International Journal of EXERCISE SCIENCE

Review

Therapeutic Importance of Exercise in Neuroplasticity in Adults with Neurological Pathology: Systematic Review

SARA V. CARDOSO*[1,2], SOFIA R. FERNANDES‡[2,3], and MARIA T. TOMÁS‡[2,4]

[1]Hospital Beatriz Ângelo, Loures, Portugal; [2]ESTeSL - Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisboa, Portugal; [3]Instituto de Biofísica e Engenharia Biomédica, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal; [4]Health & Technology Research Center, ESTeSL - Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisboa, Portugal

*Denotes undergraduate student author, ‡Denotes professional author

ABSTRACT

International Journal of Exercise Science 17(1): 1105-1119, 2024. Neuroplasticity is an essential mechanism by which the nervous system shapes and adapts according to functional requirements. Evidence suggests that physical exercise induces a cascade of cellular processes that favours brain plasticity. The Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin closely linked to neuroplasticity that can be increased due to exercise. To verify the effects of therapeutic exercise on neuroplasticity and/or peripheral BDNF levels in neurological conditions in adults, such as stroke, Parkinson's and Alzheimer's diseases and mild cognitive impairment and address its clinical relevance in the treatment of neurological dysfunctions. A systematic review was carried using PUBMED, Web of Science and Scopus databases. Inclusion criteria were: randomized controlled trials or pilot studies; humans with age > 18 yrs with neurological condition; English language; score ≥ 6 in PEDro Scale (moderate to high quality). Reviews, meta-analyses and other articles that did not meet the criteria were excluded. The PRISMA methodology was applied for studies' selection. A total of 9 studies were selected for a systematic and comprehensive analysis. According to these studies, moderate to high intensity aerobic exercise (AE), increases the level of peripheral BDNF and positively influences functional gains in neurological conditions. Larger outcomes are observed in protocols with minimum session duration of 30 minutes, frequency of 3 times/week and intervention duration of 4 weeks. Current evidence shows that moderate to high intensity AE induces neuroplasticity in neurological patients, thus being a fundamental therapeutic strategy to include in interventions aiming to repair/delay neurological dysfunctions.

KEY WORDS: Neurological, exercise therapy, physical therapy, rehabilitation, BDNF

INTRODUCTION

Neurological diseases and conditions, such as Alzheimer's disease (AD) and other dementias, brain and spinal cord trauma, stroke, are responsible for around 9 million deaths worldwide, being the second cause of death after cardiovascular pathology, and the first cause of years lived with disability, affecting near 11,6% of the world's population (9).

After brain injury acquired by external or internal causes, there are compensatory response mechanisms triggered by the nervous system, due to neuronal plasticity or neuroplasticity. It occurs at the cellular level at synapses and is characterized by changes in the strength and efficiency of synaptic connections, leading to short-term modifications that, when continuous over time, become long-term structural changes in the organization and number of synapses leading to cortical remapping of functions and memory storage (18, 31). At tissue level, neuronal plasticity can trigger the activation of parallel neuronal circuits that establish alternative pathways for functional recovery, as is the case of compensatory mechanisms that occur in the corticospinal pathway after spinal cord injury (18, 31) . Assessment of neuroplasticity in neurologic conditions can be essential to determine the dysfunction stage, while also providing valuable insights on feasibility and type of therapeutic interventions. This assessment should reflect the different levels of neuroplastic mechanisms: at cellular level, through measures of biochemical-related substances, such as the Brain-Derived Neurotrophic Factor (BDNF); at tissue level, by observing changes in cortical neuronal activity using techniques such as electroencephalography (EEG).

BDNF is a neurotrophin that regulates the development, maintenance and function of the nervous system in vertebrates. In adults, it has higher mRNA and protein levels in the hippocampus, amygdala, cerebral cortex and hypothalamus, regulating synaptic transmission and plasticity. It has very significant effects on dendritic morphology and the strength of excitatory (glutamatergic) and inhibitory (GABAergic) synapses. The hippocampus is identified as an important site of action of BDNF and is involved in synaptic plasticity events related with learning and memory (5, 17 ,32, 34).

BDNF has been associated with exercise-enhanced motor performance in neurologically injured animal models (38). Results in animals are more reliable, as it is possible to determine central BDNF levels, as in humans, only peripheral BDNF is generally measured (37). Literature on the role of BDNF in improving motor learning in the human population is still limited. Some studies in healthy individuals have observed a relationship between the intensity of an acute exercise session, increases in peripheral BDNF and motor learning (6). Thus, exercise may be a potential strategy to induce BDNF activity and potentiate its neuroprotective effect.

It has been shown that exercise provides a neuroprotective effect against age-related mental decline and neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD) and central nervous system (CNS) lesions, facilitating motor and cognitive recovery. On the other hand, a decrease in BDNF expression, together with hippocampal atrophy, have been associated with normal and pathological ageing, as well as psychiatric and neurodegenerative diseases, such as AD, PD and stroke (7, 13, 20, 25,27, 37, 38) Thus, it becomes relevant to search for a direct relationship of the results of physical exercise on neuroplasticity in humans with neurological conditions (13, 24, 38).

EEG is recognized as an effective method for analyzing comprehensive and specific properties of cortical networks in the brain involved in specific functions, such as the default mode network, the somatomotor network, and the dorsal attention network. It is an important tool to

safely explore the operational characteristics of the cortex, including neuronal activation patterns and connectivity between different regions. EEG can specifically measure brain rhythms or bands; i.e. that reflect level of synchronicity between functionally-related brain networks during task performance (2).

Two of the most relevant rhythms studied in the context of EEG are alpha and beta. Event-related desynchronization of alpha and beta rhythms is characteristic of activated cortical areas ready to process information or to prepare a movement, while event-related synchronization at the same frequency bands of these rhythms is found in resting or idling cortical areas (2, 33).

It is known that functional disturbance is correlated with amnesic mild cognitive impairment (MCI) and in AD it is correlated with neurodegeneration processes (19). Changes in alpha and beta waves measured by EEG have specific patterns according to different stages of MCI and AD, which supports the use of specific EEG rhythms as potential biomarkers for disease progression and functional performance (2, 33).

The aim of this study is to determine whether therapeutic exercise contributes to increase neuroplasticity processes in neurological conditions, through assessment of peripheral BDNF levels, neural networks and neuronal activation and excitability, and cognitive performance, favouring functional and cognitive recovery.

METHODS

The present study consisted of a systematic review, registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the reference CRD42021268618. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (30), to guide the process of searching and screening of records.

A literature search was conducted in August 2021 in PubMed, Web of Science and Scopus databases. The search strategy consisted in a sentence using relevant keywords combined with the Boolean operators AND and OR. The keywords were selected considering the PICO (Patient, Intervention, Comparison and Outcome) strategy: "neurodegenerative diseases" or "neurological diseases" and "adults" (population); "exercise" and "therapeutic exercise" (intervention), "neuroplasticity" or "BDNF" (outcome) (11). Inclusion criteria were randomised controlled clinical trials (RCT) or pilot studies; written in English; in adults with neurological disease, with a moderate to high quality on the PEDro (Physiotherapy Evidence Database) scale (score ≥ 6). Systematic reviews, meta-analyses and records not meeting the inclusion criteria were excluded (22, 23).

First screening was carried out independently by two reviewers, using the Rayyan software (https://www.rayyan.ai/). The articles were selected after reading the title and abstract, and those that met the eligibility criteria and had consensus between the two reviewers were read in full to determine eligibility for the review. Disagreements were solved by a third reviewer. Data extraction was performed for each record included, by filling a spreadsheet with the following

information: study design, sample characteristics, intervention parameters (e.g. duration, frequency, intensity), outcomes related with neuroplasticity, namely, neurophysiological measures (e.g. electroencephalography, EEG; cortical maps), functional measures (e.g. Fugl-Meyer tests; gait velocity and cadence); BDNF levels. Data extracted were organized in tabular format by the first author and checked by co-authors and subsequently submitted to a systematic and comprehensive analysis. A meta-analysis was not considered due to the high heterogeneity between the studies selected regarding interventions, participants, and outcome measures. Quality assessment of studies was performed independently by two reviewers using the PEDro scale, with discrepancies solved by a third reviewer. This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (29).

Considering the present date of publication for this article, we updated our search from August 2021 until December 2023. We found four articles eligible after first screening. After quality assessment with PEDro and full screening, only 1 article was determined to be eligible (10). However, this article was in line with the evidence reported here in our results and did not add new information to our review, thus we decided not to include it.

RESULTS

A total of 318 records were extracted from the databases, and 35 were initially selected after reading the title and abstract. Of these, 26 were excluded for not meeting one or more eligibility criteria (see Figure 1). According to the PEDro scale, five articles scored 6, three scored 7 and one scored 9 (Table 1). The items with the lowest score were participation and blinded assessment, which were found in 2 different studies; 6 studies presented randomised groups. The items with the largest score were: outcomes measured in at least 85% sample; inter-group results, presentation of measures of accuracy and variability.

Table 1. PEDro scores of included studies.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention-to-treat analysis	Between-group differences reported	Point estimate and variability reported	Total (0 to 10)
Baker et al.[3]	Y	Y	N	Y	N	N	Y	Y	N	Y	6
Enette et al.[12]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Frazzitta et al.[14]	Y	Y	Y	Y	N	N	Y	Y	N	Y	7
Klados et al.[19]	Y	N	N	Y	Y	N	N	Y	Y	Y	6
Landers et al.[21]	Y	Y	N	Y	N	N	Y	Y	N	Y	6
Marusiak et al.[23]	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Nascimento et al.[28]	N	N	N	Y	N	N	Y	Y	Y	Y	6
Velázquez et al.[39]	**N**	**Y**	**Y**	**Y**	**N**	**N**	**Y**	**Y**	**N**	**Y**	**6**
Yen et al.[40]	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**N**	**Y**	**Y**	**Y**	**7**

Abbreviations: Y: Yes; N: No

Among the 9 articles considered, 7 were RCTs that presented exercise programs incorporating aerobic exercise (AE). A total of 305 individuals participated in the studies, 40% were male and the study intervention time varied between 4 weeks and 6 months.

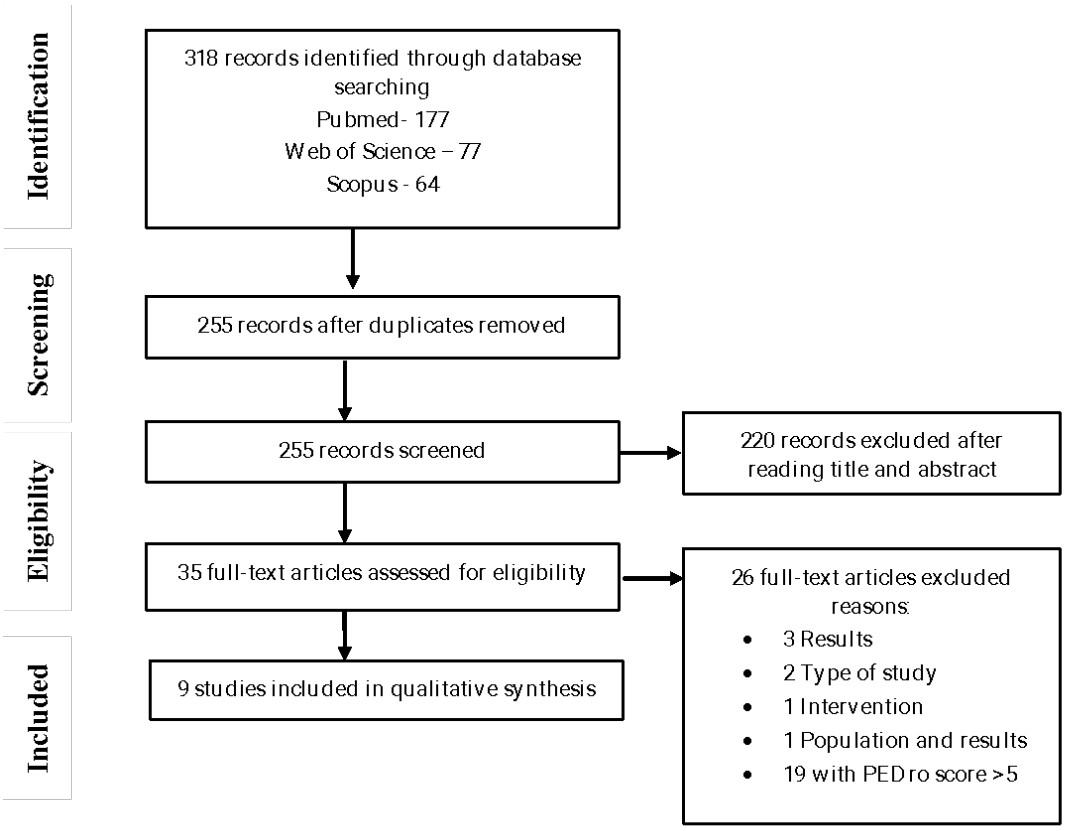

Figure 1. Flowchart of the selection of articles according to PRISMA methodology (22).

Programs were characterised in terms of type of exercise, intensity, frequency, session duration and intervention duration, except for 3 studies, in which the intensity was not specified (Table 2). Table 3 presents the outcomes related with neuroplasticity measured by: electroencephalography (Electroencephalogram - EEG) (19); motor evoked potentials and cortical mapping with Transcranial Magnetic Stimulation (TMS) (40); peripheral levels of BDNF (3, 12, 14, 28) cognitive performance scales; functional and motor recovery scales (3, 12, 14, 21, 23, 28, 40).

Exercise applied with gaming strategies (exergaming) was observed to influence communication between different brain regions, cortical activity and remapping related with motor functions. Brain functional connectivity measured by resting state EEG (rs-EEG) presented: i) increased activity in the beta band, usually associated with motor planning (2); ii) increased connectivity between cortical regions involved in resting state networks; iii) increased number of bilateral connections in the occipital, parietal, temporal and prefrontal regions after the intervention (19).

Gait training in a treadmill with weight support after stroke, combined with an exercise plan (EP) (stretching, muscle strengthening (MS) and balance) after stroke, 2-5 sessions per week for 4 weeks, significantly decreased the motor threshold for activation of the tibialis anterior (TA) muscle in the non-affected hemisphere. It also changed the cortical maps of the TA and abductor

hallux (AH) muscles. Significant functional gains were also observed in balance, gait speed, step length and cadence, with a positive correlation with changes seen in cortical excitability (40).

BDNF levels increased with AE in neurologic patients, as seen also in animals and healthy humans(13, 34). The effects of AE on BDNF levels seem to depend more on gender and not on characteristics of the training, such as the intensity mode (interval versus continuous) in neurodegenerative conditions. Including an AE component in the intervention was always associated with higher BDNF (Table 3).

Variations in training parameters, such as intensity (moderate and vigorous), mode (intermittent-interval or continuous) - did not seem to have an impact on peripheral BDNF levels, in adults with AD (12) and PD (21), using AE with a bicycle ergometer combined with MS, balance, active rest and stretching, for 8-9 weeks with 2-4 sessions per week.

There were significant increases in peripheral BDNF concentrations in PD (14) and MCI (28) in interventions including EA combined with general mobility exercises and occupational therapy, SM and coordination/balance, respectively of moderate to vigorous intensity. Patients with MCI also had a significant decrease in tumor necrosis factor-α (TNF) and interleukin-6 (IL-6) levels after 6 months of training (28).

A combined moderate to vigorous intensity AE with MS and coordination/balance during 6 months, resulted in significant improvements in cognitive functions (executive function, attention and concentration) in MCI (28). It was also found that vigorous exercise on a bicycle ergometer had evident improvements in cognitive tests, in female subjects, compared to stretching and balance exercises of light to moderate intensity, resulting in better cardiorespiratory fitness and reduced body fat (3). A 9-week EP on a bicycle ergometer revealed improvements in aerobic fitness parameters, metabolic equivalent task (MET), maximum tolerated power (MTP) and functional capacity in AD. The gains were more significant when interval training of moderate to vigorous intensity was performed, compared to continuous vigorous intensity training (12). These results are also observed in adults with PD, using combined AE training with MS, balance, active rest and stretching. The vigorous intensity interval training regime led to greater gains in balance, motor activity, endurance, fatigue and bone density, while continuous training increased only motor activity, endurance and strength in individuals with PD (21). Also in PD, it was found that interval AE on a bicycle ergometer at moderate intensity, for 8 weeks, led to improvements in executive function and parkinsonian neurological signs, reflected by a decrease in upper limb bradykinesia and increased performance in activities of daily living, mood and intellectual function (23). There was also a significant increase in all functional variables related to gait and balance with a shorter EP of 4 weeks with the moderate to vigorous intensity AE (treadmill) component (combined with general mobility exercises and occupational therapy) (14). Thus, EP with AE seems to bring benefits to cognition and functional capacity in central neurodegenerative conditions when executed at a vigorous intensity (> 70% HR), benefiting from an interval regime, even in shorter durations (4 weeks). An EP with an aerobic component also results in improvements in gait performance, namely in dysfunctions that reflect uncoordinated motor execution. When a

Table 2. Characteristics of the intervention for each study included in the review.

Study	Design	Participants	Intervention group	Control group
Klados, et al.[19]	Controlled Non-randomized	Mild Cognitive Impairment N = 50 (12 M) Mean age 68,76 yrs	N = 25 TC + Exergaming (aerobic, endurance, flexibility) Frequency = 3-5 sessions/week Session duration = 1h (TC) +1h (exergaming) Total duration = 8 weeks	N = 25 Cognitive task Frequency = 3-5 sessions/week Session duration = 1h Total duration = 8 weeks
Nascimento et al.[28]	Controlled Non-randomized	Mild Cognitive Impairment N = 67 (23 M) Mean age 67,63 yrs	N = 35 Multimodal physical exercise: strength + aerobic + coordination/balance Intensity = 60%-80% HRmax Frequency = 3 sessions/week Session duration = 1h Total duration = 6 months	N = 32 No intervention and not participating in a regular exercise program for at least one year before the start of the study or during the duration of the study.
Baker et al.[3]	Controlled Randomized	Mild Cognitive Impairment N = 29 (14 M) Mean age 70,35 yrs	N = 19 Aerobic exercise: treadmill/ bike/elliptical trainer Intensity = 75%-85% final heart resistance Frequency = 4 times/week Session duration = 45-60 minutes Total duration = 6 months	N = 10 Stretching and balance exercises Intensity ≤ 50% final heart resistance Frequency = 4 times/week Session duration = 45-60 minutes Total duration = 6 months
Enette et al[12]	Controlled Randomized	Alzheimer Disease N = 54 (19 M) Mean age 77,9 yrs	Aerobic exercise: bike A = continuous training, N = 14, intensity = 70% HRmax B = interval training, N = 17; intensity = 6 × 1 minute at 80% HRmax + 4 minutes at 60% HRmax Frequency A/B = 2 times/week, Session duration = 30minutes Total duration= 9 weeks	N = 21 Interactive information sessions on the health benefits of physical activity in the elderly. Frequency = 1 time/week Session duration = 30minutes Total duration = 9 weeks
Frazzitta et al.[14]	Controlled Randomized	Parkinson Disease N=25 Mean age 66 yrs	N = 15 General mobility exercises + aerobic exercise (treadmill with HR ≤60% max and max speed of 3.5 km/h) + Occupational ADL therapy. Frequency = 5 sessions/week, Session duration = 3h/day, Total duration = 4 weeks	N = 10 Without intervention

Footnote: M, male; yrs, years; TC, cognitive training; HR, heart rate; ADL, Activities of Daily Life

Table 2. Characteristics of the intervention for each study included in the review *(cont.)*.

Study	Design	Participants	Intervention	Control group
Landers et al.[21]	Controlled Randomized	Parkinson Disease N = 27 (19 M) Mean age 64,05yrs	N = 14 30 minutes aerobic exercise at (70%-80% HRmax) + 30 minutes trunk and limb strength (50-80% of 1RM) + 15 minutes balance training + 15 minutes active rest and stretching Frequency =3 - 4 sessions/week Session duration = 90 minutes Total duration = 8 weeks	N = 13 15 minutes aerobic exercise (50%-65% HRmax) + 15 minutes trunk and limb strength (≤ 50% of 1RM) + 10 minutes balance training + 10 minutes stretching + 10minutes rest. Frequency = 3-4 sessions/week Session duration = 60minutes Total duration = 8 weeks
Marusiak et al.[23]	Controlled Randomized	Parkinson Disease N = 10 (9 M) Mean age 73yrs	N = 10 Interval aerobic exercise on a stationary bike, 40 minutes moderate intensity interval + 10 minutes return to calm. Fast stage range: 3 minutes to ≥60 rpm (80-90 rpm); Slow stage range 2 minutes to ≤60 rpm (HR max 60%-75%). Frequency = 3 sessions/week Session duration = 1h Total duration = 8 weeks	N = 10 Maintain normal daily physical activity, receiving the usual care, including conventional physical therapy, with activities to improve motor control, without any type of moderate or high intensity aerobic exercise or continuous physical training.
Yen et al.[40]	Controlled Randomized	Stroke N = 14 (9 M) Mean age 56,78 yrs	N = 7 Stretching + strength + balance + gait Frequency = 2-5 sessions/week Session duration = 50 minutes Total duration = 4 weeks + BWSTT Frequency = 3 sessions/week Session duration = 30 minutes Total duration = 4 weeks	N = 7 Stretching + strength + balance + gait Frequency = 2 to 5 sessions/week Session duration = 50 minutes Total duration = 4 weeks
Velázquez et al.[39]	Controlled Randomized	Spinocerebellar ataxia type 2 N = 29 (7 M) Mean age 38,49 yrs	N = 7 trunk and limb strength + dynamic and static balance + indoor and outdoor gait + going up and down stairs + upper and lower limb coordination tasks. Frequency and duration of the session = 20 minutes motor control, 5 sessions/week + 45 minutes general exercises, 3 sessions/week Total duration= 12 weeks	N = 7 Without intervention

Footnote: M, Male; yrs, years; HR, Heart Rate; rpm, Revolutions per minute; 1RM, 1 Repetition Maximum; BWSTT, Body Weight Supported Treadmill Training

Table 3. Neurophysiological, biochemical and functional outcomes observed in each study.

Study	Neuroplasticity outcomes	Functional/clinical outcomes
Klados et al.[19]	Intervention vs control: ↑ brain functional connectivity measured by rs-EEG after training: ↑ beta-band activity in dorsal attention network, standard mode network and somatomotor network.	----------
Nascimento et al.[28]	Intervention vs control: ↑ peripheral BDNF ↓ TNF and IL-6	Intervention vs control: ↑ cognitive functions (executive function, attention and concentration)
Baker et al.[3]	Intervention vs control: Gender-dependent variation of BDNF positively correlated with cortisol with aerobic exercise	Intervention vs control: ↑ cardiorespiratory fitness (VO2 and treadmill performance). ↑ performance in cognitive tests – greater effect in females.
Enette et al.[12]	Intervention vs control: No changes to BDNF	Intervention vs control: ↑ maximum tolerated power (30.8% continuous training; 40% interval training), metabolic equivalent task (14.3% continuous training, 22.7% interval training) and functional capacity (4.7% continuous training; 7, 2% interval training). Continuous training: ↑ Perceived quality of life (5.9%) (QoL-AD).
Frazzitta et al.[14]	Intervention vs control: ↑ peripheral BDNF levels in the aerobic exercise group after 10 days and over time	Intervention vs control: ↑ significant of all functional variables (gait and balance) at 4 weeks.
Landers et al.[21]	Both groups: ↑ peripheral BDNF. Fall to lower levels after 6 months compared to baseline.	High intensity exercise: ↑ balance, motor activity, endurance, fatigue and bone density. Low intensity exercise: ↑ motor activity, endurance and strength.
Marusiak et al.[23]	Intervention vs control: ↑ executive function and parkinsonian neurological signs - improvement in upper limb bradykinesia.	Intervention vs control: ↑ bimanual motor control and force and activation parameters in manipulation tasks; ↑ functions of daily living, mood, and intellectual function.
Yen et al.[40]	Intervention vs control: Motor threshold measured by transcutaneous electrical stimulation to tibialis anterior ↓ significantly in the unaffected hemisphere; ↑ in cortical maps of tibialis anterior (in both hemispheres) and abductor hallux (affected hemisphere).	Intervention vs control: after BWSTT there was ↑ balance, gait speed, step length and cadence.
Velázquez et al.[39]	----------	Intervention vs control: ↓ gait time,↑ static balance and motor coordination

Footnote: rs-EEG, resting-state electroencephalography; BDNF, Brain-Derived Neurotrophic Factor; TNF, Tumor Necrosis Factor; IL-6, Interleukin-6; VO2, Volume of Oxygen; BWSTT, Body Weight Supported Treadmill Training; QoL-AD, Quality of Life questionnaire in Alzheimer Disease

physiotherapy plan, complemented by walking with suspended weight on a treadmill in post-stroke recovery, was applied for 4 weeks, significant gains were observed in balance, gait speed, step length for both limbs and cadence (40).

An EP with indoor and outdoor gait and stair training, combined with MS, dynamic and static balance and coordination tasks, performed for 12 weeks, showed significant gains in improving gait, postural and coordination deficits in spinocerebellar ataxia type 2 (SCA2) (39).

DISCUSSION

Neuroplasticity plays a key role in recovery processes by limiting brain sequelae and damage. A growing body of evidence shows that physical activity affects neuroplasticity, suggesting positive outcomes on cognition and functionality. However, there is great variability in the dose-response of exercise prescription and also in neuroplasticity gains (20, 24)

This systematic review assessed the impacts of exercise on neuroplasticity, through assessment of neural networks and neuronal excitability, measurement of BDNF value and cognitive assessment, motor recovery and functional assessment.

The main findings were a) interventions consisting of moderate to vigorous intensity AE are associated with better neuroplastic responses reflected by functional gains; b) cognitive stimuli during the exercise session appear to provide better neuroplastic benefits; c) good quality evidence is lacking given the absence of any higher standard measure of neuroplasticity, the non-uniformity of exercise interventions and the unknown dose-response relationship.

We will discuss these findings according to neurological conditions and relevance of exercise.
AD and MCI are characterised by loss of cell density and dendritic spines that secondarily affect BDNF levels. In animal models of AD, BDNF reveals potent therapeutic effects that include prevention of cell death, stimulation of neuronal function, improvement in synaptic markers, learning and memory. It thus represents a potentially promising therapeutic route in AD, which can be induced through exercise (25, 27).

Age, genetics, exercise intensity and severity of the neurological condition may attenuate the response of neurotrophic factors to exercise. BDNF is abundant in the CNS and is involved in activity-induced neuroplasticity. It is positively regulated by exercise in animal models. In healthy adults, increasing BDNF during moderate-intensity activities has been associated with improved cognition (25, 27). Our results in neurological diseases demonstrate also the importance of AE of moderate or high intensity specialy interval training and better if this type of training is combined with other strategies.

In line with this, when the results were assessed through EEG, there was an improvement in functional connectivity after AE combined with cognitive training. When compared to a stretching and balance EP, functional gains and increased BDNF levels were more relevant in females. When compared to no exercise intervention, there was an improvement in functional

and cognitive parameters, but the results of BDNF values are conflicting, with significant gains in one group versus no gains in the other (3, 12, 19, 28).

EEG and its features can reliably identify early signs of MCI and AD-related pathology. Experimental data delineate cognitive gains versus declines and neurodegenerative burden, given that, people with MCI compared to healthy people show decreased EEG synchronisation and altered functional connectivity of magnetoencephalography within the beta band (19).

Results then suggest that AE and exergaming should be combined with other strategies, such as cognitive training, to repair dysfunctional and induce neuroplasticity in adults with MCI and AD related pathology (19).

PD is a neurodegenerative disease affecting motor function and cognitive ability. Although it interferes with several neuronal systems, the cardinal component results from the progressive degeneration of dopaminergic neurons that project from the substantia nigra to the corpus striatum. BDNF has been shown to support the survival of dopaminergic neurons. Expression of BDNF protein and its mRNA is reduced in neurons of the substantia nigra in PD. The introduction of BDNF into the brain, could be a potential strategy in the treatment of PD in humans. In primates, there is a reduction in cell loss and an increase in striatal reinnervation (27, 41). Our review results found that, in adults with PD, the effects of AE resulted on positive changes in functional variables and BDNF levels, post-test and over time, however with better outcomes in moderate to high intensity exercises when compared with a non-intervention group (14, 21, 23).

After stroke, complex cognition and motor relearning are interconnected. Complex movement relearning is fundamental for neurorehabilitation, requiring most cognitive domains, including working memory, attention, and executive function. Motor learning is affected by cognitive impairment, limiting the ability of the person with stroke to understand, repeat, improve, and analyse the reacquired movement (16, 24).

SCA2 is a polyglutaminase caused by expansion of the cytosine-adenine-guanine triplet repeats in the coding region of the ATXN2 gene, the neurodegenerative changes cause a condition characterised by a progressive cerebellar syndrome, with slowing, sleep disturbances, cognitive changes, peripheral neuropathy, autonomic dysfunction and signs of motor neuron involvement (35, 39)

An AE plan for this pathology resulted in functional gains in terms of gait speed, maintenance of positions held on surfaces and improvement in motor coordination. Due to the absence of neuroprotective drugs that could slow or stop disease progression, neurorehabilitation should be is a prior therapy for the prodromal phase of SCA2 to allow a significant impact on cerebellar function and other characteristics of the disease (39).

Interventions including aerobic exercise (AE) such as exergaming and treadmill gait training have significant effects on neuroplasticity, evidenced by cortical remapping and changes in motor-related brain connectivity patterns.

Some limitations may have had some impact on our analysis. Uniformity in training may be the main factor of conflicting results. It is highlighted that lower intensity exercise does not have as many improvements when functionality is assessed, suggesting that neuroplastic adaptations are triggered by rehabilitation programs that include higher intensity exercise intervention. Cognitive impairment hinders the sensory-motor learning, necessary for recovery. In studies that used cognitive assessment and motor recovery, there was evidence of improvements in motor learning in patients with neurological disease (16, 26, 36) However, only a few studies (3, 23, 28) included assessment tools to evaluate the impact of AE in other types of cognitive functions, specifically: (a) visuospatial and executive functions - The Montreal Cognitive Assessment (MoCa) (28) and the Trail Making Test B (TMT-B) (3, 23); (b) memory – MoCa (28), Story Recall (3), List Learning (3) and Delayed-Match-To-Sample (3); (a) attention – MoCa (28) and Stroop Test II (ST-II) (3, 23); (d) processing speed – ST-I and TMT-A (3, 23). Improvements were observed in all these studies, however no direct relation was established with neuroplasticity at a functional level. Nevertheless, improved cognitive performance reflects memory enhancement through learning, which involves neurobiological mechanisms that change the way neurons are wired together. Memory and learning are deeply associated with changes in synaptic strength, recruitment and neural networks reorganisation ruled by neuroplastic events (18). Future studies should investigate the impact of AE on cognitive functions by neuroplasticity enhancement by analysing objective correlations of gold-standard measures in both fields. This will allow to establish measurable and targeted goals in physical activity strategies for cognitive rehabilitation, based on a patient specific neural phenotype.

Another strong limitation is that evidence is still scarce regarding the relation between exergaming and neuroplasticity-related outcomes, such as cortical mapping or BDNF. We only found two older clinical studies that observe an increase in BDNF peripheral levels associated with exergaming in elderly with diabetes (8) or healthy (1). Further research is also necessary to identify the interaction of individual characteristics with AE-induced effects in neuroplasticity, such as disease phenotype or gender. A recent clinical trial in patients with multiple sclerosis (15), did not find statistical significant changes in BDNF levels due to aerobic exercise, oposite of the effects observed in the conditions addressed in our review (e.g. MCI, AD). This may indicate that, in fact, different neurologic conditions can change the BDNF-related neuroplastic response to exercise. Barha et al. observed that gender gender impact the effects of AE on cognitive performance according to a specific BDNF genotype: healthy elderly males with the BDNFval66met variant did not present increased cognition associated with AE-induce increase levels of BDNF. Future clinical studies should include more robust statistical approaches for multifactorial analysis of the interaction between neuroplastic and cognitive outcomes with different disease and genetic profiles (4).

This review provides evidence that moderate to vigorous intensity AE, with a frequency of at least 3 times/week, 30 minutes, for 4 weeks, is a therapeutic intervention that should be included

in rehabilitation programmes for neurological conditions, especially in MCI, AD, PD stroke and SCA2. In addition to the known benefits related to physical conditioning, functionality, mood and cardiovascular health, AE contributes to increase neuroplasticity processes necessary for the recovery and maintenance of motor and cognitive functions (13, 20, 24, 30). A higher intensity and interval training modality when combined with other strategies such as cognitive training, has evidence of increasing gains in patients with neurodegenerative diseases.

ACKNOWLEDGEMENTS

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this work was supported by Fundação para a Ciência e Tecnologia (FCT) in the scope of the FCT-IBEB Strategic Project UIDB/00645/2020 (Sofia R. Fernandes); Maria Teresa Tomás is affiliated in Health & Technology Research Center, ESTeSL - Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa which is supported by FCT/MCTES (UIDB/05608/2020 and UIDP/05608/2020).

REFERENCES

1. Anderson-Hanley C, Arciero PJ, Brickman AM, Nimon JP, Okuma N, Westen SC. Exergaming and older adult cognition. Am J Prev Med 42(2): 109-119, 2012.

2. Babiloni C, Barry RJ, Başar E, Blinowska KJ, Cichocki A, Drinkenburg WHIM. International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies. Clin Neurophysiol 131(1): 285-307, 2020.

3. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A. Effects of aerobic exercise on mild cognitive impairment. Arch Neurol 67(1), 2010.

4. Barha CK, Starkey SY, Hsiung GYR, Tam R, Liu-Ambrose T. Aerobic exercise improves executive functions in females, but not males, without the BDNF Val66Met polymorphism. Biol Sex Differ 14(1): 16, 2023.

5. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors 22(3): 123-131, 2004.

6. Boyne P, Meyrose C, Westover J, Whitesel D, Hatter K, Reisman DS. Exercise intensity affects acute neurotrophic and neurophysiological responses poststroke. J Appl Physiol 126(2): 431-443, 2019.

7. Brattico E, Bonetti L, Ferretti G, Vuust P, Matrone C. Putting cells in motion: Advantages of endogenous boosting of BDNF production. Cells 10(1): 183, 2021.

8. Brinkmann C, Schäfer L, Masoud M, Latsch J, Lay D, Bloch W. Effects of cycling and exergaming on neurotrophic factors in elderly type 2 diabetic men – A preliminary investigation. Exp Clin Endocrinol Diabetes 125(07): 436-440, 2017.

9. Carroll WM. The global burden of neurological disorders. Lancet Neurol 18(5): 418-419, 2019.

10. Delgado-Peraza F, Nogueras-Ortiz C, Simonsen AH, Knight DD, Yao PJ, Goetzl EJ. Neuron-derived extracellular vesicles in blood reveal effects of exercise in Alzheimer's disease. Alzheimers Res Ther 15(1): 156, 2023.

11. Donato H, Donato M. Stages for undertaking a systematic review. Acta Med Port 32(3): 227-235, 2019.

12. Enette L, Vogel T, Merle S, Valard-Guiguet A-G, Ozier-Lafontaine N, Neviere R. Effect of 9 weeks continuous vs. interval aerobic training on plasma BDNF levels, aerobic fitness, cognitive capacity and quality of life among seniors with mild to moderate Alzheimer's disease: A randomized controlled trial. Eur Rev Aging Phys Act 17(1): 2, 2020.

13. Ferreira AFB, Real CC, Rodrigues AC, Alves AS, Britto LRG. Moderate exercise changes synaptic and cytoskeletal proteins in motor regions of the rat brain. Brain Res. 1361: 31-42, 2010.

14. Frazzitta G, Maestri R, Ghilardi MF, Riboldazzi G, Perini M, Bertotti G. Intensive rehabilitation increases BDNF serum levels in Parkinsonian patients. Neurorehabil Neural Repair 28(2): 163-168, 2014.

15. Gravesteijn AS, Beckerman H, Willemse EA, Hulst HE, de Jong BA, Teunissen CE. Brain-derived neurotrophic factor, neurofilament light and glial fibrillary acidic protein do not change in response to aerobic training in people with MS-related fatigue – A secondary analysis of a randomized controlled trial. Mult Scler Relat Disord 70: 104489, 2023.

16. Hasan SMM, Rancourt SN, Austin MW, Ploughman M. Defining optimal aerobic exercise parameters to affect complex motor and cognitive outcomes after stroke: a systematic review and synthesis. Neural Plast 2016, 2016.

17. Huang EJ, Reichardt LF. Neurotrophins: Roles in neuronal development and function. Annu Rev Neurosci 24(1): 677-736, 2001.

18. Kandel ER. The biology of memory: A forty-year perspective. J Neurosci 29(41): 12748-12756, 2009.

19. Klados MA, Styliadis C, Frantzidis CA, Paraskevopoulos E, Bamidis PD. Beta-band functional connectivity is reorganized in mild cognitive impairment after combined computerized physical and cognitive training. Front. Neurosci. 10(FEB), 2016.

20. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity exercise-induced response of peripheral brain-derived neurotrophic factor: A systematic review of experimental studies in human subjects. Sport Med 40(9): 765-801, 2010.

21. Landers MR, Navalta JW, Murtishaw AS, Kinney JW, Pirio Richardson S. A high-intensity exercise boot camp for persons with Parkinson disease: A Phase II, pragmatic, randomized clinical trial of feasibility, safety, signal of efficacy, and disease mechanisms. J Neurol Phys Ther 43(1): 12-25, 2019.

22. Ma L-L, Wang Y-Y, Yang Z-H, Huang D, Weng H, Zeng X-T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? Mil Med Res 7(1): 7, 2020.

23. Marusiak J, Fisher B, Jaskólska A, Słotwiński K, Budrewicz S, Koszewicz M. Eight weeks of aerobic interval training improves psychomotor function in patients with Parkinson's disease-randomized controlled trial. Int J Environ Res Public Health 16(5): 880, 2019.

24. Mellow ML, Goldsworthy MR, Coussens S, Smith AE. Acute aerobic exercise and neuroplasticity of the motor cortex: A systematic review. J Sci Med Sport 23(4): 408-414, 2020.

25. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. Front Cell Neurosci 13(August): 1-25, 2019.

26. Murawska-Ciałowicz E, de Assis GG, Clemente FM, Feito Y, Stastny P, Zuwała-Jagiełło J. Effect of four different forms of high intensity training on BDNF response to Wingate and graded exercise test. Sci Rep 11(1): 1-16, 2021.

27. Nagahara AH, Tuszynski MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat Rev Drug Discov 10(3): 209-219, 2011.

28. Nascimento C, Pereira J, Andrade L, Garuffi M, Talib L, Forlenza O. Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. Curr Alzheimer Res 11(8): 799-805, 2014.

29. Navalta JW, Stone WJ, Lyons TS. Ethical Issues Relating to Scientific Discovery in Exercise Science. Int J Exerc Sci 12(1): 1-8, 2019.

30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Syst Rev 10(1): 89, 2021.

31. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci 28(1): 377-401, 2005.

32. Pezet S, McMahon SB. Neurotrophins: Mediators and modulators of pain. Annu Rev Neurosci 29(1): 507-538, 2006.

33. Pfurtscheller G, Neuper C, Andrew C, Edlinger G. Foot and hand area mu rhythms. Int J Psychophysiol 26(1-3): 121-135, 1997.

34. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: Bidirectional transcription, complex splicing, and multiple promoters. Genomics 90(3): 397-406, 2007.

35. Sena LS, dos Santos Pinheiro J, Hasan A, Saraiva-Pereira ML, Jardim LB. Spinocerebellar ataxia type 2 from an evolutionary perspective: Systematic review and meta-analysis. Clin Genet 100(3): 258-267, 2021.

36. de Sousa Fernandes MS, Ordônio TF, Santos GCJ, Santos LER, Calazans CT, Gomes DA. Effects of physical exercise on neuroplasticity and brain function: A systematic review in human and animal studies. Neural Plast 2020: 1-21, 2020.

37. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res 60: 56-64, 2015.

38. Thacker JS, Yeung D, Chambers PJ, Tupling AR, Staines WR, Mielke JG. Single session, high-intensity aerobic exercise fails to affect plasticity-related protein expression in the rat sensorimotor cortex. Behav. Brain Res. 359: 853-860, 2019.

39. Velázquez-Pérez L, Rodríguez-Diaz JC, Rodríguez-Labrada R, Medrano-Montero J, Aguilera Cruz AB, Reynaldo-Cejas L. Neurorehabilitation improves the motor features in prodromal SCA2: A randomized, controlled trial. Mov Disord 34(7): 1060-1068, 2019.

40. Yen CL, Wang RY, Liao KK, Huang CC, Yang YR. Gait training-induced change in corticomotor excitability in patients with chronic stroke. Neurorehabil Neural Repair 22(1): 22-30, 2008.

41. Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol 5(6): 311-322, 2009.