Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors

Carlos Campos, Nuno Barbosa F. Rocha, Eduardo Lattari, Flávia Paes, António E. Nardi & Sérgio Machado

To cite this article: Carlos Campos, Nuno Barbosa F. Rocha, Eduardo Lattari, Flávia Paes, António E. Nardi & Sérgio Machado (2016): Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2016.1179582

To link to this article: http://dx.doi.org/10.1080/14737175.2016.1179582
Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors

Carlos Campos, Nuno Barbosa F. Rocha, Eduardo Lattari, Flávia Paes, António E. Nardi and Sérgio Machado

ABSTRACT
Age-related neurodegenerative disorders, like Alzheimer’s or Parkinson’s disease, are becoming a major issue to public health care. Currently, there is no effective pharmacological treatment to address cognitive impairment in these patients. Here, we aim to explore the role of exercise-induced trophic factor enhancement in the prevention or delay of cognitive decline in patients with neurodegenerative diseases. There is a significant amount of evidence from animal and human studies that links neurodegenerative related cognitive deficits with changes on brain and peripheral trophic factor levels. Several trials with elderly individuals and patients with neurodegenerative diseases report exercise induced cognitive improvements and changes on trophic factor levels including BDNF, IGF-I, among others. Further studies with healthy aging and clinical populations are needed to understand how diverse exercise interventions produce different variations in trophic factor signaling. Genetic profiles and potential confounders regarding trophic factors should also be addressed in future trials.

1. Introduction
Elderly population is rapidly increasing all around the world. In 2010, there were a total of 524 million people aged 65 or older and by 2050, this number is estimated to triple to 1.5 billion [1]. As life expectancy also increases, age-related neurodegenerative disorders, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), are becoming more prevalent and represent a major issue to health-care systems [2,3].

Neurodegenerative diseases are characterized by progressive structural and/or functional changes in the brain, leading to several degrees of cognitive impairment [4–6]. In the past few decades, researchers have accomplished to further understand age-related neurodegenerative disorders, but there is still no effective pharmacological treatment to address the needs of these patients. Recently, physical exercise has been suggested as an effective, low-cost, and low-risk alternative to tackle this public health priority.

It has been argued that exercise can be a preventing or disease-slowing therapeutic strategy for age-related neurodegenerative diseases, reducing its social and economic burden [7,8]. Several meta-analyses provide clear evidence that physical exercise promotes cognitive function in numerous domains [9,10] including in healthy older adults [11–14]. There is also a fair amount of evidence stating that physical exercise is associated with reduced incidence of dementia [15,16], Mild Cognitive Impairment (MCI; 17) and lower risk of developing PD [18,19]. Furthermore, there are also a significant number of systematic reviews reporting positive cognitive effects of exercise in AD and other kinds of dementia [20,21], PD [22], and MCI patients [21,23,24], mainly in global cognition, executive function, attention, and delayed recall.

Recent developments in neuroimaging techniques and genetics allowed researchers to explore the neuroprotective mechanisms that underlie exercise-induced improvements in neurodegenerative diseases [25,26]. In the past few decades, researchers developed several animal studies in order to further understand how these neurobiological mechanisms promote neuroplasticity and improve cognition. Some authors argue that the differences between the brain of rodents and humans (e.g. number of neurons, protein expression) do not allow the findings on neurodegeneration and cognition from animal models of neurodegenerative diseases to be relevant to human therapy [27,28]. However, using animal studies to understand the effects of exercise on the brain have been well established. Vivar and colleagues describe voluntary running in animal models as a critical tool to study exercise-induced neural changes as it seems to mimic several biological brain responses that occur in humans [29]. Using this method, researchers understood how exercise can increase the rate of neurogenesis within the dentate gyrus of the hippocampus [30,31], even in older animals [32].

In addition, the findings regarding enhanced neurogenesis have been associated with learning and memory improvements [33,34]. Neuroplasticity mechanisms activated by exercise are clearly a complex process but animal research has consistently provided evidence of an exercise-induced cascade of partially interdependent functional and structural changes.
in the brain, including increased dendritic spine density and angiogenesis, enhanced long-term potentiation, as well as augmented expression of neurotransmitters and trophic factors [29,35].

Nowadays, it is safe to say that physical exercise is able to promote synaptogenesis and maintain brain volume in elderly subjects [35,36]. Along with animal evidence, human studies suggest that exercise may attenuate progression of neurodegenerative processes and age-related loss of synapses [8]. The most emergent and popular hypothesis to explain the relationship between psychical activity, cognition, and neuroplastic mechanisms has been enhanced trophic factor signaling [37,38]. Trophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and insulin-like growth factor (IGF) have been identified as possible mediators of the protective and therapeutic effects of exercise on brain function [39,40].

Several cellular and molecular mechanisms encompassing neurotrophic factors are important to maintain neuronal function and promote synaptic plasticity. In recent years, neurotrophins and their receptors have been highlighted as important regulators of adult neurogenesis. BDNF and its main receptors (TrkB and p75NTR) have been suggested to play a critical role in dendrite/spine morphogenesis, axonal initiation, and progenitor proliferation/migration, mechanisms which support neurogenesis in the dentate gyrus of hippocampal formation [41]. Furthermore, BDNF has also been related to enhanced synaptic plasticity [42–44], late-phase long-term potentiation [45], neuronal survival and differentiation [46,47], and protection against neuronal death in the hippocampus [48,49]. IGF is another trophic factor described as a potent anabolic and mitogenic agent which activates several intracellular signaling cascades through Trk receptors, controlling cell proliferation, survival, and differentiation [50]. NGF plays a role in TrkA-mediated neuroprotection and cell survival, although there is also evidence of its involvement in apoptosis [51,52]. Finally, GDNF also has a neuroprotective role as it activates complex interactions between several signaling cascades responsible for cell differentiation and proliferation as well as survival of dopaminergic and noradrenergic neurons in adult brain [53].

Thereby, it seems increasingly more likely that exercise-induced upregulation of trophic factors can promote angiogenesis, neurogenesis, and synaptogenesis, which can ultimately prevent age-related functional and structural neurodegeneration and the concomitant cognitive decline [25,54,55]. The purpose of this paper is to review the evidence regarding the role of exercise-induced trophic factor enhancement in preventing or delaying the cognitive decline of age-related neurodegenerative disease. First, the authors will start by exploring the role of various trophic factors in aging and age-related neurodegenerative disorders. The authors will then review findings, which relate exercise, trophic factor signaling changes, and cognitive improvements in elderly individual and patients with several neurodegenerative disorders. Finally, we provide several recommendations and directions by which we can further increase our knowledge regarding the exercise-induced neuroprotection and trophic factor upregulation in patients with neurodegenerative diseases.

2. Trophic factors signaling, aging, and neurodegenerative diseases

Trophic factor signaling has been widely explored in aging and neurodegenerative diseases. Espinet and colleagues argue that the precursor proteins of neurotrophins (pro-neurotrophins) are implicated in the development of neurodegenerative diseases, as they play a role in the mechanisms related to neuron apoptosis [56]. These authors state that aging-induced oxidative stress may enhance the expression of pro-neurotrophin forms, exacerbating its neurodegenerative effects. However, as we further describe throughout this section, there is a significant amount of evidence regarding reduced trophic signaling in patients with neurodegenerative diseases, with the involvement of several trophic factors including BDNF, NGF, GDNF, and IGF-I, among others.

2.1 BDNF

BDNF is a neurotrophin, widely expressed in the human brain, and is crucial to regulate neuroprotective, neurogenesis, and neuroplasticity mechanisms [57,58]. Evidence from animal and human studies describe the relationship between aging, BDNF, and cognitive impairment [59–61]. Furthermore, dysfunction in BDNF signaling is related to the pathophysiological mechanisms of several age-related neurodegenerative diseases [62–64]. Plasma or serum BDNF levels decline with age and its decrease correlates with reduced hippocampal volume and poor cognitive performance [65–67]. Reduced brain and peripheral expression of BDNF has also been described in patients with MCI [68–70]. Moreover, Forlenza and colleagues described that reduced BDNF levels in the cerebral spinal fluid (CSF) is associated with progression from MCI to AD [71].

BDNF is the most widely researched trophic factor and in recent years, there have been a growing number of studies exploring brain and peripheral BDNF expression in AD [72–74]. Postmortem studies consistently found reduced BDNF mRNA or protein levels in the hippocampus of AD patients [75–77], among other brain regions [78–80]. Peng and colleagues found that the diminution of BDNF levels in AD was correlated with the degree of cognitive impairment [69]. The authors suggest that BDNF can be a biological marker of preclinical AD and plays an important role in the progressive neuronal loss across the course of the disease.

The main neurotrophin receptors, Trk receptors and p75NTR, have also been associated with the course of AD. Several cell survival and synaptic plasticity mechanisms are mediated by the interaction between neurotrophins and Trk receptors [81,82]. Inversely, the interaction between neurotrophins and their precursors with p75NTR normally activates apoptotic pathways in peripheral neurons and glia [83,84]. Some authors argue that the disparity between neuronal death and survival in AD may be caused by the upregulation of p75NTR and downregulation of Trk observed in these patients [85]. Furthermore, several authors reported consistently reduced NGF TrkA receptors in the basal forebrain and
BDNF also seems to be evolved in PD, since it has a crucial role in neurotoxin-induced degeneration of dopaminergic neurons, which displays an intense decline in these patients [62]. Reduced BDNF mRNA and protein expression have been consistently described in the substantia nigra of PD patients, which is the mainly affected neuronal group in PD [62,95,96]. Moreover, serum BDNF levels have been associated with disease progression and motor symptoms severity [97]. BDNF may also play a role in multiple sclerosis but findings are somewhat inconsistent, as some authors report decreased peripheral basal levels [98], while others describe no significant changes [99]. Interestingly, increased brain and CSF levels of BDNF have also been described in MS patients [100–102]. It seems that age-related neurodegenerative diseases are associated with reduced BDNF function, although BDNF levels may vary across specific brain regions and according to symptom severity.

2.2 NGF

NGF is one of the oldest described neurotrophins and is responsible for protecting neurons from chemical stressors as well as for neuronal growth and proliferation [103]. Findings from animal studies suggest that NGF decreases with aging, hindering the conservation of cholinergic neurons and playing a role on age-dependent decline in cognitive function [104,105]. The role of NGF in age-related neurodegenerative diseases has also been explored, which allowed to determine that NGF levels were augmented in the dentate gyrus [80], although another study found no brain changes in NGF expression [106]. Several authors also found no significant differences between peripheral NGF levels in comparison to the control group [106,107], although significant increases were found in CSF levels [108]. In contrast, numerous studies have described increased levels of pro-NGF in AD patients [109]. Regardless of inconsistent results, a recent study by Ferreira and colleagues found cognitive improvements and reduced levels of amyloid β after NGF treatment, which can suggest that this hormone may be an important target in AD [110].

2.3 GDNF

GDNF has a significant role in the development and maintenance of spinal motor neurons and midbrain dopaminergic neurons [103,111]. The neuroprotective effects of GDNF were explored by Pertusa and colleagues, who highlighted its role to attenuate the neuronal atrophy which underlies age-related cognitive deficits [112]. However, GDNF has a role in several neuron systems, which can explain why other authors found an increased age-related GDNF expression in the frontal cortex but not on the hippocampus [113]. Several authors have also reported reduced GDNF levels in AD and MCI patients [114,115], in spite of others describing increased levels [116] or no differences in comparison to controls [107]. Interestingly, Straten and colleagues also found increased CSF levels of GDNF in early stage AD patients in contrast to reduced serum concentration, suggesting an adaptive response of the impaired brain [117]. As highlighted before, GDNF specifically protects the dopaminergic neurons through several mechanisms and its downregulation has been implicated in PD onset mechanisms [111]. Two cross-sectional studies have found reduced levels of GDNF in patients with PD. Lower concentration of GDNF was found in the cerebellum and the frontal cortex of PD patients, although no significant changes were described in other brain regions, including the substantia nigra [118]. Conversely, Chauhan and colleagues reported reduced GDNF levels in the substantia nigra of PD patients, without any other trophic factor being affected [119]. Moreover, GDNF has been the main factor in several human trials, showing promising results as a potential therapeutic agent to treat PD through its neuroprotective and neurorestorative effects [120–122].

2.4 IGF

IGF has also been highlighted as a crucial hormone to brain cell proliferation, survival, and neurogenesis [123]. IGF-I levels have been associated to cognitive decline [124] and its level also decreases progressively as we get older [125]. Aging is associated with reduction in both serum IGF-I and brain density of IGF-I receptors in the hippocampus [126]. Moreover, higher levels of IGF-I have been associated with larger brain volumes, which point out that this factor can be crucial to prevent neurodegeneration [127]. Regarding AD patients, brain measures found reduced expression of IGF mRNA, with levels decreasing at more advanced stages of the disease [128]. Others authors state that IGF-I inhibition slows the progression to AD [129]. Changes in CSF and blood plasma levels of IGF-II have also been reported in patients with AD [130] and lower serum levels of IGF-I were also associated with a superior risk to develop AD [127].

The previously described trophic factors are those which are mainly researched when addressing age-related neurodegenerative diseases. Other factors such as stem cell factor, granulocyte-colony stimulating factor, and vascular endothelial growth factor (VEGF), among others, have also been explored [103]. All the evidence clearly suggests that trophic signaling plays a key role in aging and neurodegenerative diseases. Establishing trophic factors as potential targets to prevent neurodegeneration and promote neuroprotection can be a critical step in order to improve treatments for age-related neurodegenerative diseases.
3. Exercise, trophic factors signaling, and cognition

In the past few years, trophic factors have been explored as the possible mediators of exercise-induced brain plasticity. Evidence from animal and human studies show that exercise enhances expression of several trophic factors such as BDNF, IGF-I, NGF, among others, both in health elderly individuals (Table 1) as well as in patients with neurodegenerative disease (Table 2; [54,131–134]).

Researchers have highlighted BDNF as the neurotrophin which is more susceptible to exercise-induced changes. A recent meta-analysis by Szuhany and colleagues reported that both acute and regular exercise can increase BDNF levels in healthy subjects and clinical populations [150]. Several studies with healthy humans reported that physical exercise can increase plasma and/or serum BDNF concentration, either after acute exercise or chronic aerobic exercise [151,152].

Furthermore, the review by Coelho and colleagues highlighted that both acute or chronic physical exercise increases peripheral BDNF concentrations in healthy elderly individuals, emphasizing the role of aerobic training as well as strength exercise programs [153]. There are also several studies with healthy elderly subjects or with participants with nondegenerative diagnosis (e.g. frailty, depressive symptoms) that report exercise-induced BDNF upregulation [137,138,140,141], although two of these studies did not have any male participants. Other authors explored the effects of aerobic exercise on older adults and found no significant changes in peripheral BDNF levels after the intervention [131,139]. However, Erickson and colleagues reported a crucial finding regarding BDNF-induced neuroplastic changes, as participants with larger BDNF changes after exercise displayed higher hippocampal volume enlargement [136].

Several studies with MCI patients found increased peripheral BDNF levels after a psychical exercise intervention [144,145]. Interestingly, Baker and colleagues described an enhancement of BDNF and IGF-I plasma levels in MCI patients after a 6-month aerobic exercise program, but only male participants displayed these changes [142]. Female participants actually displayed reduced BDNF levels after the intervention. In AD patients, Coelho and colleagues also found a significant correlation between plasma BDNF levels and the level of physical exercise practiced by participants [89].

There are also two studies reporting exercise-induced peripheral BDNF levels enhancement in patients with PD. Zoladz and colleagues reported increases in serum BDNF levels after a single bout of aerobic bicycle training in PD patients [146]. A follow-up study by Marusiak and colleagues found increases in BDNF levels after interval exercise, which were correlated with improvement in motor symptoms [147]. However, both these studies did not report information regarding baseline group differences and did not use a control group with PD patients, which would be important to validate these findings.

Regarding MS, there is evidence of exercise-induced enhancement in BDNF levels after an acute exercise session [99] or following prolonged training programs [98,149]. Schulz and colleagues reported no significant changes in BDNF after an aerobic exercise intervention, but the participants only completed sessions twice a week, a reduced frequency in comparison to previously mentioned studies [148]. There is also evidence linking BDNF enhancement to cognitive performance in elderly individuals. Anderson-Hanley and colleagues found a reduced rate of conversion to MCI after a cybercycling exergame intervention, with participants also displaying a significant increase in BDNF levels which may have led to the reported cognitive effects [138]. Suzuki and colleagues also reported that elevated BDNF levels could predict cognitive improvement in older adults with MCI after an exercise intervention [143].

Exercise-induced neuroprotection in the adult brain has also been related to modulation of IGF-I levels. Animal studies suggest that exercise promotes IGF-I uptake and neurogenesis by specific groups of neurons throughout the brain [154,155]. Thereby, Carro and colleagues suggest that circulating IGF-I can be increased by exercise, providing a key factor to prevent or delay age and disease-related cognitive decline [156]. However, there is a clear need to further extend research in humans since results are inconsistent. Cassilhas and colleagues reported that resistance training increased peripheral IGF-I levels in healthy older adults [135] and Baker reported exercise-induced elevation of plasma IGF-I levels in men with MCI [142]. No significant differences were found in resting IGF-I concentration after training in MS patients [98] and some authors even report that aerobic exercise can lower IGF-I serum levels in healthy young and elderly subjects [131,157].

Although BDNF and IGF-I have been further explored, researchers have also paid attention to other trophic factors. The neuroprotective role of NGF in aging and neurodegenerative diseases has also been explored, mainly in animal studies which found exercise-induced NGF upregulation in aging rats and AD models [158,159], although findings in human studies remain fairly inconsistent. Coelho and colleagues found no changes either in NGF and GDNF levels after a resistance training intervention in elderly women. NGF has also been further explored in MS patients, with findings suggesting that acute and maintained exercise may allow for peripheral NGF improvements [99,149]. However, Schulz and colleagues actually found a trend to reduced NGF acute response after a personalized aerobic training program [148]. Animal studies have also reported increased VEGF peripheral levels after aerobic exercise, suggesting its involvement in exercise-induced neurogenesis and synaptic plasticity [160]. Baseline VEGF levels in older subjects are also correlated with enhanced exercise-induced improvements in temporal cortex connectivity, which further strengthens the role of VEGF in the brain effects achieved by exercise [131].

Finally, it is also important to emphasize that the cellular source of exercise-induced trophic signaling changes is only partially understood. It has been argued that neurotrophic factors do not readily cross the blood–brain barrier (BBB), which has hindered their use as a therapeutic target for neurodegenerative diseases [161]. However, there is also evidence describing that exercise increases BBB permeability [162,163] and that neurotrophins can cross it [164], which increases the likelihood of peripheral neurotrophins to cross the BBB after exercise in order to support neural health. For instance, BDNF can cross the BBB bidirectionally which allows to postulate several possible relationships between brain and plasma neurotrophic levels [165]. It is reasonable to assume that exercise-
Table 1. Clinical trials regarding exercise-induced trophic factors changes in healthy elderly subjects or patients with nondegenerative diseases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Type of exercise</th>
<th>Sample size</th>
<th>Mean Age (years)</th>
<th>Gender (% female)</th>
<th>Intervention length</th>
<th>Session frequency and duration</th>
<th>Intensity of exercise</th>
<th>Trophic factor measures</th>
<th>Significant trophic factors changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassilhas and colleagues [135]</td>
<td>Elderly</td>
<td>Resistance training: MRT</td>
<td>MRT: 19</td>
<td>MRT: 69</td>
<td>No female</td>
<td>24 weeks</td>
<td>3 d/week</td>
<td>MRT: 50% RM</td>
<td>Serum</td>
<td>↑ IGF-I levels after intervention in MRT and HRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRT: 20</td>
<td>HRT: 68.4</td>
<td>HRT: 67</td>
<td>participants</td>
<td>60 min/session</td>
<td></td>
<td>HRT: 80% RM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE: 23</td>
<td>SE: 67</td>
<td></td>
<td></td>
<td>6 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erickson and colleagues [136]*</td>
<td>Elderly</td>
<td>Walking AE</td>
<td>AE: 60</td>
<td>AE: 67.6</td>
<td>AE: 73%</td>
<td>52 weeks</td>
<td>No info on frequency</td>
<td>AE: 50–75% HR\text{\text{max}}</td>
<td>Serum</td>
<td>No differences between groups after intervention Greater BDNF changes were associated with increased hippocampus volume in AE participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE: 60</td>
<td>SE: 65.5</td>
<td>SE: 60%</td>
<td></td>
<td>40 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruscheweyh and colleagues [137]</td>
<td>Elderly</td>
<td>NW</td>
<td>NW: 20</td>
<td>NW: 60.1</td>
<td>NW: 70%</td>
<td>24 weeks</td>
<td>3 d/week</td>
<td>NW: 50–60% ME</td>
<td>Serum</td>
<td>↑ BDNF associated with increased levels of physical activity (trend)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GM</td>
<td>GM: 21</td>
<td>GM: 62.5</td>
<td>GM: 62%</td>
<td>60 min/session</td>
<td></td>
<td>GM: 30–40% ME</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 21</td>
<td>HC: 58.1</td>
<td>HC: 67%</td>
<td>60 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson-Hanley and colleagues [138]*</td>
<td>Elderly</td>
<td>CC</td>
<td>CC: 38</td>
<td>CC: 75.7</td>
<td>CC: 71%</td>
<td>12 weeks</td>
<td>3 d/week</td>
<td>45 min/session</td>
<td>Plasma</td>
<td>↑ BDNF levels in CC in comparison to TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TC</td>
<td>TC: 41</td>
<td>TC: 81.6</td>
<td>TC: 87%</td>
<td>45 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voss and colleagues [131]*</td>
<td>Elderly</td>
<td>Walking AE</td>
<td>AE: 30</td>
<td>AE: 67.3</td>
<td>AE: 73%</td>
<td>52 weeks</td>
<td>40 min/session</td>
<td>AE: 50–75% HR\text{\text{max}}</td>
<td>Serum</td>
<td>↑ IGF-I levels after intervention in both groups No significant differences in BDNF and VEGF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FTB</td>
<td>FTB: 35</td>
<td>FTB: 65.4</td>
<td>FTB: 71%</td>
<td>40 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker and colleagues [139]*</td>
<td>Elderly with glucose tolerance</td>
<td>Multimodal AE</td>
<td>AE: 19</td>
<td>AE: 66</td>
<td>AE: 53%</td>
<td>24 weeks</td>
<td>4 d/week</td>
<td>AE: 75–85% HR\text{\text{max}}</td>
<td>Plasma</td>
<td>No significant changes in BDNF and IGF-I levels in both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE</td>
<td>SE: 9</td>
<td>SE: 71</td>
<td>SE: 90%</td>
<td>45–60 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laske and colleagues [140]</td>
<td>DE</td>
<td>Acute AE (incremental treadmill walking)</td>
<td>DE: 35</td>
<td>DE: 61.1</td>
<td>No male participants</td>
<td>Single session</td>
<td>30 min/session</td>
<td>Until volitional exhaustion</td>
<td>Serum</td>
<td>1 BDNF levels only in MDD patients 1 BDNF after 30-min rest in both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HC: 20</td>
<td>HC: 58.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coelho and colleagues [141]**</td>
<td>Elderly women (no frail and pre-frail)</td>
<td>Resistance Training</td>
<td>20</td>
<td>71</td>
<td>No male participants</td>
<td>10 weeks</td>
<td>3 d/week</td>
<td>50–75% MR</td>
<td>Plasma</td>
<td>↑ Resting BDNF levels after intervention No significant changes in GDNF or NGF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(knee flexors, extensors)</td>
<td></td>
<td></td>
<td></td>
<td>60 min/session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Authors did not report information about baseline group differences or groups differed significantly at baseline regarding age and/or gender. However, these variables, as well as other demographic variable, were added as covariates to the analysis.

**The authors did not report any information regarding baseline group differences and did not had any variable as a covariate.

MRT: Moderate intensity; HRT: high intensity; SE: stretching exercise control; AE: aerobic exercise; NW: nordic walking; GM: gymnastics; CC: cybercycle; TC: traditional cycling; FTB: flexing, toning, and balance; DE: depressed elderly women; HC: healthy control group; HR\text{\text{max}}: maximum heart rate; RM: repetition maximum; MR: maximal resistance; ME: maximal exertion.
Clinical trials regarding exercise-induced trophic factors changes in patients with age-related neurodegenerative diseases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Type of exercise</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Gender (% female)</th>
<th>Intervention length</th>
<th>Session frequency and duration</th>
<th>Intensity of exercise</th>
<th>Trophic factor measures</th>
<th>Significant trophic factors changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker and colleagues</td>
<td>MCI</td>
<td>AE</td>
<td>AE: 19</td>
<td>AE: 67.95</td>
<td>AE: 53%</td>
<td>24 weeks</td>
<td>4 d/week 45-60 min/session</td>
<td>AE: 75–85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Plasma</td>
<td>↑ BDNF and IGF-I levels in male patients after AE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE</td>
<td>SE: 10</td>
<td>SE: 72.6</td>
<td>SE: 50%</td>
<td></td>
<td></td>
<td>SE: &lt;50% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td>↑ BDNF levels in female patients of AE</td>
</tr>
<tr>
<td>Suzuki and colleagues</td>
<td>MCI</td>
<td>Multimodal group exercise – aerobic, strength, etc. (EG)</td>
<td>EG: 50</td>
<td>EG: 74.8</td>
<td>EG: 50%</td>
<td>24 weeks</td>
<td>2 d/week 90 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>Higher BDNF levels at baseline was associated with cognitive improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG</td>
<td>CG: 50</td>
<td>CG: 75.8</td>
<td>CG: 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma levels after intervention in MCI and HC training groups</td>
</tr>
<tr>
<td>Nascimento and colleagues</td>
<td>MCI</td>
<td>Multimodal AE Training (MCI-T and HC-T) Control (MCI-C and HC)</td>
<td>MCI-T: 20</td>
<td>MCI-T: 67.3</td>
<td>MCI-T: 65%</td>
<td>16 weeks</td>
<td>3 d/week 60 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Plasma</td>
<td>↑ BDNF levels after intervention only in AE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCI-C: 17</td>
<td>MCI-C: 68.5</td>
<td>MCI-C: 78.6</td>
<td>MCI-C: 65%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Only patients with wild-type genotype displayed significant improvements in BDNF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 68.1</td>
<td>HC: 66.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nascimento and colleagues</td>
<td>MCI</td>
<td>Multimodal AE</td>
<td>AE: 24</td>
<td>AE: 67.83</td>
<td>AE: 71%</td>
<td>16 weeks</td>
<td>3 d/week 60 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Plasma</td>
<td>↑ BDNF levels only in PD patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG</td>
<td>CG: 21</td>
<td>CG: 67.5</td>
<td>CG: 71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coelho and colleagues</td>
<td>AD</td>
<td>Acute AE (submaximal)</td>
<td>AD: 21</td>
<td>AD: 76.3</td>
<td>No info</td>
<td>1 session</td>
<td>No info Until 85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td>Plasma</td>
<td>↑ BDNF levels in both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 18</td>
<td>HC: 74.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoladz and colleagues</td>
<td>PD</td>
<td>Interval training (cycling)</td>
<td>12</td>
<td>70</td>
<td>42%</td>
<td>8 weeks</td>
<td>3 d/week 60 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>↑ BDNF levels after intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marusiak and colleagues</td>
<td>PD</td>
<td>Interval training (cycling)</td>
<td>PD: 11</td>
<td>PD: 71</td>
<td>PD: 46%</td>
<td>8 weeks</td>
<td>3 d/week 60 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>↑ BDNF levels only in PD patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 11</td>
<td>HC: 77</td>
<td>HC: 82%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold and colleagues</td>
<td>MS</td>
<td>Acute AE (Bicycle ergometry)</td>
<td>MS: 25</td>
<td>MS: 39.2</td>
<td>MS: 64%</td>
<td>30 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>↑ BDNF levels in both groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 20</td>
<td>HC: 40.5</td>
<td>HC: 70%</td>
<td></td>
<td></td>
<td></td>
<td>↑ NGF levels in both groups (trend)</td>
<td></td>
</tr>
<tr>
<td>Schulz and colleagues</td>
<td>MS</td>
<td>Individualized AE Wait-list CG</td>
<td>AE: 15</td>
<td>AE: 39</td>
<td>AE: 73%</td>
<td>8 weeks</td>
<td>2 d/week 30 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>↑ NGF levels in training group (trend)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG</td>
<td>CG: 13</td>
<td>CG: 40</td>
<td>CG: 62%</td>
<td></td>
<td></td>
<td></td>
<td>No significant differences in BDNF</td>
<td></td>
</tr>
<tr>
<td>Castellano and colleagues</td>
<td>MS</td>
<td>Cycling AE</td>
<td>MS: 11</td>
<td>MS: 40</td>
<td>MS: 73%</td>
<td>8 weeks</td>
<td>3 d/week 30 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>Resting BDNF levels after 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>HC: 11</td>
<td>HC: 40</td>
<td>HC: 73%</td>
<td></td>
<td></td>
<td></td>
<td>No significant changes in IGF-I after training</td>
<td></td>
</tr>
<tr>
<td>Bansi and colleagues</td>
<td>MS</td>
<td>Endurance cycling training: LE AT</td>
<td>LE: 28</td>
<td>LE: 52</td>
<td>EG: 64%</td>
<td>3 weeks</td>
<td>5 d/week 30 min/session</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Serum</td>
<td>↑ BDNF after single bout of exercise in both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AT: 24</td>
<td>AT: 50</td>
<td>CG: 67%</td>
<td></td>
<td></td>
<td></td>
<td>↑ Resting BDNF levels after intervention in AT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Resting NGF after intervention in AT (trend)</td>
<td></td>
</tr>
</tbody>
</table>

*The authors did not report any information regarding baseline group differences and did not had any variable as a covariate.

HC: Healthy control group; CG: patient control group; HR<sub>max</sub>: maximum heart rate; VO<sub>2</sub>Max: maximal oxygen uptake; MW: maximal watts; MCI: mild cognitive impairment; AE: aerobic exercise; SE: stretching exercise control; AD: Alzheimer’s disease; PD: Parkinson’s disease; MS: multiple sclerosis; LE: land ergometer; AT: aquatic bike training; d: days.
induced blood flow to the brain enhances central neurotrophins expression [166,167], as there is evidence of BDNF release in the brain during exercise [168]. After being produced, these neurotrophins may leave the brain in order to be stored in other body regions. It is also possible that increased peripheral neurotrophin levels induced by exercise are gradually cleared after exercise [169]. It is assumed that regardless of exercise intensity, peripheral BDNF concentration returns back to baseline within 15–60 min, decreasing to sub-baseline levels after that period [170], which can indicate that these molecules are metabolized in the periphery or transported to the brain in order to promote neural health.

Furthermore, we also have to account that different trophic factors are produced in different areas. BDNF is mainly produced in the brain, but it can also be produced by tissues in the periphery, mostly being released into circulation and stored in platelets [171] or produced by muscle cells where it is used locally [172]. On the other hand, while IGF-I is primarily produced by the liver [173], when released in high concentrations it can cross the BBB barrier, triggering increased BDNF expression in the brain [37,174]. Trophic factors are synthetized and released in numerous regions, which lead researchers to struggle when trying to pinpoint whether exercise-induced peripheral neurotrophins increase is caused by changes in peripheral or central mechanisms [62,175].

4. Expert commentary

In this article, we have reviewed the link between trophic factors and age-related neurodegenerative diseases and how they play a key role on exercise-induced neuroprotective effects for these patients. There is a significant amount of clinical trials that report the effectiveness of physical exercise as an alternative intervention to address age-related cognitive impairment. Support for acknowledging exercise as a valuable intervention to the treatment of age-related neurodegenerative diseases comes from studies linking exercise to cognitive improvements and trophic signaling enhancement, which highlights trophic factors as important therapeutic targets to stimulate neuroprotective mechanisms [58,176,177].

Several trophic factors have been implicated in the pathogenesis and pathophysiology of age-related neurodegenerative diseases, but BDNF is by far the most widely studied and proven neurotrophin regarding exercise-induced neurobiological effects. There have been few clinical trials exploring the role of other trophic factors, although there are some authors reporting the involvement of IGF-I and even NGF. Furthermore, numerous questions remain to be answered regarding the cellular mechanisms of exercise-induced trophic signaling. Regardless, as the evidence regarding exercise-induced brain changes in neurodegenerative diseases gradually increases, it seems highly unlikely that peripheral neurotrophic factors do not play a direct role in the underlying neuroplastic mechanisms or are at least an important indicator of enhanced neuroplastic activity.

Finally, it is still hard to precisely define which exercise conditions (type, duration, and intensity) are recommended to trigger neuroprotective effects, in spite of some reviews suggesting moderate intensity aerobic and resistance exercise [8,132]. Knaepen and colleagues state that acute aerobic exercise is more likely to elevate BDNF concentration than acute strength exercise in healthy subjects or in patients with chronic diseases [170]. Furthermore, most studies report a significant dose–response relationship between acute aerobic exercise intensity and BDNF concentration. However, there are several biases from the reported studies which hinder the clinician’s possibility to recommend the most effective exercise intervention, as several studies have reduced samples sizes, lack an appropriate control group, or do not report accurately on data regarding exercise intensity. Most studies found no significant differences between groups regarding gender and age or accounted for potential discrepancies adding these variables as covariates, but some studies which do report significant intervention effects do not present any data regarding baseline differences (Tables 1 and 2). Regardless of all these reservations, it is safe to think about exercise-induced neuroprotective effects with two main premises. First, each exercise session results in enhanced neurotrophic activity that becomes gradually larger as we engage more regularly in physical exercise [150]. Second, as we try to accurately determine the right dosage to induce brain changes, it may be reasonable to follow the international exercise recommendations for the elderly, which advise 5-weekly 30-min sessions of moderate intensity aerobic exercise [178].

5. Five-year view

Further understanding about the role of trophic factors on exercise-induced cognitive improvement and neuroprotective mechanisms can be attained by developing clinical trials with elderly or patients with age-related neurodegenerative diseases. Researchers must be highly methodical when developing these trials, using matched control patients groups and clearly defining the characteristics of the exercise intervention they want to explore.

However, regardless of which trophic factors account for neuroprotective mechanisms, researchers and clinicians must take into account several aspects that can influence the brains’ response to physical exercise. Future studies should make an effort to accurately pinpoint the exercise components that are responsible for cognitive outcomes and their neurobiological underpinnings. Neuroprotective and neuroplastic factors have a distinct role in this process, but there is a need to further understand the mechanisms which underlie these deficits. If animal studies report that specific training procedures induce different types of brains changes [40], we can only assume that the human brain will have distinct responses as well. Thereby, there is a need to further understand and predict how does the human brain reacts to specific training procedures. Moreover, understanding proficiently exercise-induced neuroprotective mechanisms can also help to explore pharmacological alternatives that can recreate some of the effects achieved by exercise, allowing to develop alternative treatment strategies which target trophic factors [92,179–183].
Trophic factor levels vary widely across individuals and research teams should account for potential confounders (e.g. age, gender, race) when designing exercise protocols and interpreting trial results [184]. Furthermore, methods to assess trophic factor signaling are far from being perfect and there is a need to develop new assessment techniques to keep track of brain levels of trophic factors. Genetic and/or environmental factors have a role on the response of the brain to physical activity and must be addressed to develop more individualized programs that are adapted to each patient’s aging and diagnosis [37].

It is clear that nowadays we are not able to perfectly describe the pathways between exercise, cognitive improvement, and trophic factors. It is also clear that exercise has a crucial role on brain health during aging and neurodegenerative processes. This highlights the importance of developing clinical trials targeting further insights regarding how we can use exercise to prevent or treat cognitive decline associated with age-related neurodegenerative diseases, helping these patients to improve their daily functioning and their quality of life.

Key issues

- In spite of extensive research regarding age-related neurodegenerative disorders (Alzheimer’s disease, Parkinson’s Disease, among others), there is still no effective pharmacological treatments to address the needs of these patients.
- Exercise has been clearly proven as an effective and low-cost alternative to address age related cognitive decline or to slow cognitive impairment associated to age-related neurodegenerative diseases.
- Trophic factors such as BDNF, NGF, GDNF and IGF-I have been widely explored as important actors in the pathogenesis and pathophysiology of age-related neurodegenerative disorders.
- There is a growing amount of evidence supporting that neurotrophic factors play a direct role in the underlying neuroplastic mechanisms or are at least an important indicator of enhanced neuroplastic activity.
- Exercise has been postulated to enhance the expression of several trophic factors but BDNF is by far the most widely studied and proven neurotrophin regarding exercise-induced neurobiological effects.
- There is a need to develop high quality randomized controlled trials in order to strengthen the evidence regarding exercise-induced cognitive improvement and neuroprotective mechanisms in the elderly or patients with age-related neurodegenerative diseases.
- Future work should also further explore the cellular mechanisms of exercise-induced trophic signaling, in order to understand the role of central and peripheral mechanisms.
- Researchers should make efforts to pinpoint which exercise components (e.g. type, duration, frequency) are responsible for cognitive outcomes and their neurobiological underpinnings in age-related neurodegenerative disorders.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest

Updated and extensive review regarding the role of trophic factors in the neurogenesis mechanisms of adult subjects.


**Extensive review and meta-analysis regarding the cognitive effects of exercise in AD and MCI.**


81. Islam O, Loo TX, Heese K. Brain-derived neurotrophic factor (BDNF) has proliferative effects on neural stem cells through the truncated TRK-B receptor, MAP kinase, AKT, and STAT-3 signaling pathways. Curr Neurovasc Res. 2009;6(1):42–53.


129. Clinical trial which associates a 1-year aerobic exercise intervention with hippocampus increase and BDNF levels enhancement.


**Meta-analytic review of the effects of acute and chronic exercise on peripheral BDNF levels in several populations.**


**Systematic review on the effects of exercise on peripheral BDNF levels in elderly subjects.**

174. Fulford BE, Ishii DN. Uptake of circulating insulin-like growth factors (IGFs) into cerebrospinal fluid appears to be independent of the IGF receptors as well as IGF-binding proteins. Endocrinology. 2001;142(1):213–220.