

Effects of aerobic physical exercise on neuroplasticity after stroke: systematic review

Efeitos do exercício físico aeróbico na neuroplasticidade após o acidente vascular cerebral: revisão sistemática de literatura

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ABSTRACT

Background: Stroke is among the leading causes of death and disability worldwide. Interventions for stroke rehabilitation aim to minimize sequelae, promote individuals' independence and potentially recover functional damage. The role of aerobic exercise as a facilitator of post-stroke neuroplasticity in humans is still questionable. **Objective:** To investigate the impact of aerobic exercise on neuroplasticity in patients with stroke sequelae. **Methods:** A systematic review of randomized clinical trials and crossover studies was performed, with searches for human studies in the following databases: PUBMED, EMBASE, LILACS and PeDRO, only in English, following the PRISMA protocol. The keywords used for selecting articles were defined based on the PICO strategy. **Results:** This systematic review evaluated the impacts of aerobic exercise on neuroplasticity through assessment of neural networks and neuronal excitability, neurotrophic factors, or cognitive and functional assessment. Studies that evaluated the effects of aerobic exercise on neuroplasticity after stroke measured through functional resonance (fMRI) or cortical excitability have shown divergent results, but aerobic exercise potentially can modify the neural network, as measured through fMRI. Additionally, aerobic exercise combined with cognitive training improves certain cognitive domains linked to motor learning. Studies that involved analysis of neurotrophic factors to assess neuroplasticity had conflicting results. **Conclusions:** Physical exercise is a therapeutic intervention in rehabilitation programs that, beyond the known benefits relating to physical conditioning, functionality, mood and cardiovascular health, may also potentiate the neuroplasticity process. Neuroplasticity responses seem more robust in moderate to high-intensity exercise training programs, but dose-response heterogeneity and non-uniform neuroplasticity assessments limit generalizability.

Keywords: Stroke; Stroke Rehabilitation; Exercise; Neuronal Plasticity; Endurance Training; High-Intensity Interval Training; Brain-Derived Neurotrophic Factor; Nerve Growth Factor.





RESUMO

Antecedentes: O acidente vascular cerebral (AVC) é a segunda causa principal de morte no mundo. Intervenções para reabilitação dos pacientes com AVC visam minimizar sequelas, promover sua independência e potencialmente recuperar danos funcionais. O papel do exercício aeróbico como facilitador da neuroplasticidade pós-AVC em humanos ainda é questionável. **Objetivo:** Investigar o impacto do exercício aeróbico na neuroplasticidade em pacientes com sequelas de AVC. **Métodos:** Foi realizada revisão sistemática de literatura, pesquisando nas seguintes bases de dados: PUBMED, EMBASE, LILACS e PeDRO. Foram selecionados trabalhos em língua inglesa, realizados apenas com humanos, seguindo o protocolo PRISMA. As palavras-chave utilizadas para a seleção de artigos foram definidas com base na estratégia PICO. **Resultados:** Esta revisão sistemática avaliou os impactos do exercício aeróbico na neuroplasticidade através da avaliação das redes neurais e da excitabilidade neuronal, por meio de fatores neurotróficos, por meio da avaliação cognitiva e funcional. Estudos que avaliaram os efeitos do exercício aeróbico sobre neuroplasticidade após o AVC medido através de ressonância funcional ou excitabilidade cortical, são controversos, mas há dados sugerindo uma modificação da rede neural na ressonância funcional após o exercício aeróbico. Há evidências de que, associar exercício aeróbico com treinamento cognitivo melhora certos domínios cognitivos ligados à aprendizagem motora. Estudos que envolveram a análise de fatores neurotróficos, como avaliação da neuroplasticidade, tiveram resultados conflitantes. **Conclusões:** Exercício aeróbico é uma intervenção terapêutica em programas de reabilitação, pois, além de proporcionar os benefícios no condicionamento físico, funcionalidade, humor e saúde cardiovascular, pode potencializar a neuroplasticidade.

Palavras-chave: Acidente Vascular Cerebral; Reabilitação do Acidente Vascular Cerebral; Exercício Físico; Plasticidade Neuronal; Treino Aeróbico; Treinamento Intervalado de Alta Intensidade; Fator Neurotrófico Derivado do Encéfalo; Fator de Crescimento Neural.

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INTRODUCTION

Stroke is among the leading causes of death and disability worldwide¹. Atherothrombotic etiology is the main cause of ischemic stroke, and the main risk factors for this are hypertension, diabetes, dyslipidemia, smoking and sedentarism. Particularly, a sedentary lifestyle is increasingly adopted after the event, thus further compromising physical fitness and cardiovascular function². The functional consequences of stroke depend on the extent, location and area affected³, and on whether appropriate therapeutic interventions are implemented for each stage of the disease.

Interventions for rehabilitation of post-stroke patients aim to minimize sequelae, promote these individuals' independence and potentially recover functional damage, based on three basic principles: adaptation, regeneration and neuroplasticity. Individuals' recovery capacity is proportional to central nervous system neuroplasticity, defined as changes to or reconnection of the neural networks that were interrupted by the ischemic/hemorrhagic event. According to individuals' predisposition and favorable stimuli, these networks can reconnect to adjacent areas and perform similar functions in total or partial replacement of the compromised functions⁴.

One of the best-known facilitators for neuroplasticity is aerobic exercise. In experimental stroke models, moderate-intensity aerobic exercise induces neural responses that optimize motor recovery through plasticity⁵. One proposed mechanism for this relates to increases in neurotrophin levels associated with neuroprotection, neurogenesis and neuroplasticity, particularly the brain-derived neurotrophic factor (BDNF), which is induced in the brain directly through aerobic exercise. This could possibly be potentialized when combined with other forms of rehabilitation⁶. BDNF is a key mediator of motor learning and post-stroke rehabilitation⁷.

Despite the plausibility demonstrated in animal models, the facilitator role of aerobic exercise with regard to post-stroke neuroplasticity in humans is still questionable. Approximately 30% of humans have BDNF genetic polymorphism (Val66Met)⁸, which has been associated with impaired motor learning among post-stroke individuals⁹. Thus, stroke extent and localization, genetic variations such as BDNF polymorphisms and the types of intervention can all affect the response to rehabilitation and potentially modulate the effects of aerobic training on neuroplasticity⁷.

The objective of this systematic literature review was to identify the impact of aerobic exercise on neuroplasticity among patients with stroke sequelae.

METHODS

A systematic review was conducted between November 27, 2019, and February 4, 2020, with searches in the following databases: PUBMED, EMBASE, LILACS and PeDRO. The study

types included were randomized clinical trials and crossover studies. The search was done by one of the authors (LGP) and was checked by another author (JPP). Any disagreements regarding inclusion were resolved by reaching a consensus. Studies in English, conducted only on humans, were included. The PRISMA protocol was followed. The search aimed to identify studies relating to stroke, aerobic exercise, cognition, neuroplasticity and functional recovery.

The search strategy was defined based on keywords and through using the Boolean operators AND and OR. The keywords used were defined based on the PICO strategy, which was used for selecting articles as follows:

(P) - Population: Studies on post-stroke patients at any stage, of any age and gender, were included regardless of the severity of the sequelae and functionality. Key words used: "stroke" and "cerebrovascular accident".

(I) - Intervention: Aerobic exercise, of any intensity or duration, either belonging to a training program or consisting just of aerobic training sessions. Keywords used: "exercise", "endurance training", "aerobic exercise", "physical activity" and "training exercise".

(C) Comparison with a control group (conventional rehabilitation), or with interventions such as strength exercises, physiotherapy, flexibility exercises or functional exercises, provided that these did not involve aerobic exercises.

(O) Outcomes: Results relating to neuroplasticity assessment were evaluated, including neurotrophic markers such as BDNF, IgF1 and VEGF1, assessment of neuronal excitability, assessment from neuroimaging such as functional magnetic resonance (fMRI) or use of recovery scales that indicated neuro-functional improvement. Keywords used: "neuronal plasticity", "brain-derived neurotrophic factor", "recovery" and "nerve growth factor".

The articles identified through the search strategy were selected according to their titles and then according to their abstract; and lastly according to reading of the full text, as defined through the eligibility criteria of the protocol (prospective registration number CRD42020160865).

The following types of articles were excluded: systematic reviews of the literature, meta-analyses and articles that did not meet the requirements of the research strategy.

RESULTS

Figure 1 summarizes the search and selection process for the studies included, in accordance with the PRISMA protocol. Out of the 569 articles extracted from the databases, 22 were selected and six were later excluded because they did not meet the eligibility criteria or because they were prospective studies without a control group.

Among the 16 articles that thus were selected for this systematic review, nine reported on aerobic physical training

Murdoch et al.¹⁵ reported that 30 minutes of low-intensity bike exercise did not increase cortical excitability. Thus, they did not find any association with motor cortex neuroplasticity.

Neuroplasticity assessed through cognitive and motor recovery (motor relearning) evaluation

Four studies included in this systematic review evaluated the effects of aerobic physical training on neuroplasticity using scales and motor assessments before and after the intervention.

Linder et al.⁵ evaluated the effects of a moderate-intensity aerobic training program using two motor recovery scales: Fugl Meyer scale (FMA) and Wolf Motor Function Test (WMF). The main finding from their study was that “forced exercise” (defined by the authors as an exercise modality that augmented but did not replace the voluntary efforts of a participant to facilitate sustained aerobic exercise training) and moderate-intensity aerobic exercise facilitated motor recovery. The most plausible explanation for this was that moderate to high-intensity exercises induce neurophysiological and vascular changes in the central nervous system.

Ploughman et al.⁶ demonstrated that aerobic exercise associated with cognitive training had better results with regard to cognitive assessment, physical fitness and walking speed. They also demonstrated that aerobic physical training without cognitive training did not show the same results. Therefore, their study supports the notion that combined training can promote neuroplasticity, such that this is able to overcome the recovery plateau even when there is no benefit regarding improvement

of depressed mood. Although BDNF did not change with this intervention, IgF1 significantly increased.

Quaney et al.¹⁶ demonstrated that patients with chronic stroke who performed aerobic exercise significantly increased their motor learning. This finding provides evidence that eight weeks of moderate-intensity aerobic training, three times a week, leads to benefits in cognition, including improved motor learning.

Yang et al.¹⁷ suggested that a combination of cycling training and conventional rehabilitation can lead to improved functional recovery of the lower limbs, endurance capabilities, walking speed and spasticity. The FMA scale was used to assess functional recovery, with significant improvement observed.

Neuroplasticity assessed through neurotrophic factors

Aerobic training can increase the serum levels of neurotrophic factors in healthy individuals, which are considered to be potent regulators of plasticity and survival of adult neurons and glial cells. In animal stroke models, it has been observed that some neurotrophic factors may increase with moderate to high-intensity aerobic exercise^{2,9,18}.

Only one study measured the response of an aerobic training program for neuroplasticity that was measured through neurotrophic factors.

El Tamawy et al.¹⁹ evaluated patients with sequelae of stroke in anterior circulation through aerobic exercise in association with physical therapy. They showed that aerobic exercise increased BDNF levels and improved executive function, as assessed through cognitive tests. There was a positive

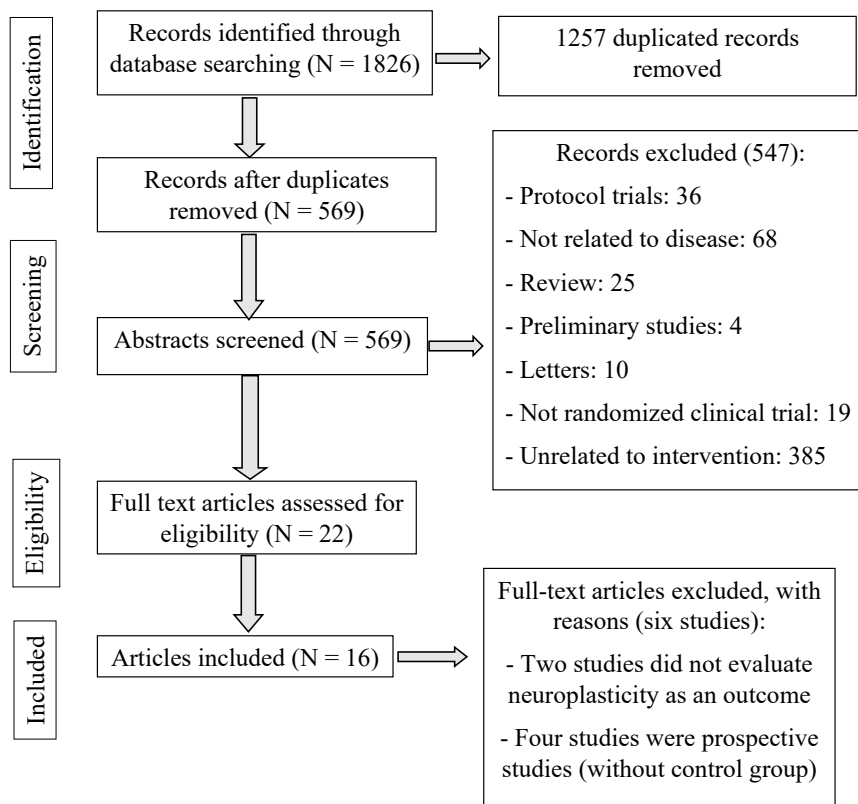


Figure 1. Study selection process in accordance with the PRISMA statement.

programs, among which eight were randomized studies and one was a crossover study. The other seven studies each evaluated single aerobic training sessions, among which five studies were randomized and two were crossover.

Regarding assessment of neuroplasticity, only one study assessed the association of neurotrophic factors with the aerobic physical training program, while four studies assessed this association in relation to a single exercise session. The other studies evaluated neuroplasticity using the following other methods: cortical excitability from motor evoked potential and electroneuromyography; functional magnetic resonance; cognitive assessment using specific scales; and motor recovery using the Fugl Meyer scale or functional recovery scales (Figure 2).

The intensity of the exercise that was used as the intervention was a very well-defined parameter in the studies and was very relevant to the results. This was the main reason why we included in this review studies involving a single exercise session. Exercise intensity was measured from heart rate using Karvonen's formula or from the results of cardiopulmonary exercise tests. Some studies also used the subjective perception of effort as a way of measuring exercise intensity.

Tables 1 shows summaries of the studies that used structured aerobic training programs and Table 2 shows the studies that used single sessions of exercise. Thus, these tables depict the associations of chronic and acute effects relating to neuroplasticity, respectively, that were included in this systematic review.

The quality of the studies was evaluated using the risk assessment tools of the PeDRO scale (Physiotherapy Evidence Database) and is shown in Table 3. Among the 16 articles, four had scores on the PeDRO scale < 6 and four studies had scores ≥ 8 . On average, the overall PeDRO grade was 6. The most common weakness was unclear blinding assessment. None of the studies blinded patients or therapists, but the patients were randomized in 11 studies. The most common strengths were the clear eligibility (a list of criteria was used to determine who was eligible to participate in the study), similar distribution of the groups (with description of at least one measurement of the severity of the condition under treatment and at least one (different) key outcome measurement at baseline), the inter-group comparisons and the measurements of variability. These

statistical assessments were important for reducing the risk of bias associated with comparisons between the results from the control and intervention groups.

Evaluation of results

The results from the studies included in this systematic review were expressed according to outcomes represented by each neuroplasticity assessment marker, as follows: 1) functional magnetic resonance and cortical excitability; 2) cognitive evaluation and motor recovery (motor relearning); 3) evaluation of neurotrophic factors; and 4) functional evaluation through functionality scales.

Neuroplasticity assessed through functional resonance and cortical excitability

Using functional MRI, other studies have shown increased activation of the contralesional cortex with movement of the paretic limb in the early post-stroke period¹⁰. Luft et al.¹¹ demonstrated that repetitive treadmill training improves cardiorespiratory capacity and recruits neural circuits in the brainstem and cerebellum as well as in the frontal, temporal and parietal cortical areas. Such overall changes in brain activation suggests potential neuroplastic mechanisms through which treadmill training can re-establish motor capacity and functional ability to walk, among post-stroke hemiparesis patients.

Nepveu et al.¹² showed that a single dose of high-intensity interval training performed immediately after physical therapy improves motor retention ability, as measured through the Montreal Cognitive Assessment (MoCA). Despite this, no statistically significant changes were observed in the assessment of cortical excitability, which could partially be explained by the older age of the sample being older and use of exercise doses that were lower than those that would be necessary to produce this effect. That study suggested that neuroplasticity might be associated with high-intensity exercise potentiated by physical therapy priming.

Abraha et al.¹³ demonstrated that there was greater latency in the motor evoked potential according to the intensity of the exercise, such that the latency of the motor evoked potential was greater after high-intensity interval training (HIIT) than after continuous training of moderate intensity. Their finding may have been related to a tendency to neuromuscular fatigue with HIIT. Their study brought up the concept that acute changes in corticospinal excitability after exercise may not be related to clinical changes in paretic limb strength and dexterity. Therefore, HIIT would not potentiate short term motor neuroplasticity.

Broderick et al.¹⁴ demonstrated that cortical-motor excitability increased after a short dose of high-intensity exercise among patients with sequelae of VCA. In their study, cortical excitability changed, as measured through the amplitude of the evoked motor potential in the injured hemisphere. However, no evaluation was performed with regard to whether motor recovery also changed with increased excitability.

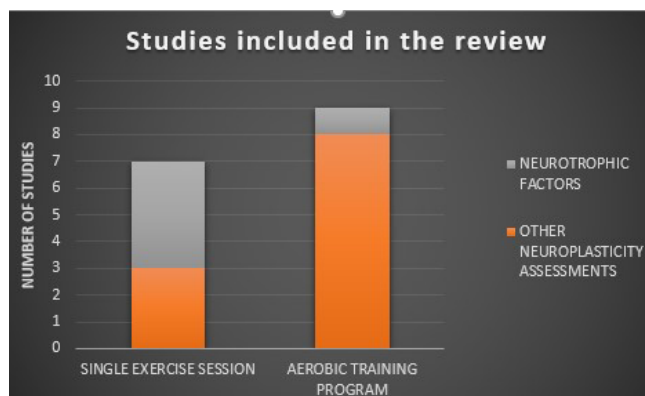


Figure 2. Studies included in the review.

Table 1. General characteristics of the studies with aerobic training

Author(s) / year/ type of study	Sampling	Experimental intervention	Control	Outcomes	Results
Luft et al., 2008/Journal: Stroke/ Randomized clinical trial	N=71 (Intervention: 37 versus Control: 34)	Treadmill training 3 times per week for 40 minutes at the intensity of 60% of the reserve heart rate (RHR).	Stretching with physiotherapist	Cerebral activation on fMRI	The intervention group improved peak VO ₂ by 18% (p<0.001), test speed of 10 meters and average speed by 19% (p=0.030) in the walking test. There was cerebral activation measured by fMRI in the posterior lobe of the cerebellum in the intervention group and not in the control group (p=0.005).
Linder et al., 2019/Journal: Neurorehabilitation and neural repair/ Randomized clinical trial	N=40 (patients evaluated, 16 in the "forced exercise group(FE)", 16 in the voluntary exercise group (VE) and 8 in the control group)	45 minutes on an exercise bike until reaching 60 to 80% of the reserve heart rate achieved in the cardiopulmonary exercise test	Educational videos and physiotherapy exercises	Change in functional scale: FMA	The outcomes evaluated were measures to improve motor recovery through functional scales. All 3 groups improved significantly on FMA by mean of 1, 6 and 9 point for the FE, VE and education groups respectively. (p= 0.001).
Ploughman et al., 2019/Journal: Neurorehabilitation and neural repair/ Randomized clinical trial	N = 52 (4 groups): - Aerobic training with cognitive training: 12 - Aerobic training with games: 13 - Physiotherapy activities with cognitive training: 15 - Physiotherapy activities with games: 12	20 to 30 minutes of aerobic physical activity with 20 to 30 minutes of cognitive training. Exercise intensity determined by 60 to 80% of peak VO ₂ of ergospirometry.	Stretching activity or functional training	Change in RPMT test	Effect of training on intelligent fluidity (RPMT test): difference between groups with p<0.05 → Aerobic + COG - increase of 47% → Activity + GAMES = 7% increase → Activity + COG = 20% increase → Activity + GAMES = 8% reduction
Quaney et al., 2009/although the learning benefits after stroke are unknown. Objective. To understand AEX-induced improvements in EF, motor learning, and mobility poststroke. Methods. Following cardiorespiratory testing, 39 chronic stroke survivors were randomized to 2 different groups that exercised 3 times a week (45-minute sessions/ Journal: neurorehabilitation and neural repair/ Randomized clinical trial	N=38 (Control: 19 versus Intervention group: 19)	Exercise bike at the intensity of 70% of HRmax, for 45 minutes, 3 times per week, 8 weeks under the supervision of the physiotherapist and exercise physiologist. Exercise is progressive in intensity until reaching the goal stipulated from the cardiopulmonary exercise test	Stretching exercises for 45 minutes, 3 times per week, for 8 weeks.	Change in score of motor learning	Vo2 max improved from 14.8 to 15.4 (p = 0.04) in the exercise group. There were no difference in VO2 max in control group (14.67 to 14.39). There was no between group, statistically significant difference regarding executive function. The exercise group significantly improved scores (p = 0.024; effect size d = 0.91) and demonstrated major effects on complex motor tasks. There was an improvement in agility measured through Time Up and Go in the exercise group: 17.42 to 15.26 (p = 0.038; effect size d = -0.70).
Yang et al., 2014/Journal: Kaohsiung Journal of Medical Sciences/Cross over study	N=30 (Group A: 15 versus Group B: 15)	30 minutes of aerobic exercise on stationary bike, 5 times per week for 4 weeks. Each session was divided into 2 15-minute periods with warm-up and active training with SPE of 13 and 60 revolutions per minute.	Conventional rehabilitation for 4 weeks.	Change in functional scale: FMA	Treatment effect of each outcome measures were significantly different in cycling period than in noncycling period. Treatment effect of each outcome measure was significant (p<0.001) for FMA, (improved: 3.9), 6MWT (improved: 44m) and 10MWT (improved 0.16 seconds). The combination of cycling training with conventional rehabilitation can lead to improved functional recovery of lower limbs, endurance ability, walking speed and spasticity. The following clinical parameters were used: functional FMA scale, 6-minute walk test, 10-meter test and Ashworth spasticity evaluation.

Table 1. Cont.

Author(s) / year/ type of study	Sampling	Experimental intervention	Control	Outcomes	Results
El-Tamawy et al., 2014/Journal: Neurorehabilitation / Randomized clinical trial	N = 30 (Intervention: 15 versus Control: 15)	30 minutes of physiotherapy + 15 minutes of rest + 40 minutes by bike - 30 minutes active and 10 minutes of warm-up and cooldown, 3 times per week for 8 weeks	Stretching, facilitation, strength, postural control, balance and functional training.	Changes in BDNF and ACER score	The mean values of subtest domains (attention, memory, verbal fluency, language and visuospatial ability) in study group post treatment were: 16.87; 21.27; 2.6; 25.27 and 15.07 respectively. Comparison of the mean value of each domain with control group revealed a significant increase in all domains in study group ($p < 0.005$) except verbal fluency. Serum level of BDNF increased in study group after intervention (19.18 to 23.83; $p = 0.0001$) and was unchanged in control group ($p = 0.698$) Pearson correlation between the post treatment changes in ACER total score and BDNF was statistically significant ($r = 0.53$, $p = 0.044$), such that cognitive improvement was associated with BDNF improvement.
Shaughnessy et al., 2012/Journal: Journal of neuroscience nurse/ Randomized clinical trial	N = 71 (Intervention: 37 versus Control: 34).	6 months of treadmill training – 3 times per week, 40 minutes per session at the intensity of 60% of RHR. Start in the individuals' capacity and progression every 2 weeks up to the goal	13 stretching exercises of large muscle groups under physiotherapy supervision	Changes in SIS scale	There was no significant difference between groups. There was an improvement in expectations associated with exercise and this was important because it shows that belief in the benefits of exercise can help in long-term adherence. Results indicated that regardless of group, all study participants experienced increased self efficacy ($F = 2.95$, $p = 0.09$) and outcome expectation for exercise ($F = 13.23$, $p < 0.001$) and improvement in activities of daily living as reported on the SIS ($F = 10.97$, $p = 0.002$).
Sandberg et al., 2016/Journal: Archives of physical Medicine and Rehabilitation/ Randomized clinical trial	N = 56 (Intervention: 29 versus Control: 27)	12 weeks of aerobic exercise, 2x per week. 60 minutes session: 15 min warm-up; 8 min of high intensity training in the ergometer cycle (SPE: 14 in 20; 75% peak VO2 and 80% of HR max); 10 min of low intensity, 8 min of high intensity training and 15 min of de heating.	Rehabilitation and physical activity advice.	Change in SIS scale	Improvement was greater in the intervention group for the following: peak work rate ($p = 0.006$), 6MWT ($p = 0.011$), maximum walking speed for 10 m ($p < 0.001$), TUG test ($p < 0.001$). Aerobic exercise was associated with improved EQ-5D scores (visual analog scale, $p = 0.008$) and perceived recovery (SIS domain 9, $p = 0.002$). These patient-reported improvements persisted at 6-month follow-up.
Nave, A. H et al., 2019/Journal: BMJ/ Randomized clinical trial	N = 200 (Intervention: 105 versus Control: 95)	50 minutes /5 times per week/4 weeks - 20 sessions in total. 25' in the exercise with a target of the HR reached (50 to 60% of HR max).	25 minutes of relaxation of the muscle groups Evaluated HR and SPE during the sessions.	Changes in Barthel index score	Compared with relaxation, aerobic physical fitness training did not result in a significantly higher mean change in maximal walking speed (adjusted treatment effect 0.1 m/s (95% confidence interval 0.0 to 0.2 m/s), $p = 0.23$) or mean change in Barthel index score (0 (-5 to 5), $p = 0.99$) at three months after stroke. A higher rate of serious adverse events was observed in the aerobic group compared with relaxation group (incidence rate ratio 1.81, 95% confidence interval 0.97 to 3.36).

N: Number of patients; RHR: reserve heart rate; fRMI: functional resonance magnetic; VO2: oxygen consumption; FE: forced exercise; VE: voluntary exercise; FMA (scale): Fugl Meyer scale; RPMT test: Raven Progressive matrices test; COG: Cognitive training; GAMES: Cognitive training with video games; HR max: heart rate maximum; SPE: Subjective perception of effort; 6MWT: 6 minutes walking test; 10MWT: 10 meters walk test; BDNF: Brain derived neurotrophic factor; ACER score: Addenbrooke cognitive examination revised; SIS: Stroke impact scale; TUG test: Time Up and Go test; EQ-5D scores: visual analog scale.

Table 2. General characteristics of the studies with a single exercise session.

Author(s) and year/ Journal/ type of study	Sampling	Experimental intervention	Control	Outcomes	Results
Nepveu et al., 2017/ Neurorehabilitation and neural repair/ randomized clinical trial ¹²	N = 22 (intervention: 11 versus control: 11).	Exercise group: 15 minutes of HIIT: 2 min of warm-up at 25% of the peak VO2 (calculated in the ergospirometry test), followed by 3 minutes of high intensity (100% of peak) interspersed with 2 minutes of low intensity at 25% of the peak effort.	Rest group	Changes in Cognitive assessment (MoCA)	Skill retention was significantly better in the HIIT group (unpaired t test, $t(19) = 2.20$; $p = 0.04$; effect size $d = 0.96$), which showed a 9% improvement in skill level, compared with the end of acquisition, while the control group showed a 4% decay. Specifically, 7 out of 11 participants in the HIIT group improved their mean score in the retention block, compared with the best block of training, while only 3 participants in the control group showed improvement.
Abraha et al., 2018/ Frontiers of Physiology/ crossover ¹³	N = 12 (MICE group: 6 and HIIT group: 6)	HIIT group: heating: 80% of VO2 max; maintained 60 to 80 steps per min alternating every 2 min with 40% of VO2 max. Total of 5 HIIT cycles, for 20 minutes	MICE group: Cadence of 60 to 80 passes per minute, at 60% of VO2 max for 20 minutes.	Changes in motor evoked potential (MEP) on electroneuromyography.	MEP latency from the ipsilesional hemisphere was lengthened after HIIT (pre: 24.27 ± 1.8 ms, and post: 25.04 ± 1.8 ms; $p = 0.01$) but not MICE (pre: 25.49 ± 1.10 ms, and post: 25.28 ± 1.0 ms; $p = 0.44$). There were no significant changes in motor thresholds, intracortical inhibition or facilitation. Pinch strength of the affected hand decreased after MICE (pre: 8.96 ± 1.9 kg vs. post: 8.40 ± 2.0 kg, $p = 0.02$) but not after HIIT (pre: 8.83 ± 2.0 kg vs. post: 8.65 ± 2.2 kg, $p = 0.29$). Regardless of type of aerobic exercise, higher total energy expenditure was associated with greater increases in pinch strength in the affected hand after exercise ($p = 0.04$) and decreases in pinch strength of the less affected hand ($p = 0.02$)
Murdoch et al., 2016/ Plos One/ crossover study ¹⁵	N = 12 (intervention: 6 and control: 6)	Cycloergometer at 50 rpm for 30 minutes and with subjective perception of light exertion (11-13/20).	Resting in a seated position for 30 minutes.	Changes in motor evoked potential (MEP) in electroneuromyography.	There was no significant effect on neuronal excitability after a single session of mild- intensity exercise with or without electrical stimulation (iTBS). There was no significant change in MEP amplitude over time with exercise alone ($p = 0.661$). Mild-intensity aerobic exercise does not result in an improvement in excitability.

Table 2. Cont.

Author(s) and year/ journal/ type of study	Sampling	Experimental intervention	Control	Outcomes	Results
Charalambous et al., 2018/ Topics Stroke Rehabilitation/ Randomized clinical trial ²⁰	N = 34 3 groups: - Control: 11 - Treadmill walk: 13 - Total body exercise: 10	Treadmill walk (TMW): 13 individuals - 15 minutes of high intensity exercise (75 to 80% of HR max. or 13-15 SPE if using BB). - Total Body exercise (TBE); Subjects pedaled at high resistance and fast speed, which we modulated throughout so that the exercise intensity was within the high-intensity range based on either HR or SPE.	Control (CON): 11 individuals - walking on the treadmill at 25% of comfortable speed (low intensity)	Changes in BDNF blood level.	Intensity significantly changed from the beginning to the end of exercise only in the exercise groups (CON: $p = 0.104$; TMW: $p < 0.001$; TBE: $p < 0.001$). Lactate levels were similar between the groups pre-exercise ($p > 0.05$ in all groups). Only the exercise groups ($p < 0.001$ in both groups) showed significant changes from pre- to post-exercise (CON: $p = 0.592$). A significant exercise effect was found for all measurements, except BDNF.
Boyne et al., 2020/ Neurorehabilitation and Neural/ crossover ²¹	N = 15 - 3 groups: - HIIT on the treadmill: 5 - Seated stepper HIIT: 5 - Continuous exercise (MCT treadmill): 5	- HIIT on the treadmill: 3 min of warm-up + 20 min of HIIT, in which the protocol was 30" acceleration with 60" rest and recovery decreasing to 30" after the first 5 min. The goal was to achieve a RHR of 60%. - Seated stepper HIIT (ergometer cycle): 3 min of warm-up + 20 min of HIIT, in which the protocol was 30" acceleration with 60" rest and recovery decreasing to 30" after the first 5 min. The goal was to achieve a RHR of 60%.	Continuous exercise (MCT treadmill); from moderate intensity to 45% of RHR	Changes in VEGF1, IgF1 and cortisol blood level.	- HIIT elicited significantly ($P < 0.05$) greater mean responses than MCT for blood lactate (HIIT-treadmill, 4.6 mmol/L; HIIT-stepper, 6.8 mmol/L; MCT-treadmill, 2.0 mmol/L), mean heart rate (HIIT-treadmill, 59.0% of heart rate reserve; HIIT-stepper, 67.5%; MCT-treadmill, 43.8%), and peak treadmill speed (HIIT-treadmill, 1.30 m/s; MCT-treadmill, 0.68 m/s) - VEGF1 significantly increased in HIIT on the treadmill, with no increase in the other groups - IgF1 increased significantly in both HIIT groups and did not increase in MICE - Cortisol decreased in all 3 groups
Boyne et al., 2019/ Journal of Applied Physiology/ crossover ²²	N = 15 - 3 groups: - HIIT on the treadmill: 5 - Seated stepper HIIT: 5 - Continuous exercise (MCT treadmill): 5	HIIT on the treadmill: 3 min of warm-up + 20 min of HIIT, in which the protocol was 30" acceleration with 60" rest and recovery, decreasing to 30" after the first 5 min. The goal was to achieve a RHR of 60%. - Seated stepper HIIT (ergometer cycle): Same HIIT protocol on the treadmill.	Continuous exercise: from moderate intensity to 45% of RHR.	Changes in BDNF blood level.	Serum BDNF significantly increased during the treadmill GXT (4.6 ng/ml [95% confidence interval: 0.7-8.4]). The increase was significantly greater for HIIT-treadmill, compared with MCT-treadmill (3.9 [0.1-7.8]) but not for HIIT-stepper compared with MCT treadmill (2.9 [1.0-6.7]). The increase in BDNF was positively related to lactate, VO2 and HR. The highest BDNF results were with lactate > 4.7 , mean VO2 $> 67\%$ peak and RHR $> 60\%$.

Table 2. Cont.

Author(s) and year/ journal/ type of study	Sampling	Experimental intervention	Control	Outcomes	Results
Morton, 2019/ Topics in Stroke Rehabilitation/ crossover ²⁷	N = 13 (HIIT and rest)	Two one-week training sessions between them – crossover: - 5 minutes of high intensity on the treadmill - 70 to 80% of HRmax.	Rest	Changes in motor evoked potential (MEP) on electroneuromyography.	All participants were able to reach the target high-intensity exercise level. Blood lactate levels increased significantly after exercise (p < 0.001; d = 2.85). Resting motor evoked potentials from the lesioned hemisphere increased after exercise, compared with the resting condition (p = 0.046; d = 2.76), but this was not the case for the non-lesioned hemisphere (p = 0.406; d = 0.25).

N: number of patients; HIIT: high-intensity interval training; VO2: oxygen consumption; MoCA test: Montreal cognitive assessment; MICE: moderate-intensity continuous training; MEP: motor evoked potential; HR max: max heart rate; iTBS: intermittent theta burst stimulation; TMW: treadmill walk; SPE: subjective perception of effort; TBE: total body exercise; CON: control; BDNF: brain-derived neurotrophic factor; MCT treadmill: moderate continuous training; RHR: reserve heart rate; VEGF1: vascular endothelial growth factor receptor 1; IgF1: insulin-like growth factor 1; GXT: graded exercise test.

Table 3. PeDRO assessment of the studies.

Author and year	Eligibility	Subjects were randomly assigned	Blind distribution	Similar groups	Subjects were blinded	Therapists were blinded	Assessors were blinded	Results measured	Intention-to-treat analysis	Intergroup comparison	Measurement of variability	Total
Linder et al., 2019 ⁵	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	8/11
Ploughman et al., 2019 ⁹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	9/11
Luft et al., 2008 ¹¹	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	6/11
Nepveu et al., 2017 ¹²	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/11
Abraha et al., 2018 ¹³	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	4/11
Murdoch et al., 2016 ¹⁵	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	4/11
Quaney et al., 2009 ¹⁶	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	7/11
Yang et al., 2014 ¹⁷	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	8/11
El-Tamawy et al., 2014 ¹⁹	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/11
Charalambous et al., 2018 ²⁰	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/11
Boyne et al., 2020 ²¹	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/11
Boyne et al., 2019 ²²	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/11
Shaughnessy et al., 2012 ²³	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/11
Sandberg et al., 2016 ²⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	8/11
Nave et al., 2019 ²⁵	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	7/11
Morton, 2019 ²⁷	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5/11

correlation ($r = 0.53$) between the increase in BDNF and the improvements in the tests.

Three studies measured the response of a single session of aerobic exercise regarding neuroplasticity, through changes in serum neurotrophins.

Charalambos et al.²⁰ were unable to demonstrate that high-intensity exercises increased serum BDNF levels after a training session, possibly due to the severe neurological damage and advanced age in their sample, which thus limited the response to the intervention.

Boyne et al.²¹ showed that the neurotrophic factors VEGF1 and IgF1 significantly increased through high-intensity interval training session, but not with moderate-intensity exercise. However, they did not measure BDNF, nor did they assess whether such results clinically impacted rehabilitation goals.

Boyne et al.²² showed that high-intensity interval exercise promoted a significant increase in BDNF, in comparison with continuous training of moderate intensity. In addition, they showed that the increase in BDNF was associated with a decrease in intracortical inhibition. Since motor relearning has been associated with lower intracortical inhibition, their findings provide support for the idea that changes in BDNF represent a potential marker of neuroplasticity.

Neuroplasticity assessed through functional scales

The three articles included in this section used functional scales as outcomes. Indeed, in assessing overall functionality, scales can provide indirect inferences about neuroplasticity, albeit not exclusively, given that other rehabilitation mechanisms (e.g. adaptation) can also improve the functional characteristics of post-stroke individuals.

Shaughnessy et al.²³ evaluated the effects of aerobic training for six months on functional independence and functional recovery. They showed that there was an increase in the ability to perform tasks of daily living and an increase in aerobic capacity. Notably, this was a self-assessment study with no objective measurements.

Sandberg et al.²⁴ showed that intensive aerobic exercise, twice a week, for 12 weeks, among patients with stroke in the subacute phase improved their physical performance and quality of life. There were improvements in aerobic capacity, speed, functional mobility, balance, quality of life and sense of functional recovery.

Nave et al.²⁵ evaluated only patients with severe motor sequelae in subacute phases after stroke and demonstrated that there was no superiority of aerobic physical activity in relation to relaxation sessions, regarding functional improvement.

DISCUSSION

Neuroplasticity plays a pivotal role in post-stroke recovery processes, through limiting sequelae and brain damage.

A growing body of evidence from experimental stroke models has shown that physical activity positively impacts neuroplasticity, thus suggesting that exercise techniques can potentially improve cognition and functionality. However, there is great variability in the dose-response of exercise prescription and in neuroplasticity metrics as well. Therefore, the clinical applicability of exercise prescription remains unknown.

To try to address this relevant clinical question, we conducted the present systematic review. Our main findings were: a) acute and chronic interventions consisting of moderate to high-intensity exercise are associated with better neuroplastic responses overall, except when assessed using functional MRI, from which the results are conflicting; b) cognitive or physiotherapeutic stimuli after an exercise session seem to provide additional neuroplastic benefit, which is greater than if these stimuli were applied without the exercise; c) good quality evidence is still lacking, given the absence of any gold-standard neuroplasticity metric, the non-uniformity of exercise interventions and the unknown dose-response relationship.

After a stroke, alterations to brain physiology and organization result in different brain activation patterns. During functional restructuration, the brain can modify its connections, thus leading to clinical changes during the rehabilitation period.

Neuroplasticity is defined as the ability of the central nervous system to undergo structural and functional adaptations as a result of new experiences⁴. Cohort studies on stroke patients have suggested that the motor recovery plateau occurs around 12 weeks after vascular ictus⁶. Several researchers have implemented forms of rehabilitation that make it possible to reopen the window of recovery and neuroplasticity after stroke⁶. Thus, aerobic physical exercise has been one of the strategies used for this goal.

The mechanisms through which aerobic exercise can enhance or intensify neuroplasticity have been described in relation to animals: these involve vascular impact through angiogenesis, glial restructuration and neurogenesis (with VEGF1 as one of the main markers); and a direct role for aerobic exercise in neuronal growth and presence of survival markers (with IgF1 and BDNF). Some authors have speculated that IgF1 elevation even with unchanged BDNF was associated with better post-stroke functional outcomes⁹. In addition, physical exercise can act on cognitive improvement and, therefore, have a direct impact on the overall motor relearning process. This can activate accessory neural networks that assist in improving motor recovery. Lastly, there was an improvement in expectations associated with doing exercise: this was important because it shows that belief in the benefits of exercise can help in long-term adherence.

This systematic review evaluated the impacts of aerobic exercise on neuroplasticity through assessment of neural networks and neuronal excitability, through neurotrophic factors and through cognitive and functional assessment.

We found that the studies that evaluated the effects of aerobic exercise on neuroplasticity after stroke, as measured

through functional MRI or cortical excitability, had divergent but promising results. Lack of uniformity in training (intensity, frequency or duration) can be the main driver of conflicting results. One important finding was that light-intensity exercises did not change cortical excitability. Conversely, moderate-intensity exercise training was associated with changes in functional MRI and excitability, thus suggesting that neuroplastic adaptations are triggered by rehabilitation programs that include higher-intensity exercise intervention. Additionally, interval and high-intensity exercises can lead to better results regarding neuroplastic outcomes, especially if associated temporally with motor physical therapy. However, it is important to note that changes in functional MRI and neuronal excitability may not correlate with clinical changes.

It is known that cognitive impairment hinders the sensory-motor learning that is necessary for post-stroke recovery. In the studies included in this review that used cognitive assessment and motor recovery (motor relearning), there was evidence that moderate-intensity aerobic exercise and “forced exercise” were able to improve motor learning among patients with stroke sequelae who were undergoing rehabilitation. The mechanisms through which these improvements occur were not evaluated in these studies, but there were suggestions that the potential mechanisms involved were increased BDNF, increased IgF1, improved synaptogenesis and cerebral flow²⁶. When the results regarding the association between aerobic training and cognitive training were analyzed, additional benefits were seen. Thus, there is evidence that associating aerobic exercise with cognitive training is better for improving certain cognitive domains linked to motor learning and is a strategy that can be implemented in a rehabilitation program.

The four studies that involved analysis of neurotrophic factors as an assessment of neuroplasticity had conflicting results. Notably, all of them evaluated moderate to high-intensity aerobic exercise. The study that involved a moderate-intensity aerobic exercise program¹⁹ showed that there was an increase in BDNF after exercise combined with motor physiotherapy. One of the studies involving a single exercise session²⁰ did not show any increase in BDNF after a high-intensity training session. Two studies^{21,22} showed that a high-intensity interval training session was able to increase circulating VEGF, IgF1 and BDNF.

Factors relating to age, genetics, exercise intensity and severity of the neurological condition could directly attenuate the response of neurotrophic factors to aerobic physical exercise. BDNF, which is currently the most studied neurotrophic factor, is abundant in the central nervous system and is involved in

activity-induced neuroplasticity. It is upregulated by exercise in animal models. In healthy adults, the increase in BDNF during high-intensity activity has been linked to improved cognition. Although beyond the objective of this review, genetic variation of BDNF can affect the response to rehabilitation training and, potentially, modulate the effects of aerobic exercise on neuroplasticity. Helm et al.⁸ found that high-intensity exercises can lead to significant increases in BDNF in patients with Val66Met polymorphism, which can be blunted at lower intensities. Therefore, greater intensity of exercise may be able to reduce the damaging effects of lower release of BDNF in individuals with this polymorphism. Thus, although the studies included in this review did not mention the important contribution of the Val66Met polymorphism in relation to circulating BDNF after aerobic exercise, the presence of better results from evaluations on high-intensity exercises may be related to this fact.

Given that knowledge in this field is still growing, the quality of evidence remains restricted. The studies analyzed had significant limitations such as small sample size and risk of selection bias; and absence of well-established correlations between laboratory/imaging findings and the clinical outcomes.

The heterogeneous interventions and outcomes precluded extraction of more objective data to calculate effect sizes and dose-response relationships. Additionally, the lack of a uniform gold-standard method for accurately measuring neuroplasticity, still limits the ability to expand its clinical applicability.

Despite these limitations, we were able through this review to compile a series of new findings that may guide the possibilities for further studies in this field, in order to systematize and optimize rehabilitation programs for patients with stroke consequences.

As a conclusion for this work, it can be stated that aerobic physical exercise is a therapeutic intervention in rehabilitation programs that, beyond the known benefits relating to physical conditioning, functionality, mood and cardiovascular health, may potentiate the neuroplasticity process. Good-quality evidence is still lacking, with regard to the limited uniformity of aerobic training prescription, the drivers of attenuation of individual responses and the equivocal metrics of matching between plasticity and clinical outcomes. Nonetheless, overall neuroplasticity responses seem more robust in moderate to high-intensity exercise training programs, to which adherence and safety are critical to achieving such benefits. A combination of cognitive training or physiotherapy training, implemented immediately after an aerobic workout, may provide additive benefit towards neuroplasticity in rehabilitation programs.

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