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REVIEW ARTICLE

The Long Run: Neuroprotective Effects of Physical Exercise on Adult Neurogenesis from Youth to Old Age

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Abstract: ***Background*:** The rapid lengthening of life expectancy has raised the problem of providing social programs to counteract the age-related cognitive decline in a growing number of older people. Physical activity stands among the most promising interventions aimed at brain wellbeing, because of its effective neuroprotective action and low social cost. The purpose of this review is to describe the neuroprotective role exerted by physical activity in different life stages. In particular, we focus on adult neurogenesis, a process which has proved being highly responsive to physical exercise and may represent a major factor of brain health over the lifespan.

***Methods*:** The most recent literature related to the subject has been reviewed. The text has been divided into three main sections, addressing the effects of physical exercise during childhood/ adolescence, adulthood and aging, respectively. For each one, the most relevant studies, carried out on both human participants and rodent models, have been described.

***Results*:** The data reviewed converge in indicating that physical activity exerts a positive effect on brain functioning throughout the lifespan. However, uncertainty remains about the magnitude of the effect and its biological underpinnings. Cellular and synaptic plasticity provided by adult neurogenesis are highly probable mediators, but the mechanism for their action has yet to be conclusively established.

***Conclusion*:** Despite alternative mechanisms of action are currently debated, age-appropriate physical activity programs may constitute a large-scale, relatively inexpensive and powerful approach to dampen the individual and social impact of age-related cognitive decline.

Keywords: Adult neurogenesis, aging, Alzheimer's disease, cognitive and brain reserve, depression, hippocampus, physical exercise, stress disorders, traumatic brain injury.

INTRODUCTION

Several studies carried out in rodents and humans reveal that physical exercise can produce a profound alteration in brain homeostasis and intellectual skills [1], with putative effects on different cerebral roles, such as memory and attention. At the same time, clinical and epidemiological data have emphasized that running helps functional rescue from brain damage, diminishes the risk of intellectual decrease in older adult [2], and provides antidepressant action in patients with mild to moderate depression symptoms [3]. Moreover, it has been clearly stated that running might contribute to ameliorate blood flow in brain and to decrease general inflammation, by affecting the deposition of abnormal protein and enhancing the expression of neurotrophic factors (such as BDNF and IGF-1) [4]. Finally, many observations indicate that physical activity highly diminishes the risk of several diseases by counteracting the onset of cardiovascular insults, stroke, osteoporosis, cancer and obesity-related complications [5]. In fact, the indication supporting the cognitive benefits of exercise is so conclusive that the collective findings from basic and preclinical studies are being studied to categorize potential molecular targets for novel "pharmacomimetics of exercise" [6]. More generally, it is widely recognized that physical activity as a lifestyle represents a pivotal issue for the enhancement and preservation of body and brain wellbeing during the different stages of life. In this regard, physical activity has recently received particular attention as a potential brain health method able to raise human cognitive function and to increase brain health throughout the lifespan [7]. In recent years, thanks to a number of investigations on mouse brain, a direct relationship between physical activity and hippocampal neurogenesis has become apparent [8, 9]. Indeed, it has been demonstrated that improvement in neurogenesis and enhanced synaptic plasticity after physical activity are strictly correlated with a significant increase in hippocampus-dependent learning and memory tasks [10-13]. Interest in adult neurogenesis has also grown because

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numerous clinical data have related mental and neurological disorders, such as drug abuse, major mood disorders and neurodegenerative diseases, with modification in the degree of adult neurogenesis [14-16]. At the same time, several pieces of evidence establish that running positively affects rodent adult hippocampal neurogenesis. Many studies state that, in rodents, voluntary exercise more than doubles the number of newly generated hippocampal granule cells in the young and aged brain [17, 18] and influences all aspects of neurogenesis, such as cell proliferation, differentiation, and survival, inducing an enhancement of LTP and synaptic plasticity [18-20]. Moreover, voluntary running is able to increase neuronal complexity by enhancing spine density, dendritic arborisation in the adult DG [21-23] and to increase hippocampal volume by inhibiting an early age-related grey matter loss, with exercise-induced increase of macroscopic brain morphology being blocked by disruption of neurogenesis following focal irradiation [24]. These events are functional to improve learning and memory performance in several hippocampus- dependent behavioural tasks, such as radial arm maze, object recognition, Morris water maze and Pavlovian conditioning [25-27]. Surprisingly, recent data show that exercise induces neurogenesis also in other brain regions such as hypothalamus and ependymal cell layer, contributing to the partial rescue of brain homeostasis after cerebral damage [28]. Conversely, the subventricular zone (SVZ), which represents the main neurogenic niche in the adult mouse brain [29], seems not to respond to exercise [30], although this issue remains debated [31], as a recent paper demonstrates that the number of SVZ-derived neurospheres raises with voluntary running in aged mice [32]. In this review we will discuss recent data regarding the beneficial effect of exercise on hippocampal neurogenesis from the developmental stage to adulthood and aging, with particular emphasis on the cellular and molecular mechanisms involved in this process and the neuroprotective actions exerted by physical exercise on healthy and diseased brain.

ADULT HIPPOCAMPAL NEUROGENESIS

The discovery that new neurons are produced in specific neurogenic niches of adult mammalian brain throughout life has triggered great interest and chief improvements in the field of neurobiology. Neural stem cells are characterized by the remarkable ability to exit from quiescence, self-renew, proliferate and produce three different cell types, neurons, astrocytes and oligodendrocytes. The production of new granule cells occurs in the adult dentate gyrus (DG), a hippocampal subfield mediating different aspects of learning and memory formation and, in particular, contributing to pattern separation - *i.e*., the ability to finely discriminate between similar to-be- remembered objects or contexts [33-35]. Adult neurogenesis in the DG is tightly regulated by multi-step mechanisms including the maintenance, recruitment and division of quiescent neural stem cells, the early differentiation and migration of neural progenitors and, finally, the maturation and functional integration of newly generated neurons. The fate of a newborn cell within the neurogenic niche can easily be determined by analyzing its morphological features, such as the expression of specific markers throughout different developmental stages of differentiation. Based on these parameters, different stages of newborn neurons maturation have been recognized: neural stem cells (type-1 cells), identified by expression of glial fibrillary acidic protein (GFAP), hairy and enhancer of split 5 (Hes5), nestin and SRY- related HMG-box gene2 (Sox2) [36-38], give rise to proliferating intermediate progenitor cells (type-2ab) which exhibit a less pronounced potential of self-renewal [39]. More differentiated progenitor cells (type-3 cells) express the neuronal marker doublecortin (DCX), and the transcription factor, NeuroD, which clearly indicates the neuronal-restricted fate of the progenitor cells [40].

The NeuroD positive neuroblasts briefly proliferate, exit the cell cycle and migrate into the external granule cell layer, where they start to form synaptic connections and mature in adult neurons [41, 42]. Morphological and electrophysiological data indicate that newly generated granule cells are functionally recruited into the DG network within 3 weeks, by spreading their axons to the CA3 area [43]. As newborn cells undergo terminal differentiation, the dendritic arborization becomes progressively more complex and the neuritis extend deeper into the granule cell layer. These cells can be recognized by their peculiar changing in synaptic input and firing patterns as they differentiate. Recent studies demonstrate that, similarly to differentiating neurons during brain development, newly generated granule cells, display limited dendritic arborization and receive excitatory GABAergic synaptic inputs. The early depolarization by GABA has been shown to facilitate the maturation of granule cells, as a significant decrease of neuronal maturation is strictly linked to the absence of the chloride ion channel NKCC1 [44]. About three weeks after birth, concomitantly with spine formation, the response of newborn neurons to GABA changes from depolarization to hyperpolarization, which coincides with the beginning of glutamatergic signaling.

During this period, the developing progenitors are highly excitable with high membrane resistance and display a lower threshold for long-term potentiation (LTP), a putative model of learning and memory processes [45], in response to theta-burst stimulation [44, 46], with a concomitant enhanced synaptic plasticity. Fully matured newly generated neurons respond to glutamatergic and GABAergic inputs, similarly to the pre-existing DG granule cells [47, 48]. Two independent studies have demonstrated that new hippocampal granule cells are recruited in learning and memory networks at a later stage of maturation (around 4-6 postnatal weeks); [49, 50]. Before this time point, the differentiating granule cells, despite their lower threshold for LTP, do not express the activity-dependent immediate early genes (IEG), which are expressed in functional activated neurons. Intriguingly, however, the animal's experience in this time-window can profoundly affect the expression of activity-dependent IEGs in newborn neurons at 6 weeks of age [48, 51]. Although convergent evidence supports the hypothesis that adult DG newly generated neurons are specifically recruited in the pre-existing memory network [52], the role of these cells in the context of hippocampal functions is still matter of discussion. Most of the relevant data on the role of the DG in learning and memory have adopted strategies of ablation of adult neurogenesis obtained by antimitotic drug administration [53], low-dose irradiation [54] or genetic manipulation to eliminate proliferating neural progenitors. While both

antiproliferative treatments and irradiation eradicate hippocampal cell proliferation non-specifically, causing detrimental effects on brain physiology and providing contradictory results, the use of more specific, non-invasive genetic approaches has provided clear proofs on the role of adult hippocampal neurogenesis in pattern separation [55, 56]. Indeed, it has been established that, impaired neurogenesis abolishes the capacity of mice to finely discriminate similar stimuli delivered with little separation in space; on the contrary, when the same stimuli are presented separated in time or space, the defective neurogenesis does not exerted any detrimental effect in recognizing these events as different [57]. Moreover, animals with defective neurogenesis are severely compromised in the discrimination of comparable contexts in a fear conditioning memory paradigm [34, 35]. Finally, computational models indicate that new hippocampal neurons would help to avoid interference between new and established memories [58, 59].

THE EFFECT OF EXERCISE ON ADULT NEUROGENESIS

As mentioned above, physical exercise represents one of the main inducer of adult hippocampal neurogenesis. To analyze the effect of physical activity in mice and rats, usually the rodents are put in a cage with a freely available running wheel [60, 61]. In many studies it has been calculated that mice run nearly from 3 to 8 km per night, reflecting their natural physical activity [60, 61]. In turn, running induces a 2-3 times increase of hippocampal newly generated neurons, an effect detected as early as 24 h after voluntary running [17, 18, 62]. Kronemberg and colleagues demonstrated that voluntary physical activity mostly influences the proliferation of type-2 and-3 precursor cells [62, 63], which consequently induces a large increment of late type-3 cells and post-mitotic granule cells localized in the subgranular zone of DG. To this regard, a recent study proposes that the S-phase length of the cell cycle may represent a key mediator of the pro-neurogenic action of physical exercise in the subpopulation of newly generated neurons expressing NeuroD1 [64]. Other morphological data demonstrate that physical exercise is able to largely enhance the length, arborisation and spine density in the newborn granule cells [65] localized in the whole granule cell layer [66], suggesting that running may also influence the synaptic plasticity and the rate of newborn cells integration into the pre-existing hippocampal memory network. These morphological modifications very likely are the cellular substrate for the lowered threshold of LTP detected in the DG, but not in CA1, of running mice, in comparison with sedentary controls, indicating that the increased synaptic plasticity of the DG is strictly dependent on the running-dependent enhanced neurogenesis [67]. An important confirmation of the positive role of physical exercise in the processes of DG-dependent learning and memory comes from a recent study in which it has been revealed that voluntary running enhances the ability of mice to discriminate between the locations of two adjacent identical stimuli. In the same study, the authors found that aged mice refractory to running have low basal neurogenesis and consequently impaired spatial pattern separation, which confirms a positive correlation between running, hippocampal neurogenesis and pattern separation [25]. Altogether, these results open new questions relating to the cellular and molecular pathways orchestrating the beneficial actions of running on neuronal morphology, function and plasticity. To this regard, convergent evidence suggests an important contribution of neurotrophins to the pro-neurogenic effects of running in the adult neurogenic niches. Indeed, different studies indicate that the increase of brain-derived neurotrophic factor (BDNF) levels might represent the main event prompting the cognitive improvement after running. BDNF is a neurotrophin that positively modulates neural survival, growth and synaptic plasticity by the induction of LTP and synaptic transmission [68, 69]. Other Authors indicate that in the adult hippocampus running is able to enhance the BDNF expression only in the DG [70], and that this increase lasts for at least two months and is re-induced after a sedentary period of up to 2 weeks [71], clearly suggesting the presence of a "molecular memory" for BDNF in mice that have previously experienced physical exercise. Interestingly, it has been shown that several genes upregulated after running specifically interacts with BDNF, confirming again the pivotal role of this neurotrophin in running-dependent neural plasticity [68].

Moreover, it has been suggested that the levels of the phosphorylated form of the BDNF receptor TrkB are strongly induced by running, and that this activation seems to be necessary for the running-induced enhancement of hippocampal function, since the addition of a TrkB antibody, which inactivates the BDNF activity, is sufficient to eliminate the enhancement of spatial learning [72]. The contribution of the BDNF pathway in regulating the positive effect of running is confirmed by a study in which its ablation by BDNF siRNA is sufficient to inhibit exercise-dependent improvement of spatial learning [73].

Other trophic factors mediating the pro-neurogenic effect of running comprise endotelial growth factor (VEGF) and insulin like growth factor I (IGF-I). The hypoxia-inducible protein VEGF induces angiogenesis by means the action of the receptor tyrosine kinase on endothelial cells [74], whose activation has been detected in the cortex and hippocampus after 6 weeks of wheel running [75], suggesting that VEGF may promote the running-dependent increase of endothelial cells [76] and angiogenesis [77, 78]. Similarly to BDNF, IGF-1 level is enhanced in both the hippocampus and the blood of mice within 1 hour of running [79]. Peripheral increase in IGF-1 plays a role in enhancing hippocampal neurogenesis and hippocampus- dependent learning and memory as depletion of circulating IGF-1 totally eliminates the exercise-induced hippocampal cell proliferation [80]. Finally, other studies demonstrate that the effects of exercise are absent in IGF-1 null mice [81], and that the injection of anti-IGF into the hippocampal region attenuates the improvement in spatial recall exerted by physical exercise [82], confirming that IGF-1 interfaces with BDNF to regulate several features of running-dependent cognitive improvements.

In another research it has been demonstrated that the negative regulator of adult neurogenesis, bone morphogenetic protein (BMP), is strictly involved in the regulation of the positive effects of running on both hippocampal neurogenesis and learning and memory [83]. Indeed, the

levels of BMP are strongly decreased after running, and a mouse model with reduced BMP expression is characterized by enhanced hippocampus-dependent memory and increased number of newborn neurons, similar to the benefit observed after physical exercise. On the contrary, the running-induced neurogenesis is totally abolished when BMP4 is overexpressed [83]. These data are fully in agreement with previous result highlighting that the BMP/BMPR1A signaling pathway plays a pivotal role in maintaining the radial stem cell quiescence in the adult dentate gyrus, indicating that running is able to trigger hippocampal neurogenesis by a specific downregulation of the negative instruction exerted by BMP [84].

Another recent study has demonstrated that the Wnt signalling inhibitor Secreted frizzled-related protein 3 (Sfrp3) plays an important role in mediating the beneficial actions of running on adult hippocampal neurogenesis [85]. Indeed, the activation of quiescent radial stem cells and the proliferation of granule cell progenitors are largely dependent on the deletion of Sfrp3, suggesting that the reduction of Sfrp3 expression is necessary for the running-dependent increase of hippocampal neurogenesis. Moreover, another research demonstrates that the adipocyte-secreted adiponectin (AND) contributes to the beneficial action of running on hippocampal neurogenesis, probably by stimulating the adiponectin receptor (ADNR1)/AMP-activated protein kinase (AMPK) signaling pathways [86].

Many pieces of evidence support the hypothesis that microglia activation plays a pivotal role in mediating the running-dependent enhancement of hippocampal neurogenesis. Indeed, in transgenic mice tagging microglia cells, it has been observed that increased neurogenesis after running is strictly dependent by the activation of endogenous microglia; moreover, when hippocampal neurosphere cultures are depleted from microglia, the beneficial effects of running on newborn granule cells are totally abolished [87].

THE NEUROPROTECTIVE EFFECT OF PHYSICAL EXERCISE

Neurodegenerative diseases have become more prevalent due to lengthening of age-expectancy, sedentary lifestyles and other multifactorial events, representing a serious issue for national healthcare systems [88]. Since inactivity represents a major risk factor for many diseases, physical activity in humans has recently emerged as topic of potential clinical interest. Many studies demonstrate that exercise has a negative relationship with the outcome of different neuropsychiatric diseases, such as stress/depression disorders, Alzheimer's disease and Parkinson's disease, being able to ameliorate the patient's quality of life, and, to lesser extent, the disease itself [89, 90]. An intriguing hypothesis states that the influence of exercise on brain functioning might be directly fixed into human evolution, in that physical activity is strictly correlated with survival and individuals who exercise might show a biological advantage over sedentary individuals [91]. This section reviews the most recent literature describing the neuroprotective effects exerted by physical exercise on rodent and human brain, from childhood/adolescence until old age.

NEUROPROTECTIVE EFFECT OF PHYSICAL EXERCISE IN CHILDHOOD/ADOLESCENCE

Although it would be particularly important to evaluate the effect of running during adolescence, the post- natal brain developmental stage of maximum plasticity [92], only few studies have investigated this issue in animal models. In a recent paper, Hopkins and colleagues have analyzed the effect of 4 weeks of voluntary running in adult and adolescent rats on a hippocampus-dependent memory task (the novel object recognition, NOR) and hippocampal BDNF levels. They found a significant age-related differences in the duration of the effect of running: two or four weeks after the end of the test, rats which had been running during adolescence could effectively discriminate between novel and familiar objects in the NOR, while the positive effect of running disappeared in the adult runners, which suggests that exercise occurring earlier in life might exert a more persistent effect on brain functioning [26]. The potentiated effect of running in adolescence is likely related to the reorganization, both morphological and functional, that occurs at this stage of life, when the transiently higher neuroplasticity may promote enduring changes in response to environmental stimuli (including exercise). Nonetheless, little is known about the neurobiological or electro-physiological underpinnings of the enhanced action of physical exercise in adolescence. Titterness and colleagues have evaluated the effects of running on synaptic plasticity in the hippocampus of adolescent rats, showing that 14 days of running greatly enhanced LTP exclusively in adolescent males. This result suggests that, despite comparable running patterns, adolescent males and females are differentially sensitive to the effect of physical exercise on hippocampal synaptic plasticity [20]. Another study aimed at evaluating the neuroprotective action of physical exercise in the fetal alcohol spectrum disorders (FASD), characterized by a range of neurobehavioral deficits including physical, cognitive and behavioral disabilities. In rodents, prenatal alcohol exposure causes a long-lasting impairment of neurogenesis in the adult hippocampus, with a reduction in the number of DG granule cells [93] and impaired hippocampal functioning [94, 95]. Similarly, prenatal alcohol exposure in humans alters hippocampal anatomy [96] and is associated with deficits in hippocampus- dependent learning and memory [97, 98]. A recent study on rats has evaluated a possible link between developmental alcohol exposure, physical activity and hippocampal adult neurogenesis, showing that 12 days of voluntary running in post-weaning rats with FASD symptoms partially restores adult neurogenesis in the DG and improves hippocampus-dependent memory [99]. Thus, the neuroprotective action of physical exercise may provide a basis for developing therapeutic interventions aimed at improving cognitive deficits associated with FASD in humans. Since any change exerted in the rodent brain by physical exercise is, conceivably, also critical with regard to the human brain functioning – in that both involve the processes of cell proliferation/apoptosis, dendritic branching/ pruning, synaptic formation/elimination, growth factors and myelination, which all have proven being highly responsive to physical exercise in animal models [100] – interest is growing on whether aerobic fitness may affect the human brain during childhood, a stage of life characterized by rapid

neural and cognitive development [101]. To this regard, it also has to be considered that, in the latest years, children are becoming increasingly sedentary [102]. A lazy lifestyle is linked with considerable increase in obesity, high blood pressure, and high risk of coronary heart disease throughout the lifespan [103], and these typically adult-onset diseases are becoming more and more prevalent during childhood [104]. Moreover, it is well established that adolescent with little physical activity display poorer academic achievement and lower cognitive performance compared to physically fit children [105-107]. This is consistent with data from research aimed at evaluating the neuroprotective effect of exercise in the young population. A recent study has demonstrated that, in childhood, high levels of aerobic fitness are associated with a superior ability in the retrieval of relational material [108]. Another study, with 15-18 year-old children, found a positive association between physical activity and spatial learning performance in a virtual Morris water maze task [109]. Moreover, a recent neuroimaging study using brain magnetic resonance revealed that 9-10 year-old children with higher aerobic fitness levels had larger bilateral hippocampal volume compared to less fit controls; significantly, the volume increase was correlated to higher relational memory [108].

NEUROPROTECTIVE EFFECT OF PHSYCAL EXERCISE IN ADULTHOOD

This section focuses on the neuroprotective action of physical exercise in relation to widespread adult brain disorders – *i.e*., depression/anxiety disorders and traumatic brain injury (TBI).

Depression and Anxiety Disorders

In adulthood, neuropsychiatric disorders represent debilitating conditions that severely degrade the quality of life [110-112]. Among these, major depression is the most prevalent disorder worldwide, and chronic stress represents one of the major risk factors for developing depression [113, 114]. In adult humans, the depressed mood can disrupt fundamental activities, such as eating and sleeping; and the rate of suicidal behavior is significantly higher in depressed patients compared to the general population [115, 116]. It has been suggested that defective adult neurogenesis may result in stress/depression disorders [117]. In fact, adult neurogenesis is altered following stress paradigms in rodents [118]. It has been hypothesized that, in major depression, the brain may be unable to respond to stressful stimuli with appropriate adaptive plasticity [119] – and impaired neurogenesis may represent one factor contributing to such a reduction of plasticity. The "neurogenesis hypothesis" of depression came from research carried out in rodent stress models. In particular, stressful stimuli such as sleep deprivation [120], subordination to a dominant animal [121], social isolation [122] and exposure to predator odor [123] have all proven to reduce neurogenesis, although not necessarily through the same mechanisms [124, 125]. Such hypothesis seems partly corroborated by three main lines of evidence [126]: (i) a volumetric decrease of the human hippocampus has been found in depressed patients, likely due to a reduced rate of neurogenesis (as neural degeneration does not occur in these patients [127, 128]); (ii) antidepressant medications, such as selective serotonin reuptake inhibitors, have been demonstrated to enhance neurogenesis in the adult mouse DG, and a similar effect has been detected after electroconvulsive treatment [117, 129]; (iii) the latency to the onset of therapeutic effect of antidepressant medications equals the time required for maturation of newly generated neurons (around 4-5 weeks), supporting the hypothesis that partial rescue from depressive symptoms may depend on the recruitment of new DG granule cell into the pre-existing neural circuitry [130]. However, the idea that reduced neurogenesis plays a causal role in the onset of depressive disorders has not been conclusively demonstrated so far, and a number of conflicting results have to be taken into account when attempting to assess its robustness [*e.g*., 131-133]. In recent years, some literature on the antidepressant effect of physical exercise has begun to emerge. Indeed, several epidemiological studies [134, 135] have shown that individuals who followed different programs of exercise displayed milder depressive symptoms and were less likely to develop major depressive disorder (MDD). Moreover, physical activity strongly reduced symptoms in non-diagnosed adults [136, 137], while adequate exercise has been found to alleviate symptoms of moderate-to-severe MDD significantly more than low-intensity aerobic exercise and flexibility exercise [138]. Accordingly, it has been shown that the antidepressant effect of moderate exercise extends past the treatment period, lasting up to 21 months [139, 140]. However, the neuro-chemical mechanisms mediating resistance to stress and depression are still unknown, given the difficulty of identifying molecular correlates of adult neurogenesis in humans. To this regard, studies in mice suggest that exercise-induced expression of hippocampal BDNF could be linked to the antidepressant action of physical exercise. Indeed, BDNF-knockout mice shows impaired antidepressant response [141] and either BDNF infusion or the overexpression of TrkB receptors in the hippocampus are able to induce a strong antidepressant-like response [142, 143]. This evidence provides useful insights on the function that running can exert to induce structural and functional modifications in the brain, and helps to elucidate the nature of MDD and to develop new therapeutic approaches. Many issues, however, have yet to be solved. Above all, it must be considered that most of the research on the effects of voluntary running on neurogenesis has been conducted in rodents and, at the moment, experimental data from human studies are only sporadic and correlational [144]. Therefore, additional work is needed to determine whether increased neurogenesis following exercise plays a causal role in mitigating MDD, or whether it is a mere epiphenomenal event associated with some other factors, such as BDNF. Finally, the results from two interesting studies implicating a direct link between adult neurogenesis and anxiety-related behaviour deserve to be mentioned. Fuss and colleagues found that mice performing voluntary wheel running had both increased neurogenesis and anxiety in three different behavioral paradigms. Intriguingly, decreasing neurogenesis by focalized irradiation of the hippocampus abolished the running-dependent enhancement of anxiety [145]. In the same vein, Onksen and colleagues observed that wheel running resulted in both increased neurogenesis and anxiety

in anxiety-sensitive behavioural paradigms. Also in this case, a reduction of neurogenesis achieved through conditional deletion the cell cycle checkpoint kinase ATR attenuated the anxiety-related behavior [146]. These observations suggest that neurogenesis may be directly implicated in – or a major mediator of – exercise-induced anxiety. More generally, they illustrate the case for wheel running as being potentially linked to negative side-effects which may give cause for concern. As an example, analogies can be found of wheel running with stereotypic or addictive behavior exerted by an otherwise non-rewarding laboratory environment. This hypothesis and its relevant implications are thoroughly discussed in [147].

Traumatic Brain Injury

Traumatic Brain Injury (TBI) refers to a mechanical insult to the brain, which results in neurodegeneration and cell death [148]. Individuals suffering from TBI often display disabilities ranging from long-term sensorimotor deficits, to cognitive impairment and vegetative state. TBI consists of two distinct phases, termed primary and secondary insults. Primary insults, completed within seconds from impact, are due to mechanical damage. Secondary insults result from a cascade of events including ischemia, exocitotoxicity, and metabolic failure [149]. Initially, rescue from TBI was believed to be severely limited, due to irreversible neuronal degeneration and loss [150]; however, increasing evidence indicates that endogenous neural stem and progenitor cells may exert a regenerative action following brain injuries. Studies from different laboratories have indicated that TBI significantly enhance cell proliferation in both SVZ and DG of adult rodents [151-153] and, furthermore, that injury-induced newborn neurons are able to integrate into the existing circuitry [154, 155] and promote cognitive recovery [155]. Accordingly, a recent study has found, in human brain specimens, a significantly increase of cells labelled with specific stem/progenitor markers in the perilesion cortex of the damaged brain [156]. In this context, a number of experimental results suggest a potentially important role of physical exercise in endogenous regeneration post-TBI. Exercise in the early aftermath of TBI largely increases the number of nestin-positive cells around the damaged area, including *in vitro* cultured neural stem cells isolated from injured brain tissue [157]. Also, the neuroprotective effect of exercise on the post-TBI brain is indicated by reduced volumetric differences between the damaged and contralateral hippocampus and lateral ventricle, and the density of mature neurons in the hilus and the perirhinal cortex [158]. Finally, 4 weeks of voluntary running preceding TBI in mice improved the recovery of sensorimotor performance, as well as cognitive/affective functions, compared to sedentary controls [159]. Notably, pre-exercise decreased lesion size, reduced neuronal loss in the hippocampus, activated the BDNF pathway and intensified the injury- dependent rise of heath shock protein 70 expression, thus antagonizing different apoptotic pathways. Altogether, these results support the notion that exercise treatment in the initial phase after TBI may represent an important aid for neuroprotection from induced cerebral dysfunction [159].

NEUROPROTECTIVE EFFECT OF PHSYCAL EXERCISE IN AGING

The rise of life expectancy has intensified the necessity to provide new approaches for the prevention and improvement of age-related brain dysfunction. Normal aging is characterized by modifications in brain structure and function, and consequential cognitive weakening, mainly due to inflammatory processes, oxidative stress, reduced synaptic plasticity and neurogenesis, leading to an irreversible loss of neurons and white matter volume [160]. Aging is characterized by a progressive memory impairment which is associated with a decline of hippocampal neurogenesis, although a definitive causal evidence of this relationship has not been established [161]. Several researches, performed in different species, have revealed that neurogenesis progressively drops with age, to the amount that, in the DG of 21-month-old rats, the number of newborn neurons is only 10% of what is detectable in 6-month-old rats [162]. The high decrease of newborn neurons in the aged hippocampus could be correlated with the sharp reduction of the division rate detected in the neural stem cells, which becomes gradually exhausted due to cell death, or differentiation into a variety of cell types such as astrocytes [37]. An alternative explanation hypothesizes that neurogenesis declines as a consequence of unfavorable changes of the cellular, molecular stem and environmental neurogenic niche composition, that progressively weakens the recruitment of neural stem cells from quiescence and their expansion [163]. The aged-dependent impairment of neurogenesis could also be influenced by the shortening of telomeres and by the loss of chromosome protection, which results in replicative senescence or genetic instability with loss of cell viability [164, 165]. Finally, chronically-elevated levels of corticosteroids may exert negative effects on hippocampal neurogenesis in later life, as adrenalectomy performed in aged animal restores neurogenesis up to the level observed in younger controls [166]. Despite the remarkable diminution in the level of hippocampal neurogenesis in the aged DG, other data concerning hippocampus-dependent cognitive performance are still ambiguous. In an investigation on three groups of rats of different ages, the oldest group - having a massive depletion of neurogenesis - did not display any significant alteration in test performance [167]. On the other hand, impairments in long-term potentiation, synaptic plasticity and behavioral functions have been detected in aged animals [168, 169]. While the aged-related reduction of hippocampal neurogenesis has been observed across several species [170], it has yet to be definitively assessed in humans, even though recent studies based on the expression pattern of cell markers in human samples [171] and MR imaging [172] provide evidence of a reduction of cell number and volumetric extension in the aged human DG. Several lines of evidence suggest that physical activity counteracts the cognitive decline occurring in late adulthood [173]. Prospective studies have shown that physical exercise correlates with lower incidence of dementia [174], and randomized clinical trials have revealed that aerobic exercise can lower the rate of cognitive decline in the elderly [89]. The improvement may be linked to structural variations in the central nervous system, since greater extents of physical activity are

prognostic of larger hippocampal volume in healthy elderly individuals [175]. In fact, it has been observed that regular exercise during old age is able to enhance hippocampal volume up to 2% and to ameliorate performance in spatial and episodic memory tasks [176, 177], as well as attention [178]. However, whether physical exercise – when begun later in life – can arrest the cognitive decline associated with aging is unknown. The mechanism through which physical activity counteracts cognitive decline is also unclear, but imaging studies have demonstrated a lower amount of aged - dependent brain atrophy among those who exercise [179]. Recent investigations have also focused on neurogenesis and synaptogenesis. Several studies have demonstrated that exercise improves neurogenesis and learning in aged mice [17, 25, 63, 180]. In particular, Wu and colleagues have observed that voluntary running rescues impaired pattern separation in aged mice, in association with a large enhancement of immature neurons with tertiary dendrites [181]. Moreover, Siette and colleagues have found that 12 weeks of voluntary running in aged rats are sufficient to increase hippocampal neurogenesis, presynaptic density, synaptic connectivity and place recognition performance, raising the possibility that exercise started in elderly may counteract some forms of intellectual decline [180]. Whether the different effects of running on the aged hippocampus share a common signaling pathway is still unclear, but there is evidence that BDNF could be among the major mediators. In fact, the BDNF gene expression in the hippocampus declines sharply with age; however, the deficit is significantly improved in mice that engage in voluntary running [182]. This bulk of data suggests the intriguing possibility that a lifestyle, or pharmacological intervention, aimed at improving hippocampal neurogenesis might be at least partially effective in reversing some aspects of cognitive decline observed during aging.

Alzheimer's Disease

Although epidemiological studies have related a regular physical activity with a reduced risk of developing Alzheimer's disease (AD), the biological underpinnings of such benefit remain inconclusive [183]. AD –the most common cause of senile dementia – is characterized by synaptic pathology, intracellular accumulation of tau protein, extracellular accumulation of β-amyloid, and loss of specific neuronal populations [184]. It has been proposed that abnormal hippocampal neurogenesis may contribute to cognitive worsening in AD [185, 186], as a consequence of the changes of amyloid precursors and tau metabolism that disrupt the permissive cues within the neurogenic niche for the genesis and maturation of new neurons [186-188]. Epidemiological data give support to the idea that exercise reduces the incidence of AD [189, 190], suggesting that physical activity is correlated with decreased frequency of AD [191] and higher rate of survival in patients diagnosed with AD [190, 192]. Other clinical evidences indicate that regular exercise reduces Aβ deposition and preserves from brain atrophy and temporal lobe volume loss [193, 194]. Finally, a recent study has confirmed that 30 min of daily physical training significantly reduces the number of hospitalizations in AD patients, decreasing depressive symptoms and improving their quality of life [195]. In the last years, the use of transgenic mice models of AD has become a priority in exploring potential therapeutic strategies, while recent findings suggest that physical exercise reduces AD-like pathology in mouse models of AD. Moreover, in transgenic mice (tgCRND8 and Tg2567) expressing human mutant amyloid precursor protein (APP), physical exercise not only decreases the levels of soluble fibrillar Aβ oligomer [196] and brain Aβ load [197], but also causes a large improvement in hippocampus- dependent learning and memory. In other transgenic lines, running preserves hippocampal structure and function and results in strong improvement in several memory task performances [198-200]. However, conflicting reports have showed that, in transgenic mice APP-23, voluntary running fails to decrease Aβ levels [201], and others have detected no effect of environmental enrichment on Aβ, despite improvements in learning and memory [202]. These results suggest that Aβ becomes resistant to running-dependent clearance once it reaches a plateau of deposition with age. With regard to the neuroprotective role of physical exercise on hippocampal neurogenesis, recent findings indicate that prolonged voluntary running induces hippocampal neurogenesis in the double transgenic APPswe/PS1ΔE9 mouse line, concurrently reducing spatial memory loss [203], and a previous study found a beneficial effect of running on neurogenesis in the 3xTg mouse model of AD, without detecting any change in Aβ neuropathology and tau accumulation [204]. Other works, however, have failed to observe any significant improvement of neurogenesis in AD transgenic mice [201, 205]. Such discrepancies are possibly explained by different characteristics of transgenic mouse strains, the age of mice, the stage of neurodegenerative processes and/or different voluntary running protocols.

The Brain and Cognitive Reserve Hypothesis

The idea of a reserve against brain damage was originally proposed to explain the lack of relationship between the extension and clinical manifestations of the damage. This hypothesis was further applied to explain individual differences in cognitive performances, particularly in situations in which people have to perform at maximum level [206]. The concept of reserve entails both a passive and an active model. The first refers to a quantitative model, derived from the threshold model [207], according to which quantitative differences in brain resources (*i.e.*, a larger brain, more neurons and synapses) can explain individual differences in task performance or in coping with neuropathologies. The second refers to the cognitive capacity of information processing and predicts that differences in the efficiency or flexibility of the brain network underlying task performance affect the individual capability to cope with brain pathology. Thus, the cognitive reserve is a functional concept suggesting that brain can compensate pathological decline by using pre-existing cognitive processes [206, 208, 209]. Recently, Whalley and colleagues [210] considering data from a program on brain aging and health in the Aberdeen Birth Cohort, found a relationship between socioeconomic factors in the life course (*i.e.*, educational and occupational levels), cognitive function, hippocampal size and the risk of developing cerebrovascular diseases or dementia. On this basis, the authors proposed that the

promotion of cognitive reserve through a healthy lifestyle (educational programs, social engagement, cognitive demand and diet) could mitigate adverse effects due to aging [210]. There are also epidemiological studies showing that lower educational attainment and occupational levels, as well as a sedentary lifestyle, are strong predictors of increased risk for dementia and worsened clinical changes in several other conditions, including TBI [211] and Parkinson's disease [212]. Conversely, a correlation between better cognitive functioning in old age, and a greater engaging in leisure activities, higher educational attainment or higher cognitive level of occupation in the middle adulthood has recently been found [213]. Moreover, engagement in intellectual or social leisure activities and physical exercise can protect against the clinical manifestations of Alzheimer's disease through neuronal compensation [214, 215]. In this context, the effect of physical exercise on adult neurogenesis might contribute to a structural or neural reserve that, in turn, provides a compensatory buffer of brain plasticity in the face of increasing neurodegeneration or age-related cell loss [216]. For this reason, an increasing number of studies are being investigating specific factors linked to physical activity that may be relevant to brain and cognitive reserve [217].

CONCLUSION

The data reviewed here indicate that physical activity may have a positive effect of brain function throughout the lifespan, providing a non-pharmacological approach to reduce age-related cognitive decline in older adults. In fact, higher levels of physical exercise are correlated with decreased risk for intellectual impairment and neurodegenerative disease, highlighting the importance of developing social programs aimed at promoting physical activity across the lifespan, in order to reverse the growing obesity and cardiovascular disease trends as well as the neural degeneration and cognitive decline [218]. Further research is necessary to ascertain the most beneficial characteristics of exercise programs, even if some pieces of evidences support long-term and multi-component exercise programs to enhance overall functioning in humans [3]. However, in the recent years it became increasingly clear that physical activity might play a different effect on the physical/mental wellbeing and also on adult neurogenesis, depending on the strength and lengthening of exercise. As to regard the adult neurogenesis, some studies have shown that an excessive load of physical activity can have deleterious effects on BDNF expression [219], newborn immature neurons [220] and spatial memory [221], by returning the abovementioned parameters to the values measured in the sedentary animals. Taking inspiration from these evidences a very recent work has proposed an interesting hypothesis suggesting that adult neurogenesis might display a putative hormetic-like biphasic dose-response to exercise [222]. Research on rodent has begun to elucidate the molecular and cellular mechanisms activated by voluntary running that are likely to sustain the positive effect of physical exercise on cognition and memory, which is mediated, at least in part, by increased angiogenesis, synaptogenesis and hippocampal neurogenesis. In the hippocampus, structural modifications of dendritic morphology are thought to play a major role in neuronal functioning [223]; in this context, adult neurogenesis in the DG provides additional plasticity to the hippocampal circuitry [224, 225]. The increase of neural stem/progenitor cells in the DG neurogenic niche, together with the increase of synaptic plasticity in existing neurons, may be essential mediators of the improvement of hippocampus-dependent memory exerted by physical exercise. The recent observation that, in the absence of anti-proliferative inhibition, voluntary running is sufficient to activate and expand the pool of quiescent neural stem cells in the adult DG [50, 226], provides an interesting starting point for the investigation of the "run-activated" neural stem cells as a potential tool for the replacement of neurons lost because of aging or neurodegenerative diseases.

CONFLICT OF INTEREST

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

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