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Duration and Efficiency of Combined versus Isolated Aerobic Training Interventions in Post-Stroke Cognition: A Systematic Review

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Keywords
Stroke · Physical exercise · Cognitive rehabilitation · Intervention type · Intervention duration

Abstract
Background: This study aimed to evaluate the effects of physical activity on the cognition of patients with stroke, comparing the effectiveness of using isolated or combined rehabilitation, as well as the duration and intensity of training, to identify the characteristics of optimal training programs for post-stroke cognitive rehabilitation. ***Methods:*** For this systematic review, we followed PRISMA guidelines and searched Web of Science, Scopus, PEDRo, SPORTdiscus, PubMed, Trial Registries, and Google Scholar for studies published between 2013 and April 12, 2023. We included randomized controlled trials (RCTs) of interventions that measured the effect of physical activity on cognition in patients with stroke. We restricted our search to reports published in the English language. Evidence from the RCTs was synthesized. The risk of bias was assessed using the Cochrane risk of bias tool. ***Results:*** Of the 1,755 records identified, 34 were eligible, and data were available, with mainly low to moderate risk of general bias. The combined rehabilitation training programs proved more efficient when compared with isolated rehabilitation training programs in several cognitive domains. A moderate-intensity, 12-week intervention duration, with three weekly sessions, proved adequate. ***Discussion:*** It seems that combined rehabilitation training programs are efficient for patients with stroke as these alter neuroplastic conditions due to synergistic or additional onset of action. Future research should investigate combined rehabilitation training programs, with follow-up, to assess how long the recorded improvements last. The protocol of this study is registered in PROSPERO, number CRD42021248533.

Duração e eficácia de intervenções de treino aeróbio combinadas ou isoladas na cognição pós-AVC: Revisão sistemática

Palavras Chave
Acidente vascular cerebral · Exercício físico · Reabilitação cognitiva · Tipo de intervenção · Duração da intervenção

The protocol of this study is registered in PROSPERO, number (CRD42021248533).

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Resumo

Introdução: Este estudo pretende avaliar os efeitos da atividade física na cognição de pessoas com acidente vascular cerebral (AVC). Aqui, pretendemos comparar a eficácia do uso de programas de reabilitação isolada ou combinada, bem como a duração e intensidade dos programas, para identificar as características de programas de treino ideais para reabilitação cognitiva pós-AVC. ***Métodos:*** Usámos as diretrizes PRISMA para realizar esta revisão sistemática e pesquisámos as seguintes bases de dados: Web of Science, Scopus, PEDRo, SPORTdiscus, PubMed, Trial Registries e Google Scholar para estudos publicados entre 2013 e 12 de abril de 2023. Incluímos ensaios clínicos aleatorizados (ECA) de intervenções que mediram o efeito da atividade física na cognição em pacientes com AVC. Restringimos a nossa busca a estudos publicados no idioma inglês. As evidências dos ECA foram sintetizadas e o risco de viés foi avaliado usando a ferramenta de risco de viés Cochrane. ***Resultados:*** Dos 1755 registos identificados, 34 eram elegíveis e os dados estavam disponíveis, maioritariamente com risco baixo a moderado de viés geral. Os programas de treino de reabilitação combinados revelaram-se mais eficientes quando comparados com programas de treino de reabilitação isolados, em vários domínios cognitivos. Uma intervenção de intensidade moderada, duração de 12 semanas, com três sessões semanais, mostrou-se adequada. ***Discussão:*** Parece que os programas combinados de treino de reabilitação são eficientes para pessoas com AVC, já que alteram as condições neuroplásticas devido à ação sinérgica ou adicional. Investigações futuras devem investigar programas combinados de treino de reabilitação, com *follow-up* para avaliar quanto tempo duram as melhorias registadas. O protocolo deste estudo está registado no PROSPERO, número CRD42021248533.

Introduction

Stroke is classically characterized as a neurological deficit resulting from an acute focal lesion of the central nervous system from vascular causes, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage [1, 2]. Impairments in cognitive function usually accompany the occurrence of stroke in people's lives with an impact on daily life [3, 4], which are manifested in the 3–6 months after stroke [5]. Post-stroke cognitive impairments are currently the most disabling after-effects [6], with a prevalence of 16–53%, with approximately 10–20% of strokes being hemorrhagic and the remainder ischemic [7]. A 2011 study reported that worldwide, stroke is responsible for about 5.5 million deaths annually [8]. Evidence shows that one of the ways to reduce cognitive impairment is through cognitive rehabilitation, as it impacts even patients with chronic conditions. Cognitive rehabilitation can be accomplished in several ways, including through physical activity [9], since the regeneration of motor and cognitive functions is based on the plastic properties of the central nervous system and compensatory strategies to recover lost functions [10]. Evidence shows that physical activity improves muscle function, motor skills, cardiorespiratory function, and metabolic regulation [11–14].

Further, it decreases anxiety and depression levels and increases self-esteem [15], promotes social integration and the learning of social rules [16], and improves global cognitive functions [17]. It is well known that blood flow and oxygenation in cortical regions are influenced by the intensity of the exercise session [18, 19]. Further, increased prefrontal cortex oxygenation may indicate greater cortical activity, leading to enhanced cognitive processes such as working memory and attention [18, 20]. There is a consensus that physical activity is associated with a lower risk of stroke and mortality, as it is a potential preventive measure against cognitive decline [21].

Although a growing body of literature addresses the effect of physical activity on cognition, few address the post-stroke physical activity prescription and the impact of physical activity on post-stroke cognitive performance [21]. In a review, Barker and Eickmeyer [22] present general guidelines for physical activity, where the recommendation is that adults perform aerobic physical activity, emphasizing resistance or strength training, twice a week. Another study by Gambassi et al. [23] addresses resistance training for motor recovery of patients with stroke. Further, in a recent study, Izquierdo et al. [24] explain that the ideal prescription of exercises for preventing or treating dementia has yet to be defined.

There needs to be more literature clearly describing which type of physical activity training program is adequate to reduce post-stroke cognitive impairment and optimize recovery. Should the training program be isolated or combined? What should its duration, intensity, and weekly frequency be? In this context, an isolated intervention program is considered when only one type of activity is used during all interventions; in this case, only aerobic activity can be used, or resistance activity, strength activity, or postural balance, among others. When it comes to combined physical activity, there is a combination of physical activity, which can be aerobic with resistance or strength activity, among others. For example, in this line, it is known that aerobic activity improves cardiorespiratory fitness, increases the expression of neurotrophic factors, and increases hippocampal size [4, 25]; resistance activity increases muscle mass, strength, and power and improves executive function and selective attention [4, 26]; and strength activity enhances bone mineral density and neuromuscular performance, increases proteins involved in neuronal survival and synaptic plasticity in the hippocampus, improves memory [27, 28]. Thus, considering the gains each type of activity could bring the participants, a program that combines different types of activity per session throughout an intervention program might be even more efficient. Concerning duration, we find a variation of 1 day to more than a year. As for exercise intensity, there is also a variation from low to moderate to high intensity [29–31]. This shows that there is still debate about the type of physical activity program, ideal duration, and exercise intensity to lead to therapeutic benefits after stroke. Thus, this review aimed to evaluate the effects of physical activity programs on the cognition of patients with stroke, comparing the effectiveness of isolated or combined rehabilitation training programs and the duration and intensity of training to identify the most effective training programs for post-stroke cognitive rehabilitation.

Methods

Eligibility Criteria

Study eligibility was determined using the following criteria.

Population

Men and women 18 years of age and older with acute or chronic stroke in various stages participated.

Intervention

All types of physical activity for patients with stroke rehabilitation, defined as any bodily movement produced by the skeletal muscles that results in energy expenditure above resting levels, are performed in isolation or combination with other activities. There is no restriction on the duration of intervention programs, intensity, and frequency.

Comparator

Any type of activity was used as a control, from usual care, recreational activities, cognitive training, or even physical activity.

Outcome

Studies that assessed cognition in its various domains (such as attention and concentration, executive functions, memory, language, visuospatial ability, abstract thinking, calculation, and orientation) using either neuropsychological testing or imaging were included.

Study Design

Only randomized controlled trials were included. Non-experimental studies, single experimental designs, review and opinion articles, studies not published in English, and those published before 2013 were excluded.

Search Strategy

On April 12, 2023, the first author searched five databases, namely PubMed, Web of Science, Scopus, and SPORTDiscus, using the following search words and Boolean operators: (“physical training” OR exercise OR “physical activity” OR “physical intervention”) OR (“physical training” OR exercise OR “physical activity” OR “physical intervention”) AND (“Cognitive Rehabilitation” OR Cognition) OR (“Cognitive Rehabilitation” OR Cognition) AND (CVA OR Stroke OR “cerebrovascular accident”) OR (CVA OR Stroke OR “cerebrovascular accident”). In the PEDro database only, we used the following search terms: cognitive*, aerobic*, and stroke*. We also searched the reference lists of all included studies to identify any other studies that our search strategy might have missed. We used a combination of medical subject title (MeSH) terms where available, free text search terms, and Boolean operators. MeSH search terms using “Exercise,” “Cognition,” and “Stroke” were combined with “physical training” OR exercise OR “physical activity” OR “physical intervention,” “Cognitive Rehabilitation” OR “Cognition,” and “CVA OR Stroke OR “cerebrovascular accident.” Additionally, a manual search of peer-reviewed articles on the cognitive benefits of physical activity after stroke, considering the type of intervention program (combined or isolated, i.e., a combination of different types of physical training or a single type of physical training activity) and duration, was also performed to locate potentially eligible studies for inclusion in the review [32].

Selection Process

All studies were imported into Excel using Zotero (reference management software), facilitating screening and eliminating duplicate records. The three investigators conducted a comprehensive search of studies, independently reviewed titles and abstracts of the imported registries, and discussed inconsistencies until a consensus was reached. Then, two researchers independently examined the titles and abstracts of all articles retrieved. In case of disagreement, consensus on which reports to display in full-text was reached through discussion. If necessary, the third researcher was consulted to make the final decision. Subsequently, two researchers independently screened the full-text articles for inclusion. Again, in case of disagreement, consensus on inclusion or exclusion was reached through discussion, and, if necessary, the third investigator was consulted [33, 34].

Data Collection and Extraction

Two reviewers independently collected information from eligible studies using the data extraction form based on Lumley et al. [35]. A third reviewer arbitrated the discussion to resolve discrepancies between the two review authors. For each study, information collected included descriptive details about the first author's last name and year of publication, study design and period, study methods, study participants (age group, eligibility criteria), interventions (type, duration, intensity), and outcome data.

Study Risk of Bias Assessment

The risk of bias for each study was assessed using the Cochrane Risk of Bias (RoB 2.0) tool [33, 36]. Domains in this checklist include: (1) selection bias (including random sequence generation and allocation concealment); (2) performance bias (including participant concealment); (3) detection bias (including blind assessment); (4) attrition bias (including incomplete result data); (5) reporting bias (including reporting of selective results); and (6) other biases (any other bias observed). Two reviewers independently applied the tool to each included study and recorded supporting information and justifications for judgments of risk of bias for each domain (low, some concerns, and high). The lack of consensus on the risk of biased judgments was resolved by discussion to reach an agreement between the two review authors, with a third review author acting as arbiter when necessary.

Results

In the five databases searched, we found 1,755 records: 922 in Scopus, 368 in Web of Science, 349 in Pubmed, 92 in PEDRo, and 24 in SPORTDiscus. After removing duplicates, we examined 1,157 records, reviewing 79 full-text documents. Subsequently, we searched for documents that cited any of the initially included studies and the references of the included studies. However, no extra articles meeting the inclusion criteria were found in these searches, as shown in the flow diagram in Figure 1.

Study Characteristics

The studies included in the review present data collected in thirteen countries on three continents (online suppl. Material 1; for all online suppl. material, see https://doi.org/10.1159/000535272). We found fourteen studies in Asia, twelve studies in Europe, and eight studies in America.

We included a total of 34 randomized controlled trials, of which three were double-blind [37–39], 22 were single-blind, and the remaining nine, although obeying randomization of participant recruitment, did not present any information about the concealment process, both for the participants and the evaluators. The sample size in the studies ranged from 18 to 362 participants. The mean age of the participants in the reviewed studies was 61.91 years. Concerning sex, 27 included men and women in their sample [29–31, 37, 40–62], four had a sample composed only of men [38, 39, 63, 64], two composed only of women [65, 66], and one did not specify the gender in its sample [67]. Regarding the types of exercises targeted at the intervention groups, the combined rehabilitation training programs involved: dual-task gait training [45, 58, 62], aerobic and cognitive training [29, 40, 54, 59, 60, 66], aerobic activity and strength activity [44, 46], Tai Chi [41, 56], aerobic and endurance training [30, 50, 63, 64]. The isolated aerobic training programs involved: aerobic training [31, 42, 48, 49], high-intensity training [37, 39, 53, 57], and yoga training [43, 67]. On the other hand, the control groups participated in programs involving single-task gait training with a treadmill [45, 62], performing conventional exercises [29, 31, 38, 39, 42, 43, 46, 48, 49, 55, 63, 64, 67], daily routines [30, 41, 61, 65], which included mobilization of upper and lower limbs, stretching and muscle strengthening with elastic bands and walking [51, 52]. An overview of the study and participant characteristics is listed in Table 1.

Risk of Bias in Studies

We note that of the 34 studies reviewed, sixteen had a low risk of bias, eleven had a high risk, and seven presented some concerns, as illustrated in Figure 2.

Results of Syntheses

Of the 34 included studies, 23 used three types of combined rehabilitation training programs, essentially involving combinations of aerobic and cognitive training, aerobic exercise and strength training, and aerobic and resistance training. The remaining 11 studies used isolated rehabilitation training programs primarily involving aerobic exercise (online suppl. Material 2).

Cognitive Function Outcome Measures

Regarding the use of neuropsychological instruments at baseline, of the 23 studies that used a combined rehabilitation training program, only 13 assessed cognitive function as shown in online supplementary material 3, with cases using a single test [29, 41, 50, 61, 63, 65], two tests [38, 44, 46, 51, 59, 64], and three tests [52]. In the 11 studies using an isolated rehabilitation training program, 10 assessed cognitive function, either using a single test [37, 48, 53, 57, 67], two tests [39, 49, 55], three tests [31], or four tests [42].

Global Cognitive Function

Of the 23 studies that used combined rehabilitation training programs, only seven reported global cognitive functions assessed by neuropsychological tests [46, 50, 51, 60, 61, 63, 64], as detailed in online supplementary material 3. Of these, three reported significant

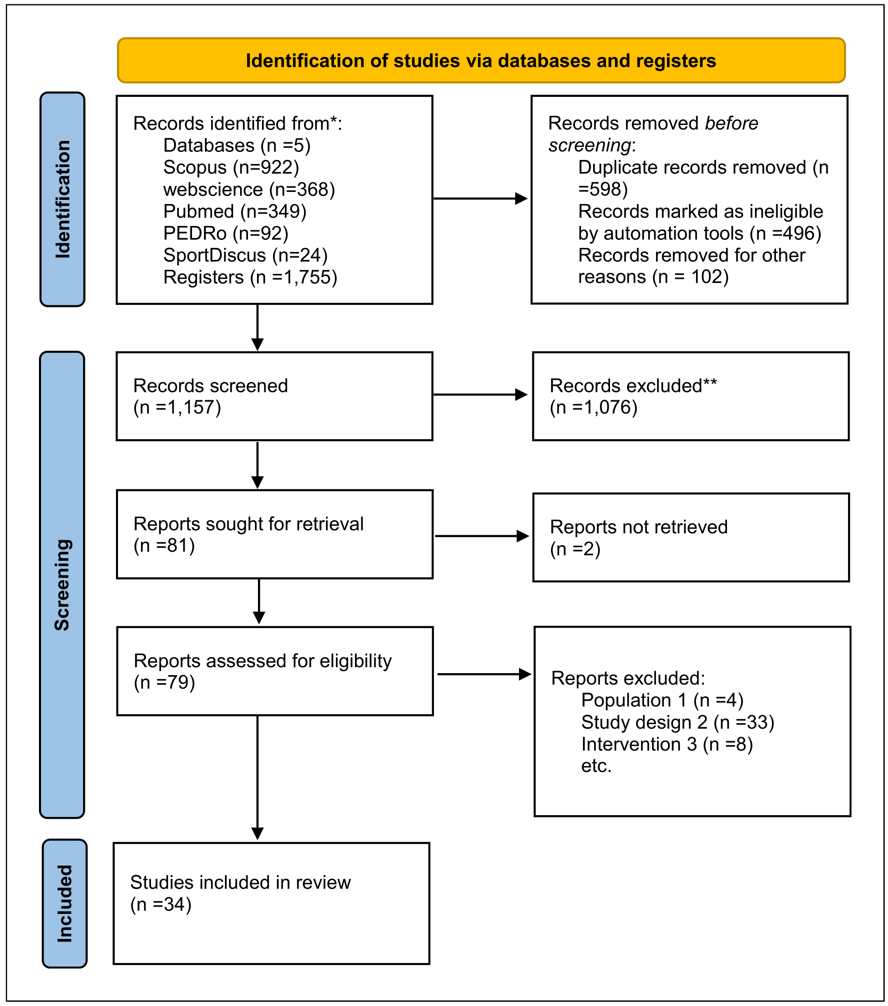

Fig. 1. Study flow diagram.

improvements in the intervention group but not in the control group [50, 51, 60], and only three reported no between-group differences in global cognitive functioning [46, 61, 64]. One reported significant improvements in the control group but not in the intervention group [63]. Of the 11 studies that used an isolated rehabilitation training program, only three documented global functions [31, 48, 49]. One study reported significant improvements in the intervention group but not the control group [31]. In contrast, the other two reported no relevant benefit of this program in cognitive functioning [48, 49], as shown in Table 1.

Specific Domains of Cognition

Memory

Ten studies using a combined rehabilitation training program reported memory outcomes assessed by neuropsychological tests [29, 30, 40, 46, 47, 50, 52, 58, 63, 66], as shown in online supplementary material 3. Of these, eight reported significant improvements in the intervention group but not in the control group [29, 30, 47, 50, 52, 58, 63, 66], and only one [46] reported that self-reported physical activity was not associated with cognitive performance. However, one study reported no significant effects for short delays in working memory (Brown-Peterson paradigm: $p = 0.92$) or episodic memory (revised Hopkins Verbal Learning Test: $p = 0.26$) [40]. Of the 11 studies that used a rehabilitation training program alone, six reported on memory [39, 42, 48, 53, 55, 57]. Of these, only one reported improvements in the intervention group but not in the control group [55], two reported no significant effects of the intervention in both groups [42, 53], and three [39, 48, 57] showed no evidence of the impact of a rehabilitation training program alone on memory in patients with stroke, as shown in Table 1.

Table 1. Characteristics of the included studies

Author (year)	Study design	Country	Sample size	Age, mean	Gender	Intervention	Program types	Intensity and duration	Outcomes
Baek et al. [62] (2021)	RCT	South Korea	34	T – 56.94 C – 56.13	Female/male	T– dual-task gait training with treadmill C – single-task gait training with treadmill	Combined exercise	Speed ≥80%, 60 min, twice a week, for a period of 6 weeks	In the experimental group, the attentional capacity for dual-task processing improved
Blanchet et al. [40] (2016)	RCT	Canada	21	All – 61.93	Female/male	T – aerobic training alone T – combined aerobic and COG C – relaxation group	Combined exercise	60–70% of the heart rate reserve and 20–30 min, twice weekly, 8 weeks	Attention improved after an 8-week intervention for both the aerobic training alone group and the combined aerobic and COG group. The results of the control group were suppressed from the final analysis.
Bo et al. [29] (2019)	RCT	China	225	T Comb – 66.68 T – PE – 65.12 T – CT – 67.51 C – 64.36	Female/male	T – combined intervention of physical exercise and cognitive T – physical exercise T – COG C – usual care and watched video documentaries	Combined exercise	Moderate intensity, and 50 min, 3 times/week, 12 weeks	Combined training produced significantly greater gains in cognitive function after the intervention compared to aerobic training alone or COG alone in stroke survivors with vascular cognitive impairment.
Boss et al. [46] (2017)	RCT	The Netherlands	120	63.00	Female/male	T – aerobic exercise and strength training C – usual care	Combined exercise	Intensity will gradually be increased, and two 1 h exercise sessions per week, 12 weeks	There was no improvement in either group, as self-reported physical activity was not associated with cognitive performance.
Chan and Tsang [68] (2017)	RCT	China	26	TC – 63.90 CE – 63.20 C – 63.20	Female/male	T – Tai Chi group T – conventional exercise C – regular activities	Combined exercise	Unspecified and two 1 h training sessions each week, 12 weeks	Improvement in the Tai Chi group from the pre-assessment to the post-assessment than that of the other groups
Debreceni-Nagy et al. [42] (2019)	RCT	Hungary	37	T – 59.00 C – 62.00	Female/male	T – aerobic training by cycle ergometer C – conventional physiotherapy	Isolated exercise	Low intensity and 30–60 min, 4 weeks	The low-intensity aerobic training group had an additive positive effect on improving special domains of cognitive function compared to the control group.

Table 1 (continued)

Author (year)	Study design	Country	Sample size	Age, mean	Gender	Intervention	Program types	Intensity and duration	Outcomes
Deijle et al. [64] (2022)	RCT	The Netherlands	119	T – 34.00 C – 36.00	Male	T – aerobic and strength training C – usual care	Combined exercise	Started at 40%, and was then gradually increased to 80% heart rate, 1-h, 2–3 sessions per week, 12 weeks	No between-group differences were found on global cognitive functioning with the MoCA at 12 weeks
Fernandez-Gonzalo et al. [30] (2016)	RCT	Spain	32	T – 61.20 C – 65.70	Female/male	T – resistance training C – daily routines	Combined exercise	High intensity and 2 times/week, 12 weeks	The resistance training group recorded better results in attention, working memory, speed of information processing, executive functions, and no improvement in the control group.
Fischbacher et al. [65] (2020)	RCT	Switzerland	18	76.40	Female	T – Dalcroze eurhythmics program T – simple home exercise program C – non-exercise control group	Combined exercise	Low intensity, 3 × 30 min/week, 12-month	In the two intervention groups, there was no improvement in cognitive performance; on the contrary, there was a decline of −1.0 points for Dalcroze and −1.7 points for SHEP, while in the control group, there was a non-significant improvement of 0.6 points.
Gjellesvik et al. [48] (2021)	RCT	Norway	70	T – 57.60 C– 58.70	Female/male	T – treadmill training C– usual care	Isolated exercise	High intensity, 3 times per week, 8 weeks.	No benefit found for high-intensity on cognitive function as measured by the MoCA. The intervention group showed significantly greater improvement on TMT-B.
Hsu et al. [37] (2020)	RCT	Taiwan	25	T – 58.50 C – 53.10	Female/male	T – high-intensity interval training C – moderate-intensity continuous training	Isolated exercise	40% to 80% heart rate, 2 to 3 sessions/week, 36 sessions	The high-intensity interval training group showed an increase in cerebral O2 utilization, associated with an increase in serum BDNF levels compared to the moderate-intensity continuous training group.
Hsu et al. [31] (2018)	RCT	Canada	70	T – 71.70 C – 72.30	Female/male	T – aerobic training C – usual care and educational materials	Isolated exercise	Moderate intensity, 60 min, 3 times per week, 6 months	The aerobic training group significantly improved reaction time performance compared to the control group.

Table 1 (continued)

Author (year)	Study design	Country	Sample size	Age, mean	Gender	Intervention	Program types	Intensity and duration	Outcomes
Hung et al. [38] (2017)	RCT	Taiwan	43	T – W – 55.66 T – 60.90 C – 51.75	Male	T– Wii fit T – Tetrax C – conventional weight-shifting training	Combined exercise	Unspecified, 30 min, 2 times per week, 12 weeks	The Wii Fit group had greater gains in abstraction/judgment domain, and language domain than the other 2 groups after intervention
Ihle-Hansen et al. [49] (2019	RCT	Norway	362	T – 71.40 C – 72.00	Female/male	T – aerobic C – usual care	Isolated exercise	Moderate to intensity, 30 to 45–60 min, 2–3 times per week, 18 months	No clinically relevant effect of this program was found on cognitive functioning after 18 months compared with usual care
Ji and Yu [67] (2018)	RCT	China	58	T – 62.17 C – 61.29	Unspecified gender	T – yoga training C – conventional rehabilitation therapy	Isolated exercise	Unspecified, 30–60 min, 12 weeks	The mean and standard deviation of brain wave fluctuations in the experimental group were significantly higher than those in the control group.
Kashyap et al. [43] (2022)	RCT	India	80	T – 52.85 C – 55.18	Female/male	T – yoga training C – usual care	Isolated exercise	Unspecified, 4–5 days/week, 3 months	Significant improvements in both groups were more pronounced in the yoga group.
Kim and Yim [44] (2017)	RCT	South Korea	29	T – 50.71 C – 51.87	Female/male	T – handgrip strength and walking training C – neuro-developmental treatment	Combined exercise	Intensity increased according to the participant's level, 30–60 min, 5 times per week, 6 weeks	Significant increase was found only in the exercise group on K-MoCA test. However, the difference between the two groups was not significant on TMT and Stroop test
Koch et al. [50] (2020)	RCT	USA	131	T – 59.00 C – 58.00	Female/male	T – combined aerobic and resistance training C – sham combined aerobic and resistance training	Combined exercise	50–65% of heart rate reserve, 40–60 min, 3 times per 12 weeks	Significantly improved in the intervention group, but not in the control group.
Steen Krawcyk et al. [39] (2019)		Denmark	71	T – 63.70 C – 63.70	Male	T – high-intensity interval training C – usual care	Isolated exercise	High intensity 3 × 3 min with 2 min of active recovery, 5 days per week for 12 weeks	No changes were detected between groups in cognitive performance.
Liu-Ambrose et al. [51] (2022)	RCT	Canada	120	T – 70.65 T – 71.29 C – 70.42	Female/male	T – multicomponent exercise training T – cognitive and social enrichment activities C – stretching and toning exercises	Combined exercise	60 min, twice weekly, 6 months	Multicomponent exercises induced clinically important improvements in cognitive function. Stretching and toning exercises improved compared with cognitive and social enrichment activities

Table 1 (continued)

Author (year)	Study design	Country	Sample size	Age, mean	Gender	Intervention	Program types	Intensity and duration	Outcomes
Liu-Ambrose and Eng [63] (2015)	RCT	Canada	25	T – 62.90 C – 66.90	Male	T – resistance, aerobic exercise C – usual care	Combined exercise	Unspecified, 60 min, 2 times per week, 9-month	The experimental group significantly improved selective attention and conflict resolution, working memory compared to the control group
Meester et al. [45] (2019)	RCT	UK	50	T – 60.85 C – 62.25	Female/male	T – dual-task treadmill training C – control treadmill training	Combined exercise	55–85% heart rate maximum, 30 min, 20 sessions divided over 10 weeks	Experimental group increased mean (SD) two-minute walking distance from 90.7 (8.2) to 103.5 (8.2) meters, compared with 86.7 (8.5) to 92.8 (8.6) in the control group. There were no differences in other measures
Moore et al. [52] (2015)	RCT	UK	40	T – 68.00 C – 70.00	Female/male	T – warm-up, stretching, functional strengthening C – stretching training	Combined exercise	40–80% of their maximum heart rate, 45–60 min, 3 times/week, 19 weeks	Significant within-group improvements were only made in the exercise group in cognition and stroke recover.
Pallesen et al. [53] (2019)	RCT	Norway	30	T – 55.00 C – 50.00	Female/male	T – high-intensity exercise C – low-intensity exercise	Isolated exercise	60–70% heart rate, 20 min, 2 times per week, 4 weeks,	The high-intensity group, compared to the low-intensity group, achieved significant improvements in cognitive performance.
Ploughman et al. [54] (2019)	RCT	Canada	52	63.00	Female/male	T – aerobic + COG T – aerobic + games T – activity + COG C – activity + games	Combined exercise	Moderate to vigorous intensity, 20–30 min, 3 times, 10 weeks,	The aerobic + COG group was the only group in which the improvement was significantly greater than the active control group (activity + games)
Rathnamala et al. [66] (2020)	RCT	India	60	Unspecified	Female	T – physical activity with COG group C – COG group	Combined exercise	Moderate-high, 50 min, 5 days per week for 12 weeks	The experimental group significantly improved cognitive performance compared to the control group
Rosenfeldt et al. [47] (2019)	RCT	USA	40	T – 51.00 T – 60.00 C – 58.00	Female/male	T – FE + RTP T – VE + RTP C – EDU+RTP	Combined exercise	High intensity, 90 min, 8 weeks	The FE + RTP group showed improvements in the cognitive domain of memory, and in the other two groups there was no improvement in any cognitive domain.

Table 1 (continued)

Author (year)	Study design	Country	Sample size	Age, mean	Gender	Intervention	Program types	Intensity and duration	Outcomes
Shang et al. [55] (2021)	RCT	China	76	T – 63.68 C – 64.13	Female/male	T – grip training + conventional physiotherapy C – conventional physiotherapy	Isolated exercise	50 min/5 sessions/ 12 weeks	The experimental group significantly improved their MoCA score compared to the control group.
Song et al. [56] (2021)	RCT	Korea	34	T – 58.72 C – 57.18	Female/male	T – Tai Chi group C – symptom management program.	Combined exercise	Low-intensity, 50 min, twice a week for 6 months	Compared with control group, the participants in the Tai Chi showed significant improvements cognitive function
Tang et al. [57] (2016)	RCT	Canada	50	T – 66.00 C – 64.00	Female/male	T – high-intensity aerobic exercise C – balance and flexibility	Isolated exercise	High versus low intensity, 60 min, 3 times/week, 6 months	There was no association between pre-exercise cognitive function and post-exercise improvement
Timmermans et al. [58], (2021)	RCT	The Netherlands	40	T – 52.00 C – 59.00	Female/male	T – treadmill-based C-Mill therapy C – standard overground FALLS	Combined exercise	Unspecified, 90 min, twice a week, 5 weeks	Group showed a tendency to a greater improvement in cognitive with cognitive dual-task compared to the FP group
Yeh et al. [59] (2021)	RCT	Taiwan	56	Seq – 53.05 AE – 57.36 Cog – 60.17	Female/male	SEQ AE COG	Combined exercise	40–50% gradually increased to 60–70% heart rate, 30–60 min, 12 weeks	The SEQ group improved significantly at the MoCA compared with the AE and COG groups, but no between-group difference was found for the AE and COG groups.
Yeh et al. [60] (2019)	RCT	Taiwan	30	T – 50.63 C – 60.21	Female/male	T – SEQ C – nonaerobic physical exercise	Combined exercise	30 min and 40–70% heart rate, 12–18 weeks	The SEQ group had significantly improved cognitive performance after training compared to the control group
Zheng et al. [61] (2020)	RCT	China	48	T – 61.63 C – 62.75	Female/male	T – Baduanjin training C – any specific exercise training	Combined exercise	Low to high intensity, 3 days a week and 40 min, 24 weeks	Improvement significant in the Baduanjin group for MoCA. Mean between-group differences were significantly lower ($p < 0.05$) for TMT-A and TMT-B tests in the Baduanjin group compared with controls

AE, aerobic exercise training; C, control; COG, cognitive training; TMT, Trail Making Test; T, treatment; RCT, randomized controlled trial; FE + RTP, forced exercise repetitive task practice; MoCA, Montreal Cognitive Assessment; SEQ, sequential training; VE + RTP, voluntary exercise + repetitive task practice; EDU + RTP, education + repetitive task practice.

Attention

Ten studies that used a combined rehabilitation training program assessed attention using neuropsychological testing [30, 40, 44, 46, 51, 56, 59, 61, 63, 66], as illustrated in online supplementary material 3. Of these, eight reported improvements in the intervention group. Still, not in the control group [30, 40, 44, 51, 56, 59, 63, 66], one reported no significant difference between the Baduanjin group and the controls for attention [61], and a single one [46] did not report improvements. The seven studies that used a stand-alone rehabilitation training program also assessed attention using neuropsychological tests [31, 39, 43, 48, 53, 55, 57]. Of these, four showed improvement in the intervention group but not in the control group [31, 43, 53, 55], and three did not report any improvement [39, 48, 57], as shown in Table 1.

Visuospatial Ability

Four studies using a combined rehabilitation training program assessed visuospatial ability [56, 59–61], as depicted in online supplementary material 3. Three reported improvements in the intervention group but not in the control group in visuospatial ability [56, 59, 60], and one reported no significant difference between the Baduanjin group and the controls [61]. Three other studies that used a stand-alone rehabilitation training program also assessed visuospatial ability [39, 43, 48]. Of these, one reported improvements in the intervention group but not in the control group [43], and two reported no improvements at all [39, 48], as shown in Table 1.

Language and Processing Speed

Of the five studies that used a combined rehabilitation training program, one assessed language [56], and the remaining studies assessed processing speed [30, 50, 61, 66], as illustrated in online supplementary material 3. In five studies that assessed language and processing speed, four reported improvements in the intervention group but not in the control group [30, 50, 56, 66], and one reported no significant differences between the Baduanjin group and the controls for processing speed [61]. Of the five studies that used a stand-alone rehabilitation training program, two considered language [39, 48], and both did not show improvement. For the remaining three studies, which also used a rehabilitation training program alone, they assessed processing speed [42, 49, 53], with improvements in the intervention group but not in the control group [42, 53] and without improvements [49], as depicted in online supplementary material 3.

Executive Functions

Nine studies that used a combined rehabilitation training program assessed executive functions through neuropsychological tests [30, 41, 46, 50, 51, 56, 59, 61, 62], as shown in detail in online supplementary material Table 3. Eight of these nine studies reported improvements in the intervention group but not in the control group after the intervention; only one [46] did not report gains. Seven studies assessed executive functions [31, 39, 48, 49, 53, 55, 57] regarding the isolated rehabilitation training program. Of these studies, three showed improvements in the intervention group but not in the control group after the intervention [31, 53, 55], while four showed no improvements [39, 48, 49, 57], as shown in Table 1.

Type of Intervention Programs

Regarding the type of rehabilitation training program, of the 23 studies that used combined rehabilitation training programs, 20 recorded cognitive improvements after completing the recommended exercise sessions [29, 30, 38, 40, 41, 44, 45, 47, 50–52, 54, 56, 58–63, 66], while three did not record cognitive improvements [46, 64, 65]. Concerning the 11 studies that followed an isolated rehabilitation training recovery program, seven reported cognitive improvements [31, 37, 42, 43, 53, 55, 67], and four reported no cognitive improvements [39, 48, 49, 57] (online suppl. material 4).

Regarding the type of exercise most used in each rehabilitation training program, we note that combined rehabilitation training programs used a combination based on strength physical activity in nine studies [38, 41, 44, 47, 51, 52, 56, 61, 64]. In general, these studies included an active control group based on usual care [38, 41, 64], stretching and toning exercises [51, 52], education, and repetitive task practice [47]. One study included a passive control group, wherein the participants did not exercise or perform any other activity [61]. Further, ten combined rehabilitation training program studies used aerobic physical activity [29, 40, 45, 46, 54, 58, 59, 62, 65, 66] and included an active control group based on usual care [29, 46], relaxation or activity with games [54, 66], single-task gait training with treadmill [45, 62], standard overground FALLS [58], aerobic exercise training and cognitive training [59, 60]; and resistance physical activity [30, 50, 63], wherein the control group used usual care [63], sham combined aerobic and resistance training [50], and daily routines [30]. Concerning the isolated rehabilitation training programs, ten used aerobic physical activity [31, 37, 39, 42, 43, 48, 49, 53, 57, 67], and the control group used usual care [31, 39, 42, 43, 48, 49, 57, 67], moderate-intensity continuous training [37], low-intensity exercise [53], and only one study used strength exercise [55], and his control group received usual care. Most included studies compared an experimental exercise intervention to standard care or an alternative intervention, as illustrated in online supplementary material 5.

Duration of the Intervention Programs

The duration of the rehabilitative training programs varied from 4 weeks to a maximum duration of 18 months [49]. Specifically for the combined training programs, we noticed a variation from less than 11 weeks [40, 44, 45, 47, 54, 58, 62] to more than 6 months [29, 30, 46, 50–52, 56, 59–61, 64, 65]. Studies lasting up to 11 weeks all reported improvements [40, 44, 45, 47, 54, 58, 62], the studies up to 6 months or more, nine registered improvements [29, 30, 50–52, 56, 59–61], and three did not register improvements [46, 64, 65]. Concerning the isolated rehabilitation training programs, the duration ranged from less than 11 weeks [42, 48, 53, 57] to more than 1 year [31, 37, 39, 43, 49, 55, 67], as depicted in online supplementary material 6. In studies lasting up to 11 weeks, two showed improvements [42, 53], and two did not show improvements [48, 57]. Concerning studies lasting up to 1 year or more, five showed improvements [31, 37, 43, 55, 67], and two did not show improvements [39, 49]. As for the frequency with which rehabilitation training was carried out, we noted that there was a predominance of three times a week in 15 out of the 34 studies included, and the time spent for each session ranged from 20 min [40, 53, 54] to 90 min [47, 58].

Exercise Intensity in Interventions

Regarding the intensity with which the exercises were performed, in the studies reviewed here, three presented low-intensity physical activity [42, 56, 65], twelve presented moderate-intensity physical activity [29, 31, 40, 44, 46, 50, 53, 54, 59–61, 64], eleven presented high-intensity physical activity [30, 37, 39, 45, 47–49, 52, 57, 62, 66], and eight did not specify intensity [38, 41, 43, 51, 55, 58, 63, 67]. In studies with low-intensity physical activity, two recorded improvements [42, 56], and one did not show improvements [65]. In the studies using moderate-intensity physical activity, ten recorded improvements [29, 31, 40, 44, 50, 53, 54, 59–61], and two did not register improvements [46, 64]. Concerning the high-intensity physical activity studies, seven reported cognitive improvements [30, 37, 45, 47, 52, 62, 66], and four did not record improvements [39, 48, 49, 57]. Regarding the studies that did not specify the intensity, all presented improvements [38, 41, 43, 51, 55, 58, 63, 67].

Stroke Severity

Regarding stroke severity, in the studies reviewed here, 16 records involved participants with chronic stroke from 6 months to 1 year [30, 31, 43–46, 48, 51, 52, 54, 55, 57, 58, 60, 63, 65], 16 involved participants with subacute stroke [29, 37–42, 47, 49, 50, 53, 56, 59, 61, 62, 64], and two did not specify stroke severity of the involved participants [66, 67]. Regarding the studies in which the sample was composed of participants with chronic stroke, we noticed that 14 showed improvements [30, 31, 43–46, 48, 51, 54, 55, 57, 58, 63, 68], and only two showed no improvements [52, 65]. In studies in which the sample consisted of participants with subacute stroke, we noticed that 11 showed improvements [29, 37, 38, 41, 42, 47, 49, 50, 53, 56, 61] and five showed no improvement [39, 40, 59, 62, 64]. Regarding the studies that did not specify stroke severity, all showed improvements [66, 67].

Discussion

This review aimed to evaluate the effects of physical activity on the cognition of patients with stroke, comparing the effectiveness of isolated or combined rehabilitation training programs and the duration and intensity of training to identify the most effective training program for post-stroke cognitive rehabilitation. Thus, we systemized data that might allow for a recommendation for patients with stroke concerning the practice of physical activity safely and efficiently. Considering the potential benefits for cognition and mobility, since physical activity is linked to several physiological and neurological factors that promote longevity [69, 70], participating in physical activity post-stroke rehabilitation should benefit protective and regenerative functions [71]. However, considering the pre-defined eligibility criteria, there are still few published original studies with stroke rehabilitation programs using isolated and combined training, compared to a predominance of pharmacological therapies to lower blood pressure and conventional programs of muscle strength. Among the studies analyzed in this review, the combined rehabilitation training program appears to be more effective than the isolated rehabilitation training program, showing more significant improvements in several cognitive domains in the experimental group compared with the control group. One reason for this result is that the combined interventions offer favorable conditions for neuroplastic alterations due to the beginning of the synergy of action provided by the combination of physical activities [6] since each type of activity that intervenes in

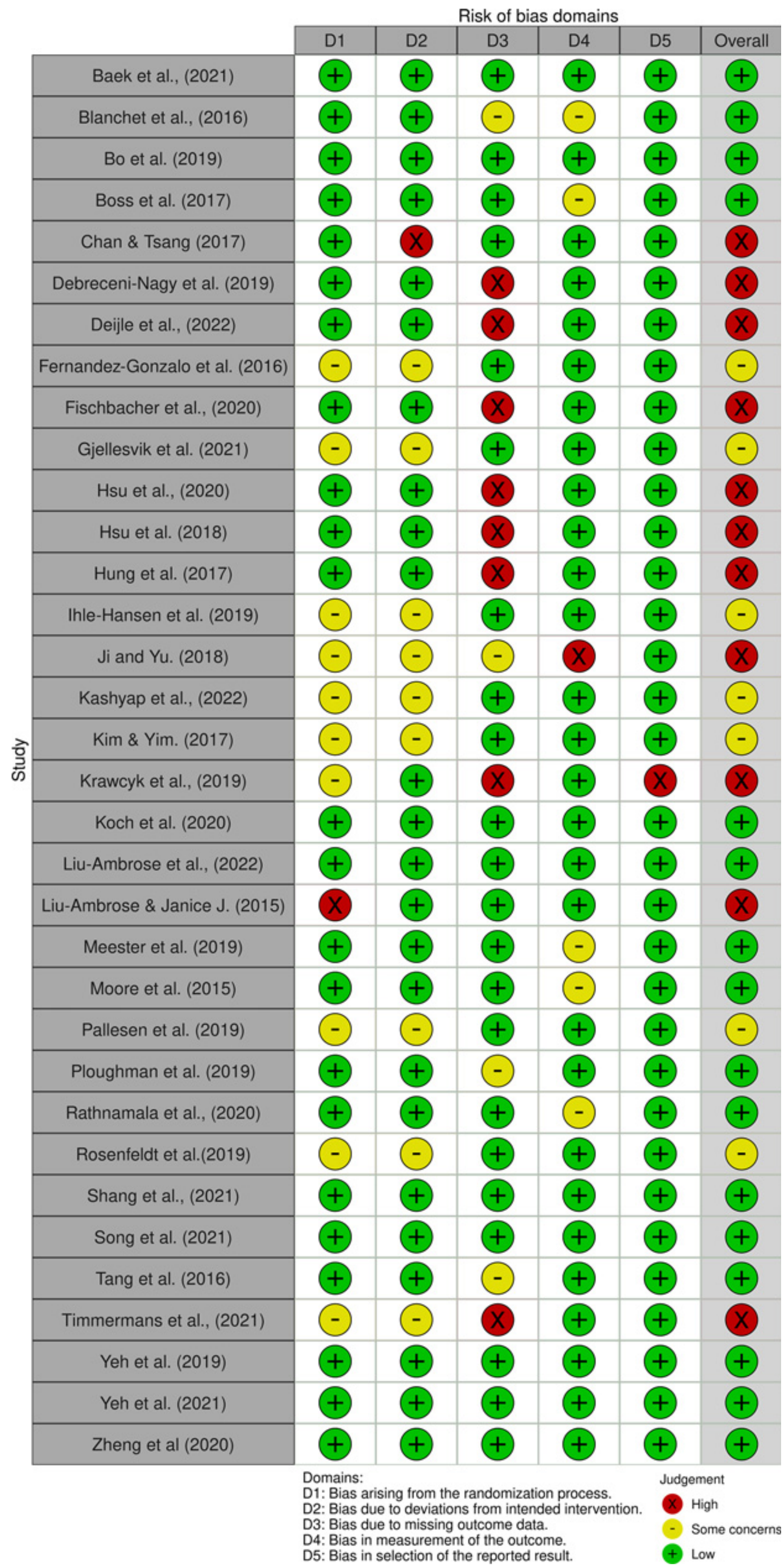

Fig. 2. Risk of bias assessment.

the combined training program has its specificity in terms of contribution. For example, it is known that aerobic exercise alone improves cardiorespiratory fitness and increases the expression of neurotrophic factors and hippocampal size [4, 25]. Resistance exercise, on the other hand, increases muscle mass, strength, and power and improves executive functions and selective attention [4, 26, 72]. Moreover, strength exercise improves bone mineral density and neuromuscular performance, increases proteins involved in neuronal survival and synaptic plasticity in the hippocampus, and improves memory [27, 28]. The combined benefits of at least two types of physical activity thus have the potential to increase the cognitive benefits compared to an isolated physical activity.

There are also differences between the two rehabilitation training programs regarding the type of physical activity that each rehabilitation training program uses. In the combined rehabilitation training programs, we identified a predominance of combinations involving physical activity, as with physical activity of strength. Of these, eight studies that performed strength activity recorded cognitive improvements in the experimental group compared to the control group [38, 41, 44, 47, 51, 52, 56, 61]. Despite these widespread improvements in various cognitive domains, we also note a study [61] that found no significant differences between the Baduanjin group and controls about processing speed. This study tries to create a cause-effect relationship between attention and processing speed by explaining that for attention, there was a significant effect on the response time of a Go/No Go test [61], as processing speed is usually described in relation to reaction time, i.e., the time elapsed between the relatively rapid presentation of a stimulus and the behavioral response [73]. This result is similar to those of a systematic review conducted by Wang et al. [74], as it also recognizes that Baduanjin training benefits people with stroke in several domains, such as global cognitive function, including memory and executive functions. However, it did not find any significant difference in attention. In combinations involving physical resistance activity, all three studies reported cognitive improvements in the experimental group compared to the control group [30, 50, 63]. For studies that performed aerobic physical activity combinations, six out of eight reported improvements in the experimental group compared to the control group [29, 54, 58, 59, 62, 66]. A similar situation to the one presented above is also noted for the memory domain, as neither group reports significant differences in memory [40]. This study rightly points to the lack of improvement seen in the memory domain, taking into account the duration of the intervention program (8 months), as it explains that cardiorespiratory fitness and memory require a more extended intervention, where fitness values must be high for exercise to induce physiological changes [40]. This finding is supported in the literature, as studies have shown that most motor recovery is almost completed within 10 weeks after stroke [75], while neuronal recovery can occur within weeks or even years [76]. Some studies did not record improvements in strength combinations. We believe this is due to the methodology chosen [46], as the rehabilitation program occurred at home and data were self-reported. One of the problems that negatively affects the practice of post-stroke physical activity has to do with the fear of falls, which generates a vicious cycle that leads to intolerance to physical activity, in addition to not helping to overcome post-stroke fatigue that is often experienced in patients with stroke [71, 75]. Therefore, the successful implementation of a physical activity program at home must be accompanied by motivational strategies that might help to increase the motivational rate [77–79]. As for another study [64], it is suggested that the lack of improvements results from the fact that the participants have mild cognitive impairment (MoCA scores of 24.9 ± 3.2 for the experimental group and 25.5 ± 2.9 for the control group), associated with the relatively young age of the participants (average age of participants of 64.30 years). Another study further confirms that the benefits resulting from rehabilitation for mild cognitive deficits may be low [70].

Regarding the study that involved the combination of aerobic physical activity [65], we believe that the lack of cognitive improvement verified after the rehabilitation training program that aimed to improve cognitive deficits is associated with adherence problems. Adherence was low since three in five participants did not attend the sessions. Evidence shows that the degree of commitment strongly influences clinical findings since adherence to a physical activity program improves post-stroke recovery [79, 80].

Regarding the isolated rehabilitation training program, where the predominance of aerobic physical activity was notorious, nine of the 11 studies registered cognitive improvements in the experimental group compared to the control group, and three did not report gains. The explanation for the lack of improvement is possibly linked to the heterogeneity of the study participants [49], as both patients with ischemic and hemorrhagic stroke were included, subacute to chronic patients were also included, and there was also a disparity between the ages of the participants (18–75 years). A change in the study methodology carried out at 6 months and then at 18 months after onset, associated with the type of intervention, i.e., high-intensity physical activity performed at home [39], might also explain the lack of improvements. It is possible that, in the face of high-intensity physical activity that occurs at home, stroke survivors become highly anxious about the risk of a new event. This fact can lead to fear or lack of desire to practice physical activity [75, 81]. Furthermore, the lack of improvements verified [57] might be due to the extensive duration of intervention, as the literature reports that the most significant gains in post-stroke recovery occur in the first 3 months [75, 76, 81].

Our results align with previous studies, demonstrating that combined training programs promote significant improvements in several domains, such as attention, memory, language, orientation, visuospatial ability, and executive functions, compared to isolated training programs [6, 80–82]. Since patients with stroke present cognitive problems [83], they should participate in combined rehabilitation programs.

Regarding the duration of rehabilitation training programs, it is essential to understand what predicts the effectiveness of exercise, as it can guide clinicians on how to better design exercise programs for people with stroke, as programs lasting less than 8 weeks are not long enough to elicit noticeable cognitive gains [84]. A moderator-effect analysis revealed that the 12–14-week exercise interventions are associated with the most significant magnitude of cognitive gains [85]. These results reinforce the need to use relatively long programs to rehabilitate people with stroke [85–88]. However, contradictions persist regarding the duration that best optimizes cognition, as seen in a recent review where the analysis showed no difference between using a program of more than 12 weeks or less [89]. This information is essential as it impacts doctors' decisions. When relating the lack of improvements with intensity, the influence of low intensity is noted, as one study presented low-intensity physical activity [65]. In another, the intensity was gradually increased [64]. We suggest that the intensity of physical activity may have been too low, which failed to create physiological changes that led to the awakening of neuronal plasticity [78, 85].

Regarding the studies contemplating high-intensity physical activity [48, 57], we think that given the fear of falling and the risk of a new stroke event [75, 76], this fact may have led to adherence problems from the perspective of adequately taking advantage of physical activity sessions [80]. The study with the most extended duration used an isolated rehabilitation training program lasting 18 months. Interestingly, the two studies lasting longer than 1 year and the one lasting 18 months did not register improvements. As Yang and Wang [85] explain, when the exercise program goes beyond 14 weeks, the previously acquired cognitive benefits disappear again. This may indicate that longer-term rehabilitation training programs are poorly tolerated by patients with stroke since the time course after stroke is characterized by more significant improvements during the first few weeks after stroke. This might reflect the concomitant intrinsic pressure known as "neurological recovery" [90–93].

Two very recent meta-analyses by Yang and Wang [84, 85] also consolidate this idea of long-term exercise (exercise programs for 12 weeks) because it explains that the cycle of intervention with exercise after stroke is mainly controlled at 12 weeks since this period has good patient tolerance, as well as potentiation of long-term effects on physical and mental health, and further explains that 8 weeks of post-stroke aerobic training is more or less the ideal period to have a positive impact on cardiopulmonary and cognitive function [85].

Concerning exercise intensity, in the studies reviewed here, there is a predominance of moderate-intensity physical activity; this fact seems to result from the need to safeguard the health of the participants (patients with stroke), as post-stroke exercise recommendations include moderate-intensity continuous cardiovascular exercise with a suggested intensity of 40–70% maximum oxygen consumption or heart rate reserve of 50–80% of the maximum heart rate [94–96]. On the other hand, it is possible that higher-intensity exercises were not chosen because evidence indicates that high-intensity physical activity does not generate greater cognitive gain [85]. However, this is a controversial position, as studies show that intensity only mediates domains of gain [97].

It is important to emphasize that previous reviews offer relatively little information about the ideal prescription of physical exercises for cognitive health. There is still no clarity in most guidelines on the methodology, essentially in terms of the frequency with which physical activity should be performed, the time that the rehabilitation program should last as well as the activity that should be performed [98]; little is discussed about the need to adapt exercise based on an individual's skill level, mobility, basic fitness level. However, a review [80, 99] states that at least 30 min of moderate-intensity physical exercise five times a week for at least 150 min can be efficient. However, it is essential not to forget that post-stroke physical activity is not risk-free [98, 100], so before starting physical activity, patients with stroke should go through a medical assessment to identify medical conditions that require special consideration or constitute a contraindication [100].

The results of this review further reinforce the underlying idea that physical activity benefits post-stroke physical and cognitive recovery, a fact that supports the need to prescribe physical activity as a therapy in the treatment of patients with stroke, as it can be safe, efficient, and allow the patient with stroke to adhere to a less sedentary lifestyle resulting from their pathology [75, 76]. Regarding the severity of the stroke, although the results of this review show that 16 of the 34 studies involved participants with chronic stroke, these data do not seem to have had a negative influence on cognitive performance because of the 34 studies included, of which 27 reached the purpose to reduce the post-stroke cognitive impairments after a rehabilitative training program. Of the seven studies that do not improve, four pertain to subacute stroke occurring within a month, and the lack of improvement might be associated with inadequacy of the intensity of the training programs, as exercise intensity should be monitored to ensure that it is strong enough to promote relevant physiological changes [81].

Although domain-level judgments provide the basis for a general assessment of the risk of bias [101, 102], and based on this rationale, we refer that, in general, there is no high risk of bias since most of the evaluated studies presented a low risk of bias; having given evidence on the effectiveness of a combined rehabilitation training program, moderate intensity, with a frequency of three times a week and duration of the program of 12 weeks, caution is needed when interpreting these results. The Cochrane tool for risk of bias led us to analyze the risk as not high. However, this must be interpreted cautiously because the ten included studies present concerns in the first and second domains, which denote problems with randomization [102]. We must also interpret these results cautiously since we systemized relatively few studies. These involve diverse neuropsychological instruments used to assess cognitive deficits since a variety of neuropsychological tests in use present one or more deficiencies linked to reliability or validity, standardization, lack of alternative forms, and lack of ecological validity [103].

Limitations of This Study

The present study provides an updated and extensive qualitative overview of the literature on the most effective rehabilitation training program to be used in the cognitive rehabilitation of patients with stroke. Our findings largely align with previous results that synthesized evidence on the effectiveness of post-stroke activity [78].

The major limitation of this study lies in the fact that it included methodologically heterogeneous studies, which made it difficult to compare the data, limiting the synthesis of the results. Heterogeneity was found concerning the sample, the duration of rehabilitation programs, the intensity of physical activity, the frequency with which sessions occurred, the severity of patients, and the diversity of neuropsychological tests used. In the future, these issues should be addressed, and given an array of more homogeneous studies, a meta-analysis might be an option, as it allows for transparent decisions supported by statistical analyses that help to limit biases [104].

Conclusion

This systematic review suggests that cognitive performance may improve more in people with stroke after combined rehabilitation training programs compared to rehabilitation training programs alone. This improvement seems to result from the synergistic effect of physical activity, which may be beneficial for the quality of life of this clinical group.

Recommendations

Physical activity for people with stroke should be preceded by a few precautions and guidelines:

- For people with stroke, before starting physical activity, they should undergo a medical assessment to rule out or identify medical conditions that require special attention, as well as those that could be aggravated by physical activity.
- The practice of physical activity for people with stroke should consider the principle of gradualism on an individual basis since cardiovascular fitness, essential in reducing the risk after stroke, is gradually achieved with regular physical activity.
- The frequency, duration, and intensity of the physical activity session must be gradual to minimize adverse events and make it safe and motivating. A rehabilitation training program for people with stroke should combine different physical activities (e.g., aerobic and strength exercise, or aerobic, strength and endurance, or aerobic and cognitive training) to take more significant advantage of their synergistic action. The intensity with which each session is performed must be moderate enough to promote physiological changes that lead to cognitive optimization of physical activity.

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Statement of Ethics

This systematic review and its protocol were registered in the international prospective review registry (PROSPERO) under the registration number CRD42021248533.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.M. collected the data, developed the first draft of the manuscript, and extracted the studies. A.M.A. reviewed the first and subsequent versions and untied selection decisions. I.S.M. and R.M. decided which studies to include. I.S.M. and A.M.A. suggested improvements across all phases of the manuscript elaboration. All authors approved the final manuscript.

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