in animals [69] and humans [70]. Dysfunction of the GABAergic system is heavily implicated in anxiety and depression in both clinical and preclinical research [71]. Therefore, decreased GABA in the brain may contribute to problematic mood and anxiety symptoms during aging. In addition to changes in classical neurotransmitters, decreased expression of the neuropeptide somatostatin is observed in the prefrontal cortex of aged humans [72] and, interestingly, similar changes have been reported in patients with major depression disorder [73], again illustrating the common pathophysiology of ageing and depressive disorders. Neuropeptide Y (NPY) is another neuropeptide subjected to expressional change during brain aging with decreases reported in several regions including the hippocampus and the hypothalamus [74]; since NPY has been shown to have antidepressant properties [75], it is possible that dysfunctional NPY signalling contributes to behavioral deficits in aging. Besides, other variety of neuromolecular substances, such as PACAP [76], HDAC6 [77], DRR1 [78], PGC-1α-1 [79] or urocortin 3 [80] have been involved in resilience.

On ther other hand, Chronic Mild Stress rat model is a valid model of stress-induced depression [81, 82]. A recent study has assessed the level of neuronal activity in specific brain regions involved in stress response by measuring *c-Fos* expression [83] in a control, resilient and anhedonic groups. The authors found that the anhedonic group had a higher neuronal activity in the basolateral amygdala and medial habenula respect to the rest of groups. The habenula is an important brain region mediating the response in stressful situations and it seems to be a key region in the selection of appropriate behaviors particularly in stressful environments [84].

All in all, there is little doubt that these previous alterations occur during normal aging in at least some individuals. The variability in these alterations between individuals is likely to be a result of combined environmental and genetic factors. For example, individuals that age more 'successfully' are likely to have normal HPA axis activity and a better ability to cope with stress. Therefore, it is necessary to understand the brain and behavioral mechanisms involved in the relationship between stress resistance and slowed aging. Animal models and experimental paradigms, as EE, have contributed to shed light to this question. Nevertheless, we must take into account that there is a huge variability in the EE protocols carried out in the diferent experiments, so variables as age and sex of the animals, degree and duration of enrichment, or type of stimuli can give us different results. For example, the resilient effect of EE conditions seems to be dependent on the period in which this exposure takes place or even, the type of stressor employed in the experiment [85]. Hence, mice housed in communal nest condition were more resilient to social stress, but not to physical stress condition [85]. Is suggests that the stressor to which mice are resilient is similar to the stimuli that they have experienced previously [85].

Other interventions, such as aerobic exercise or the regular consumption of omega-3 polyunsaturated fatty acids (n-3 PUFA), have also demonstrated to have a positive impact on reducing stress-related behaviors [86, 87]. However, we focus on EE intervention since we consider it as the most complex and similar to human daily experiences in which sensorial, motor, social and cognitive stimuli are present.

3. RESILIENCE, ENVIRONMENTAL ENRICHMENT AND AGING

3.1. Effects on Stress-related Behaviors

The effects of cognitive, social, sensorial and motor stimulation on the brain and behavior are modeled in rodents using a paradigm called EE. EE produces a protective antidepressant-like phenotype. In humans, three hallmark symptoms of depression are anhedonia, social withdrawal and behavioral despair. Compared to isolated rats, enriched rats consume more sucrose in a sucrose preference test, indicat-

ing decreased anhedonia-like behavior; longer grooming time in the social contact test, suggesting decreased social withdrawal; and greater mobility time in the forced swim test (FST), suggesting reduced "behavioral despair" [88-90]. On the other hand, multiple labs have demonstrated reduced anxiety-like behaviors after EE. For example, enriched rats display lower basal locomotor activity, yet increased distance traveled in the center of the arena in the open field test, indicating an anxiolytic effect [91, 92]. This lower locomotor activity has been also interpreted as an enhanced habituation to the novelty of the testing environment [93]. In addition, enriched rats and mice were found to spend more time in the open arms in the elevated plus maze (EPM), and showed lower amounts of defensive burying and less defensive behavior when in close proximity to a predator, also suggesting reduced anxiety [94, 12]. Finally, we found that enriched aged rats showed a reduced emotional reactivity to the conflict approach/avoidance and an improvement in decision making in the elevated-zero maze (EZM) test. Recently, pre-reproductive maternal enrichment was reported to influence offspring's coping response to stress and expression of c-Fos and glucocorticoid receptors (GRs) [95].

Thus, although there are multiple good lines of evidence suggesting that EE produces benefits on stress response, none of the reports gives a possible explanation for how enrichment produces this effect. Some behavioral researchers have explained the effect of EE on stress-response in terms of the sense of control over the environment. Enrichment provides the animals with opportunities to structure and organize their environment, giving them a sense of control over the surroundings [96]. Increasing the sense of controllability is known to reduce the stress level of the animal [97]. Thus, gaining controllability was suggested to be associated with the development of stress resilience [98]. Besides, EE has been suggested to represent a mechanism of stress inoculation [99].

The repeated introduction of new objects and the opportunity to explore them is comparable to repeated mild stress exposures [100]. In fact, some studies showed that relative to controls, enriched animals express slightly elevated levels of corticosterone at baseline [101, 102]; however, these increases in corticosterone levels may be attributable to increased physical activity of animals in EE. On the other hand, brain networks linked to reward have been also involved in stress resilience. The mesolimbic dopamine pathway is the major reward pathway which carries dopamine from the ventral tegmental area to the nucleus accumbens, and also to other brain regions such as amygdala, hippocampus and mPFC [103]. This pathway favors decision-making, positive emotions and optimism, which are the very essential traits of resilience, so when it becomes dysfunctional, mood disorders appear [104]. In addition, there is some evidence about age-related functional and structural alterations of the reward system which could be modulated by EE due to its rewarding effect [105].

Other authors suggest that noradrenaline system could be an important mechanism involved in the positive effects of EE on cognition [106]. Specifically, Naka *et al*. (2002) have

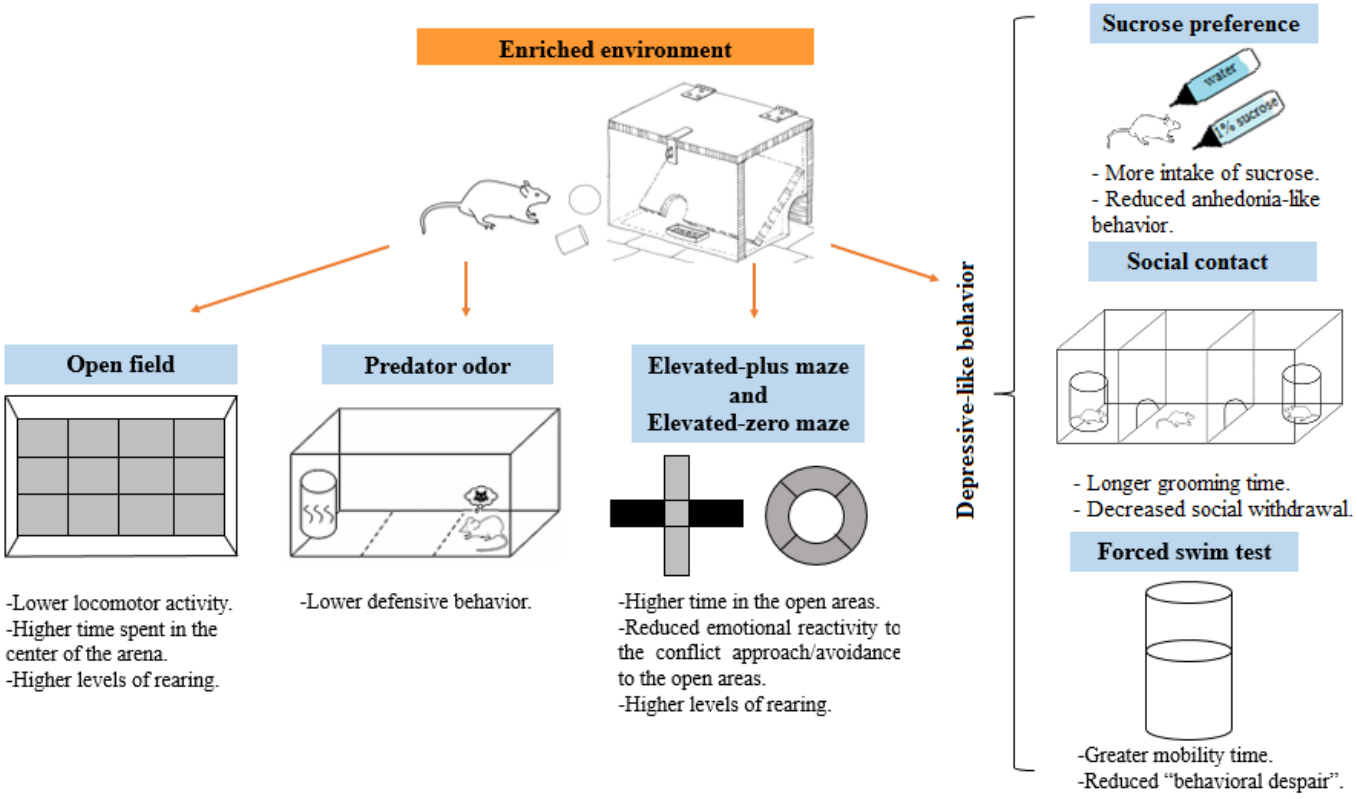

Fig. (1). Behavioral performance of a enriched rat in different tasks related to stress and depression measures. As can be seen in this figure, rats housed in EE conditions show a good behavioral pattern to cope with stressful situations.

only described an increase of this neurotransmitter after EE conditions in mice, with no changes in serotonin or dopamine levels in brain regions as parieto-temporo-occipital cortex, cerebellum and the pons /medulla oblongata [107] (Fig. **1**).

Nevertheless, as we commented before, there is a huge variability in the EE protocols carried out in the diferent experiments which could explain the different results described. Hence, we must take into account different parameters such as, the structural complexity of the environment, the timing of the intervention, the nature of the control conditions, the frequency of objects change, the presence of running wheel and the number of cage mates [108, 109]. For example, some evidences have shown that mice prefer shelters and retreats to hide [110], three dimensional cage structure which facilitates climbing and locomotion [111], naturalistic nesting material to control their thermoregulation [112], between others. Moreover, the control conditions employed in the experiment are important when interpreting the impact of EE due to rodent living in standard housing conditions are not valid models because they represent a deprived experimental condition. Thus, we need to standardize the EE protocols to make more valid and comparable the results between different laboratories [113].

3.2. Effects on Neurobiological Resilient Mechanisms

There has been too little clinical research on neurobiological factors that may convey protection from anxiety disorders and promote psychobiological resilience. This type of research may facilitate the discovery of preventative approaches to anxiety disorders.

The neurobiological mechanisms involved in the protective effects of EE on aging processes remain poorly understood, but some evidence suggests that EE renders the HPA axis response more adaptive and efficient [100]. EE may decrease emotional reactivity by lowering stress hormone levels such as ACTH and CORT. Researchers disagree on the effect of EE on stress hormones. While some studies have found that EE decreased resting CORT levels [106] or following exposure to stressors [114], others have found that resting levels in EE animals did not differ from those of non-enriched animals [115], or EE animals had higher basal levels of CORT [116, 101, 102]. The cause behind high baseline CORT levels may be the continual mild stress induced by repetitive exposure to new objects [116] or the increased aggression among males that has been observed in enrichment settings [117]. It is worth noting that CORT levels are elevated not only by aversive events, but also by appetitive events. The controversy in the effect of EE on stress hormones extends to its upstream stimulating hormone, ACTH. EE was able to lower basal ACTH levels in one study [106] but seemed to have no effect on ACTH in another study [118]. Enriched animals also express a relative increase in GR levels and gene expression in the hippocampus upregulating glucocorticoid sensitivity [119]. According to this, a study of our group also found an increase of GRs expression in some hippocampal subregions, preferently in the ventral hippocampus which is known to be more involved in anxiety-related behaviors [8]. Nonetheless, while the role of the GRs in stress has been extensively studied, the role of mineralocorticoid receptors (MRs) has received less attention, although they are also involved in processing stressful information [120]. The high affinity of MRs for cortisol results in a high MR occupancy rate, even under basal conditions in order to maintain an efficient negative feedback on HPA axis [121]. Ter Horst *et al*. [122] have found that mice lacking forebrain MRs display enhanced and prolonged CORT levels in response to restraint stress, showing that these receptors may inhibit HPA-axis activity. Recent findings have shown that GRs and MRs work in a complementary way, so the combination of high forebrain MRs and a reduction of GRs restores HPA axis activity under stressful situations, suggesting that in case of reduced GR activity, MRs are able to normalize HPA-axis activity [123]. During aging, one consistent result is that regardless of the strain of rats studied, a reduction in MR binding capacity is found [124]. Besides, a reduction of MR mRNA and GR mRNA has been found in the hippocampus of aged rats suggesting a decreased transcriptional activity in this area [125]. Respect to the impact of EE on MRs, no study has been carried out with aged rodents. Nevertheless, some evidences in adult rodents have shown that EE is able to restore and enhance MRs protein levels [126, 127]. Recently, a novel insight about corticosteroid-binding globulin (CBG) had a great relevance to shed light on the mechanisms involved in resilience. It was found that strong stressors, such as forced swimming or restraint, were able to produce a higher increase of plasma CBG compared to mild stressors like novelty, suggesting a role of this protein in regulating the glucocorticoid homeostasis [128]. Specifically, it was suggested that CBG controls the degree and time in which different tissues are exposed to glucocorticoids [129].

As it was cited before, a reduction in neurogenesis has been described in aged rats altering cognitive performance and stress-related behaviors [130]. In contrast, EE was able to increase neurogenesis in aged rodents by potentiating neuronal differentiation and new cell survival [131-133]. Surprisingly, Speisman *et al*. (2013) [134] found similar enrichment-induced increases in the number of new cells surviving 4-5 weeks in the dentate gyri of young and aged rats. Hence, while physical exercise has been shown repeatedly to play a crucial role in EE, the impact of the complexity and exploration of the EE cage itself on neurogenesis and cognition should not be underestimated. Thus, several studies have shown that EE without a running-wheel is able to induce neurogenesis, specifically EE only may exert a more specific influence on postmitotic type-3 cells [135, 136]. Indeed, it seems that EE requires adult hippocampal neurogenesis to promote stress resilience [137]. In fact, it has been demonstrated that when neurogenesis-ablated animals were housed in EE conditions, they presented a submissive behavior facing a stressful situation, confirming the relevance of adult hippocampal neurogenesis to favor resilient behaviors [137]. Going further, it was found that a certain level of glucocorticoid secretion during EE housing condition is necessary to promote neurogenesis [138].

On the other hand, acetylcholine (ACh) neurons in the basal forebrain have been shown to be activated by different mild stressors leading to an increase of acetylcholine release in the PFC [139, 140]. In this regard, Segovia *et al*. (2006)

[133] have reported that the release of ACh in the PFC is reduced in enriched animals during aging, suggesting a lower reactivity of the prefrontal cholinergic system to handling stress. In the same way, Segovia *et al*. (2009) [141] have also found that the overall release of dopamine produced by stress was lower in animals housed in the enriched environment when considering all groups of age. These effects of EE on stress reactivity of acetylcholine and dopamine during aging might provide the aged animals with an advantage in their abilities to cope with stress.

There has been a growing interest in the role of the inhibitory networks composed of different types of GABAergic neurons on anxiety and mood disorders [142]. In particular, altered function or reduced number of these neurons in brain regions, such as the medial prefrontal cortex (mPFC), has been found in depression and bipolar disorder and also during aging, which could explain, in part, the higher vulnerability to anxiety disorders at advanced ages [143-145]. However, aged rats exposed to EE for 8 weeks have shown an increase in the extracellular levels of GABAergic compared to standard-housing condition rats [133]. Related to this, our group found that EE increased the expression of parvalbumin-positive cells in some medial prefrontal regions, such as cingulate and prelimbic cortices involved in the regulation of stress-related behaviors [12].

A very recent study has suggested a relationship between affective behaviors and nitric oxide synthase (nNOS) expression in aged mice [146]. nNOS is rich in the limbic system [147], an area involved in affective behaviors. Moreover, a recent study reported that coupling between nNOS and its carboxy-terminal PDZ ligand (CAPON) in the hippocampus can serve as a target for anxiolytic drugs [148]. With age, it has been described an increase in nNOS protein levels, which induce abnormalities in affective behaviors. Tomiga *et al*. (2016) [146] have found that EE reduced anxiety-like behaviors in aged mice and reduced nNOS expression levels in the cerebellum, but not in the cortex. However, as the authors mention, further studies are needed to determine the mechanisms that may mediate this process.

Interestingly, in a mice model of accelerated senescence (SAMP8) characterized by cognitive and emotional disturbances, EE was able to induce beneficial changes in behavior and cognitive parameters. The behavioral tests demonstrated an increase in locomotion and reduced anxiety, leading mice to be quieter and more sociable [149]. Moreover, the LOU/C/Jall rat is described as a model of successful/healthy aging. As compared to the Wistar strain from which it is originated, LOU/C/Jall rats have higher longevity, living 5–8 months longer than other commonly used strains and displaying delayed-onset cognitive deficits associated with age [150]. Recently, further experimental evidence showed that aged LOU/C/Jall rats display potent neuronal–glial cross-talk within the glutamatergic tripartite synapse [151, 152]. It could, therefore, be speculated that such a crosstalk may be used as a mechanism to mitigate late life depression. Indeed, it was recently reported that mice displaying overexpressed D-serine-dependent neuronal–glial cross-talk showed a reduced depression-related behaviors in several specific tests [153]. This type of animal models can give us more information about neurobiological mechanisms of resilience.

Furthermore, Lehmann and Herkenham [154] have found that EE could induce resilience by increasing infralimbic outputs toward limbic regions, and even lesions in the prefrontal subregions abolished the resilience afforded by EE. In support of this idea, it has been also suggested that EE increases the control exerted by infralimbic cortex over the HPA axis [155]. On the other hand, several studies have found that resilient mice exposed to predator or social defeat stress showed an increase of c–Fos, FosB, or ΔFosB expression in glutamatergic neurons of infralimbic cortex [156-158]. Related to this hypothesis, it has been shown that the stimulation of mPFC neurons with optogenetic mechanisms (rhodopsin, ChR2) promoted resilience to social defeat stress [157] and the specifically stimulation on glutamatergic neurons in this brain region showed that the optogenetic stimulation of the glutamatergic microcircuit from mPFC to accumbens nucleus is antidepressant [158]. Hence, it seems that glutamatergic circuits take part of the brain basis of resilience.

Of interest, several studies have highlighted the role of the neuropeptide oxytocin (OT) in reducing anxiety, fear and increasing social behaviour, being a resilience trait [159-161]. However, the involvement of this hormone as a stress buffer during aging is not well examined [162]. Studies with aged rats have found an age-related decrease in the central OT activity [163] and also, a reduction in the number of OT receptors in several brain areas [164]. Nevertheless, although rodent studies have provided evidence for age-related decrease in OT, human studies have provided mixed evidence [165, 166]. Respect to EE, none study has tested the effect of this housing condition on OT levels during aging, but notably, EE has shown to improve the attachment behavior by modulating estrogen receptor and OT brain levels [167]. In contrast, it was found that the resilience-inducing properties of EE are linked to NPY. Specifically, NPY KO mice did not show the beneficial effects of EE when they are exposed to a stressful experience, such as in the EPM [168].

Finally, cytochrome C oxidase activity (COX) is a good technique to detect regional brain activity changes relative to control conditions allowing to link information about neurometabolic profiles and behavioral phenotypes [169, 170]. Our group have found that aged, enriched rats, subjected to a stressful situation such as spatial learning task in the radial-arm water maze, had lower metabolic activity (COX activity) in brain areas involved in stress response (bed nucleus of the stria terminalis and basolateral and central amygdala, among others) [7]. Hence, we hypothesize that the improved performance of aged rats in cognitive tasks could be explained, in part, by a better control and coping with stressful situation during aging.

CONCLUSIONS AND FUTURE DIRECTIONS

Firstly, it is important to define and measure resilience reliably in old humans. Thus, future research should include reliable and validated measures of biopsychosocial aspects of resilience and associated biomarkers to design effective interventions. Ongoing work is identifying those biological changes that underlie flexible adaptability, as well as recognizing gene pathways, epigenetic factors and structural

changes that indicate lack of resilience and which may lead to negative outcomes. The major problem to study and measure resilience is the lack of an accepted operationalization of this construct due to its multidimensional nature [171].

Recently, one of the most emerging areas of resilience research has been focused on micro-RNAs as regulators of our behavior when we have to cope with adverse situations [172]. For example, a recent study of Chen *et al*. (2015) [173] have found that rats with enhanced vulnerability to chronic stress exhibites reductions in circulating miR-24-2-5p, miR-27a-3p, miR-30e-5p, miR-3590-3p, miR-362-3p, and miR-532-5p levels. In contrast, resilient rodents displayed reduced levels of miR- 139-5p, miR-28-3p, miR-326-3p, and miR-99b-5p compared to controls.

On the other hand, in this review we have focused on the central nervous system, but some evidences have related the autonomic nervous system with resilience and vulnerability [174]. Thus, using the methodology called *heart rate variability*, it was found that an increase in basal vagal tone is associated with an increase in stress resilience due to its involvement in faster stress recovery [175]. Hence, this physiological parameter could be used as reliable measure of resilience. However, we are just beginning to identify such resilience factors due to the lack of coordination between human and animal studies.

Secondly, it would be interesting to identify compounds known as *environmetics drugs* that mimic or enhance the effects of environmental stimulation with the aim to prevent, treat and cure psychopathological disorders [176]. Furthermore, that knowledge will be important to develop novel interventions to increase the well-being in older age.

LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
ACTH	=	Adenocorticotropic hormone
BDNF	=	Brain derived neurotrophic factor
CORT	=	Corticosterone
COX	=	Cytochrome c oxidase activity
CRH	=	Corticotropin-releasing hormone
DA	=	Dopamine
EE	=	Environmental enrichment
EPM	=	Elevated plus maze
FST	=	Forced swim test
HPA	=	Hypothalamic-pituitary-adrenal axis
GC	=	Glucocorticoid
GR	=	Glucocorticoid receptor
mPFC	=	Medial prefrontal cortex
MR	=	Mineralocorticoid receptor
nNOS	=	Nitric oxide synthase
NO	=	Nitric oxide
NPY	=	Neuropeptide Y
OT	=	Oxytocin
PFC	=	Prefrontal cortex
PVN	=	Hypothalamic paraventricular nucleus
VP	=	Vasopressin

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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