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Reviews in neurorehabilitation

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Reviews in neurorehabilitation

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Editorial: Reviews in neurorehabilitation

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Editorial on the Research Topic
Reviews in neurorehabilitation

Introduction

The Research Topic on "*Reviews in neurorehabilitation*" has collected several systematic and scoping reviews and meta-analyses about relevant rehabilitation topics. The emerging picture underscores the complexity of the issues connected with caring for patients with neurological disabilities of all ages and places. Rehabilitative care in neurological disorders presupposes an individual rehabilitation plan based on the alliance of a multidisciplinary team aimed at recovering function by combining traditional techniques with the most innovative and novel models of robotic rehabilitation and virtual reality.

Functional motor recovery

Traditionally, several rehabilitative interventions are connected to different aspects of motor function. In the Research Topic, two articles analyse the recovery post-stroke. Specifically, Khan et al. review the effects of various forms of functional electrical stimulation on upper limb in post-stroke recovery. This evidence may be instrumental in identifying areas for further research with this promising paradigm. It is commonly observed that lower limbs recover faster than upper limbs. Abdullahi et al. present a theoretical analysis of the possible reasons for such asymmetry. The authors posit that it is the more frequent use of the lower limb to carry out this asymmetry. Based on this interpretation, upper limb rehabilitation may be aided by paradigms which allow highly repetitive practice, such as robotic rehabilitation, Wii gaming, and constraint-induced movement therapy.

Other reviews are concerned with various neurological conditions. Faccioli, Pagliano et al. focus on the management and motor rehabilitation of cerebral palsy in children and adolescents. Evidence has accumulated over the years, indicating the importance of setting updated, evidence-based guidelines for clinical practice. The authors underscore the importance of identifying individual goals and interventions within a multidisciplinary, family-centered, evidence-based management. Considering the young age of patients, it is

advised to use motor rehabilitation programs which actively engage the subject, preferably through intensive and time-limited practice. Faccioli, Cavalagli et al. systematically review the evidence on the gait analysis patterns and rehabilitative intervention in hereditary spastic paraplegia and indicate some avenues of possible interventions.

A critical aspect of rehabilitation is the long-term effect on the patient's wellbeing. In their scoping review, Paolucci et al. examine the various options available for stroke patients in the chronic stage and underscore the importance of pursuing rehabilitation goals and not limiting them to maintenance. Indeed, the analysis of the relevant literature supports the efficacy of rehabilitative treatments over motor function following rehabilitation in the chronic stage with improvements in the quality of life.

The element that emerges from these various reviews is the need to have rehabilitation protocols that are more shared in terms of duration and intensity in the neurorehabilitation paths, both in the acute and chronic phases of the post-stroke patient.

A relevant point for patient recovery and successful rehabilitation is the association of conventional rehabilitation techniques with innovative systems, especially in rehabilitation training. Wu et al. illustrate the use of the Lokomat® robotic-orthosis system in patients with stroke and examine this new paradigm compared to conventional physical therapy for gait training and balance. Similarly, Cheng et al.'s scoping review focuses on the putative neuroplastic mechanisms of transcranial magnetic stimulation (rTMS) in stroke rehabilitation path. Their analysis underscores the presence of excitation and synchronization of neural activity as well as changes in functional connectivity between brain regions as assessed by functional magnetic resonance imaging (fMRI). TMS represents a supportive therapy to increase the recovery of residual motor function of the upper and lower limbs in the post-stroke patient.

In the context of instrumental physical therapy, the systematic review and meta-analysis by Wang et al. analyses the effectiveness of neuromuscular electrical stimulation (NMES) in the treatment of post-stroke dysphagia. NMES appears to have positive effects when combined with standard therapy on the quality of life, reducing the incidence of complications and promoting the recovery of swallowing function. However, its safety needs to be further confirmed.

Overall, the last years have seen an impressive growth of technologies generating innovative interventions for selective problems due to neurological conditions. The accumulation of evidence allows us to draw some conclusions on the relative efficacy of the various techniques and paradigms.

Telerehabilitation and computer-assisted rehabilitation

Telerehabilitation approaches could represent a novel resource supporting traditional rehabilitative paths because they make rehabilitation usable even at the patient's home, including the caregiver, throughout the treatment process and in the neurological chronic phase. In their mini-review, Xing et al. illustrate the characteristics of information and communication technologies (ICTs) that are most relevant for stroke interventions and discuss which types of training could be effectively offered with this paradigm. Overall, there is more and more evidence that telerehabilitation is not generally inferior to classical therapies carried out in the clinical setting when doses and intensities are comparable.

A relevant target of telerehabilitation is intervening in cognitive disturbances, a crucial sequela of stroke and other neurological conditions. Maggio et al. present an expert review highlighting software and devices currently available for training cognitive processes at home. Vuori et al. carry out a systematic review of the pertinent literature. In general, adherence and patient satisfaction are positive aspects of these interventions; by contrast, evidence supporting the usefulness of these trainings is still insufficient and based on studies with low methodological quality. Despite these limitations, the perspective opened by telerehabilitation approaches is promising and more high-quality studies are urgently needed.

A potentially promising area of use of telerehabilitation concerns mental health. While there is considerable evidence on the effectiveness of this paradigm on depression and anxiety in adults, less is known in the case of patients with neurological disorders. Zhang et al. systematically review this recent literature, underscoring the effectiveness of web-based interventions on depression and anxiety symptoms in patients with neurological disorders. They note that different variables, including intervention type and duration, modulate the efficacy of these interventions.

Telerehabilitation represents a key avenue for developing interventions for neurological conditions. It appears that more high-quality evidence needs to be acquired to reach definite conclusions on the effectiveness of the various therapeutic programs. However, even the current limited knowledge underscores the far-reaching potentiality of this approach in various areas of cognitive and mental disturbances, notwithstanding the possibility of selective use also for motor deficits. Importantly, in the ever-increasing need for neurorehabilitation interventions closely associated with an aging population, telerehabilitation may favor the expansion of rehabilitation services by significantly reducing costs and reaching patients in remote areas.

Additional therapeutic interventions for cognitive problems

One relevant area in cognitive disturbances concerns the interventions aimed at reducing the incidence of perioperative neurocognitive disorders. In a systematic review and meta-analysis of the relevant literature, Zhao et al. examine the effect of these interventions on postoperative delirium as well as on possible decline in cognitive performances.

In the field of complementary and alternative therapies (CAM-Therapy), Liu et al. analyse the efficacy and safety of multiple acupuncture therapies for post-stroke cognitive impairment, specifically ophthalmic acupuncture plus cognitive training. Due to the low methodological quality of the included studies, the findings need to be treated with caution. However, there were no reports of serious adverse effects, and acupuncture treatment appears safe and reliable.

Sensory-perceptual rehabilitation

Two reviews examine interventions for selective sensory-perceptual problems following neurological conditions. The study by Xie et al. examines the respiratory difficulties and mortality following severe cervical spinal cord injury (CSCI) as a primary consequence of malfunctions of respiratory pathways and the paralyzed diaphragm but also tries to respond to the question of whether there are other potential therapeutic targets to consider. The authors propose that magnetic resonance neuroimaging holds promise in examining respiratory function post-CSCI, studying respiratory plasticity in the brain and spinal cord to guide future clinical work.

Chen et al. present a meta-analysis of the effects of vestibular rehabilitation training (VRT) combined with anti-vertigo drugs on vertigo and balance function in patients with vestibular neuronitis. Evidence generally favors the use of this combined therapy to alleviate vestibular dysfunction, such as vertigo and vomiting, improving the quality of life of affected patients. The paucity of adverse reactions is another positive asset of this type of intervention.

Final remarks

In conclusion, some emerging properties arise from an overview of the reviews and meta-analyses of the Research Topic. First, the accumulating evidence on different rehabilitative interventions fosters the possibility of developing individualized, patient-centered management of patients with neurological disorders; this may entail engaging the patient in goal-directed, skill-based rehabilitative interventions suitable for the needs and preferences of the person and their family. Second, the complexity and articulation of available techniques call for a multidisciplinary and interdisciplinary rehabilitative teams. Third, several technological advancements bloomed in the last years, opening new frontiers in neurorehabilitation. The reviewed evidence points to the efficacy of some of these techniques in enlarging the portfolio of rehabilitators. It appears that combining traditional rehabilitative techniques with new innovative technologies opens an ever more promising perspective in neurorehabilitation. Fourth, one area connected with technological advancements is that of telerehabilitation. We are only starting to see the potentialities of this perspective. Of particular interest is the possibility of broadening the scope of rehabilitation services that are offered to patients with neurological syndromes and their families.

While technological advances are fundamental to increasing the effectiveness and pervasiveness of rehabilitation techniques, it is important to stress that, however elaborate, technologies do not abolish the need for accurate functional diagnosis that remains the essential basis for optimally setting up a person-centered rehabilitative project. Furthermore, we still need to better understand the individual characteristics of those who most likely will respond to one intervention versus another.

As Guest Editors for this Research Topic, we hope that you enjoy these extremely interesting manuscripts.

Author contributions

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Effects of transcutaneous neuromuscular electrical stimulation on post-stroke dysphagia: a systematic review and meta-analysis

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Background: Dysphagia is one of the common complications after stroke. It is closely related to lung infection and malnutrition. Neuromuscular electrical stimulation (NMES) is widely used in the treatment of post-stroke dysphagia, but the evidence-based medical evidence of NMES is limited. Therefore, this study aimed to evaluate the clinical efficacy of NMES in patients with post-stroke dysphagia by systematic review and meta-analysis.

Methods: We searched the CNKI, Wanfang, VIP, SinoMed, PubMed, Embase, Cochrane Library, and Web of Science databases for all randomized controlled trials (RCTs) of NMES in the treatment of post-stroke dysphagia from the establishment of the database to 9 June 2022. The risk of bias assessment tool recommended by Cochrane and the GRADE method was used to assess the risk of bias and the quality of evidence. RevMan 5.3 was used for statistical analysis. Sensitivity and subgroup analyses were performed to evaluate the intervention effect more specifically.

Results: A total of 46 RCTs and 3,346 patients with post-stroke dysphagia were included in this study. Our meta-analysis showed that NMES combined with routine swallowing therapy (ST) could effectively improve swallowing function in Penetration-Aspiration Scale (MD = −0.63, 95% CI [−1.15, −0.12], $P = 0.01$), Functional Oral Intake Scale (MD = 1.32, 95% CI [0.81, 1.83], $P < 0.00001$), Functional Dysphagia Scale (MD = − 8.81, 95% CI [−16.48, −1.15], $P = 0.02$), the Standardized Swallowing Assessment (MD = −6.39, 95% CI [−6.56, −6.22], $P < 0.00001$), the Videofluoroscopic Swallow Study (MD = 1.42, 95% CI [1.28, 1.57], $P < 0.00001$) and the Water swallow test (MD = −0.78, 95% CI [−0.84, −0.73], $P < 0.00001$). Furthermore, it could improve the quality of life (MD = 11.90, 95% CI [11.10, 12.70], $P < 0.00001$), increase the upward movement distance of hyoid bone (MD = 2.84, 95% CI [2.28, 3.40], $P < 0.00001$) and the forward movement distance of hyoid bone (MD = 4.28, 95% CI [3.93, 4.64], $P < 0.00001$), reduce the rate of complications (OR = 0.37, 95%CI [0.24, 0.57], $P < 0.00001$). Subgroup analyses showed that NMES+ST was more effective at 25 Hz, 7 mA or 0–15 mA, and at courses (≤4 weeks). Moreover, patients with an onset of fewer than 20 days and those older than 60 years appear to have more positive effects after treatment.

Conclusion: NMES combined with ST could effectively increase the forward and upward movement distance of the hyoid bone, improve the quality of life, reduce

the rate of complications, and improve the swallowing function of patients with post-stroke dysphagia. However, its safety needs to be further confirmed.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO, identifier: CRD42022368416.

KEYWORDS

stroke, dysphagia, neuromuscular electrical stimulation, meta-analysis, evidence-based medicine

1. Introduction

Stroke has become the second leading cause of death and the first leading cause of disability worldwide due to its high morbidity, disability, and mortality (1, 2). Moreover, some studies have shown that dysphagia is one of the most common complications in stroke patients. Approximately 37%−78% of stroke patients have dysphagia (3). The clinical manifestations of dysphagia include swallowing disorder, drinking cough, salivation, and other symptoms. Dysphagia after stroke is closely related to malnutrition, dehydration, electrolyte disorder, pulmonary infection, anxiety, and depression (4, 5), and it also leads to prolonged hospitalization, decreased quality of life, and further increased risk of death (6). Currently, swallowing therapy (ST) is mainly used for post-stroke dysphagia, including swallowing muscle strength and coordination exercises, posture changes, and diet adjustments (7).

However, the single ST takes a long time and has poor patient compliance, with a limited effect on severe dysphagia. More than 10% of patients have residual swallowing problems after ST (8). Therefore, how to effectively improve the swallowing function of patients, achieve oral feeding, and reduce the rate of complications is of great significance (4).

Neuromuscular electrical stimulation (NMES) has been a promising treatment for dysphagia in recent years. It can improve swallowing function by stimulating peripheral nerves to trigger swallowing muscle contraction, promote motor cortex repair, and enhance motor relearning ability (9).

Although some reviews claimed that NMES contributed to the rehabilitation of patients with dysphagia after stroke (10, 11), the number of evaluation measures used in these reviews is small, the number of included trials is limited, and the frequency, current intensity, and duration of electrical stimulation are not explored. Therefore, our study conducted a meta-analysis of the clinical efficacy of NMES in the treatment of post-stroke dysphagia in recent years to further provide valuable guidance and evidence-based medical evidence for the clinical use of NMES in the treatment of post-stroke dysphagia.

2. Methods

2.1. Protocol and registration

This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (12), and the protocol has been registered with PROSPERO (Registration number: CRD42022368416).

2.2. Data sources and search strategy

We searched eight scientific databases, namely, CNKI, Wanfang, VIP, SinoMed, PubMed, Embase, Cochrane Library, and Web of Science. The retrieval time was from the establishment of the database to 9 June 2022. There were no restrictions concerning publication source or language. The searched MeSH terms are listed as follows: ["Transcutaneous Electric Stimulation"[MeSH] OR "Percutaneous Electric Nerve Stimulation" OR "Percutaneous Neuromodulation Therapy" OR "TENS" OR "PENS"] AND ["Stroke"[MeSH] OR "cerebral hemorrhage" OR "cerebral ischemia" OR "cerebrovascular disease"] AND ["Dysphagia"[MeSH] OR "Deglutition Disorder" OR "Swallowing Disorder"] AND ["randomized controlled trial"[MeSH] OR "RCT"]. In addition, a supplementary search was conducted for the references included in the literature. Specific information is given in the Supplementary material.

2.3. Inclusion criteria

The inclusion criteria for this meta-analysis were as follows: (1) patients with ischemic or hemorrhagic stroke with clear imaging evidence of relevant pathology on magnetic resonance imaging (MRI) or computed tomography (CT); (2) patients with dysphagia after stroke diagnosed by clinical examination; (3) the participant with no other neurological diseases or other dysphagia; and (4) the same ST intervention (acupuncture, transcranial electrical stimulation, and transcranial magnetic stimulation are not included) performed in the experimental and control groups except the experimental group that received NMES.

2.4. Exclusion criteria

The exclusion criteria for this meta-analysis were as follows: (1) non-RCT studies, such as cross-sectional studies, case–control studies, case reports, systematic reviews, and animal experiments; (2) studies in which the baseline consistency test was not given; (3) studies with incomplete data, or studies whose full text could not be obtained; and (4) repeatedly published articles.

2.5. Outcomes

The outcome indicators were as follows: (1) Functional Oral Intake Scale (FOIS); (2) Penetration-Aspiration Scale (PAS–Fluid);

(3) Functional Dysphagia Scale (FDS); (4) the Swallowing Quality of Life questionnaire (SWAL-QOL); (5) the forward movement distance of the hyoid bone (FMHB); (6) the upward movement distance of the hyoid bone (UMHB); (7) the complication rate (CR); (8) the Standardized Swallowing Assessment (SSA); (9) the water swallow test (WST); and (10) the videofluoroscopic swallow study (VFSS).

2.6. Data extraction and management

The retrieved literature was imported into EndNote software for unified management. Two researchers (YW and LX) performed literature screening independently according to the proposed inclusion and exclusion criteria. First, we used EndNote to exclude duplicate literature and then conducted the preliminary screening. The two researchers independently read the title of the literature, keywords, and abstracts and initially excluded the documents that did not meet the inclusion criteria; after that, they downloaded and read the full text to determine whether the literature met the inclusion criteria. If necessary, we would contact the original author by mail or phone to obtain undetermined but important information for this study. The researchers independently extracted the data by a pre-designed data extraction form. The data extraction included (1) basic information about the study: research topic, first author, and publication year; (2) the number of cases, intervention, and course of treatment; (3) key elements of bias risk of assessment; and (4) outcome indicators and outcome statistics concerned. If there was any disagreement, it would be referred to a third researcher (LZ) to determine the final result.

2.7. Assessment of risk of bias

According to the bias of risk assessment tool recommended by Cochrane (13), the included literature studies were evaluated, including the random sequence production of the literature, the allocation concealment, the implementation of the blind method, whether the blind method was implemented for the result evaluation, the integrity of the result data, whether the results were selectively reported, and whether there were other biases. When the evaluators (YW and LX) had different opinions, they would discuss or ask for a third party (LZ). The risk of bias figure was drawn by RevMan5.3 software.

2.8. Data synthesis and statistical analysis

2.8.1. Measurement of therapeutic effects

In this study, odds ratio (OR) with a corresponding 95% confidence interval (CI) was used for binary variable data, and mean difference (MD) was used for continuous variable data.

2.8.2. Assessment of heterogeneity

After extracting and collating relevant data, this study used RevMan5.3 software for data analysis, and then used I^2 statistics and Q-test (χ^2) to assess the heterogeneity of results. The heterogeneity was considered low when $P > 0.10$ and $I^2 < 50\%$ (14, 15). The heterogeneity was considered high when $P < 0.10$ or $I^2 > 50\%$.

2.8.3. Data synthesis

If the heterogeneity of each group was small ($P > 0.10$, $I^2 < 50\%$), the fixed effect model was used. When the heterogeneity was considerable ($P < 0.10$, $I^2 > 50\%$), the random effect model was used after excluding the influence of significant clinical heterogeneity.

2.8.4. Subgroup analysis and sensitivity analysis

When $P < 0.10$ or $I^2 > 50\%$ in the χ^2 test, the source of heterogeneity was identified by extracting eligible articles one by one to make the sensitivity analysis. If not, subgroup analyses would be performed to identify the sources of heterogeneity according to age, duration of disease, duration of treatment, intensity of electrical stimulation, and frequency of electrical stimulation.

2.8.5. Grading of quality of evidence

This study used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (16) to assess the quality of evidence. GRADE divides the quality of evidence into four levels: ① High quality: further research is unlikely to change our confidence in effect estimates. ② Medium quality: further research may significantly impact our confidence in effect estimates and may change estimates. ③ Low quality: further research is likely to have a meaningful impact on our confidence in effect estimates and may change estimates. ④ Very low quality: any estimate of the effect is very uncertain (17). Two researchers (YW and LX) independently assessed the quality of the relevant evidence, and a third researcher (LZ) was notified of any disagreement for consultation.

3. Result

3.1. Literature search results

A total of 1,734 articles were retrieved, and 706 duplicate articles were excluded. After reading the title and abstract, we excluded 875 articles. After reading the complete text, 107 articles were excluded, and 46 articles were included finally. The research selection process is detailed in Figure 1.

3.2. Characteristics of the included studies

A total of 46 RCT studies were included, including 3,346 patients with post-stroke dysphagia. Among them, 1,679 patients received NMES + ST, and the other 1,667 received ST. The included studies were from China, the United States, Britain, Italy, Spain, and South Korea, and the treatment course ranged from 2 to 12 weeks, as shown in Table 1.

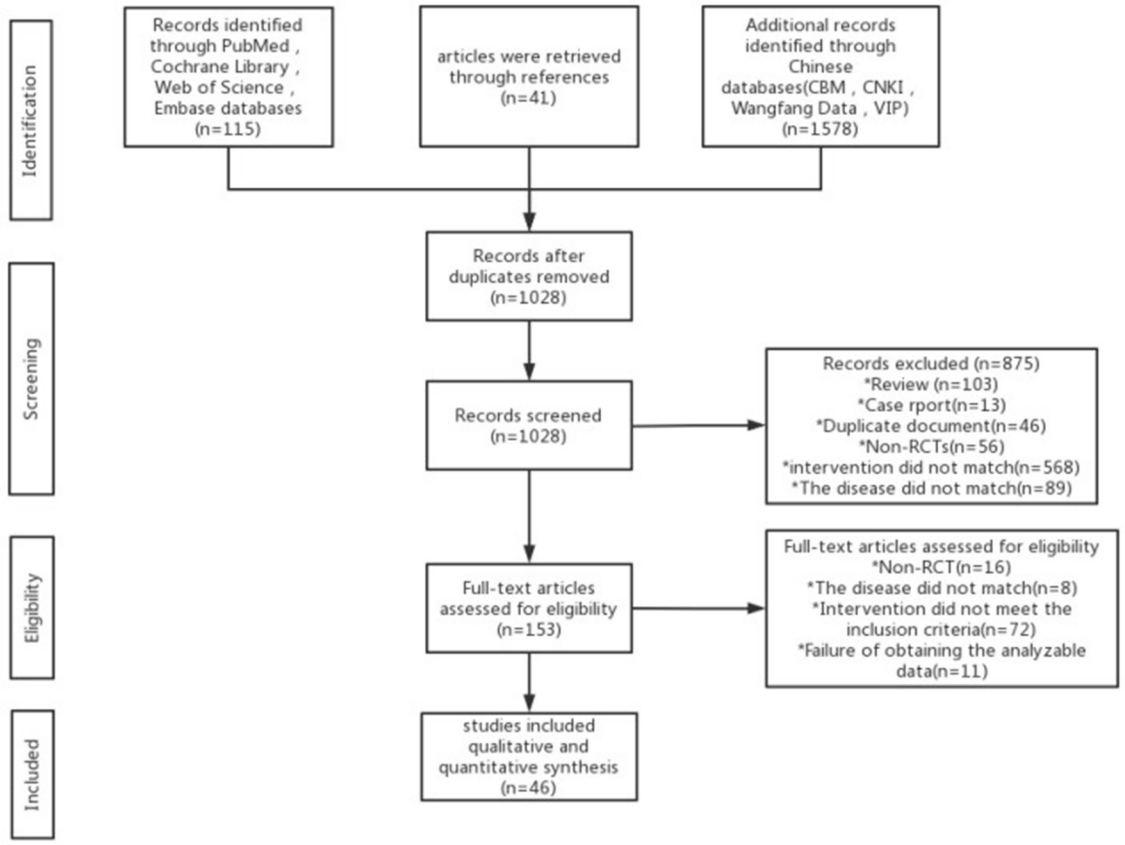

FIGURE 1
PRISMA flow diagram for study selection.

3.3. Bias risk evaluation of the included studies

The risk of bias assessment is shown in Figures 2, 3.

3.3.1. Generation of random sequence

Among the 46 studies included, 29 studies (18, 20, 22, 23, 25–27, 29, 32–34, 36, 37, 39, 42, 46, 48, 51–62) selected and reported appropriate randomization methods, such as random number table, so they were assessed as low risk of bias, the other 17 studies (19, 21, 24, 28, 30, 31, 35, 38, 40, 41, 43–45, 47, 49, 50, 63) only mentioned randomization allocation, so they were assessed as having the unclear risk of bias.

3.3.2. Allocation concealment

Nine studies (20, 32, 51–53, 55, 57, 59, 62) followed the appropriate protocol to hide treatment allocation, so they were considered to have a low risk of bias. A total of 37 studies did not mention whether they followed the allocation hiding principle, so they were assessed as having an unclear risk of bias.

3.3.3. Blinding of participants and personnel

Two studies (55, 57) explicitly proposed that the control group used sham NMES to blind participants and personnel, so they were assessed as having a low risk of bias because studies did not show that the control group received sham NMES. Instead, they only mentioned that the control group received ST and the experimental group received NMES + ST. We considered that participants were not blinded and rated studies as high risk of bias.

3.3.4. Blinding of outcome assessment

Seven studies (26, 53, 55–58, 62) reported the blinding of outcome assessment, identifying it as a low risk of bias. The other 39 studies did not report whether to adopt the blinding of outcome assessment, identified as the unclear risk of bias.

3.3.5. Incomplete outcome information

All studies thoroughly reported the test results data, so they were identified as having a low risk of bias.

3.3.6. Selective reporting of study results

A total of 25 studies (18, 22, 25–27, 29, 31, 33, 35, 37, 39, 46, 51–63) reported the registration and ethical review of clinical RCTs,

TABLE 1 Basic characteristics of the included RCTs.

Study	Location	Sample size (gender)		Age (year)		Intervention		Period of treatment (week)	Outcome measure
		T (male/female)	C (male/female)	T	C	T	C		
Chang (18)	China	41 (21/20)	42 (23/19)	65.84 ± 6.93	66.43 ± 7.29	NMES + ST	ST	8	1. SSA 2. SWAL-QOL 3. FMHB 4. UMHB
Chen et al. (19)	China	30 (16/14)	30 (15/15)	76.87 ± 9.24	77.04 ± 9.30	NMES + ST	ST	4	1. SSA 2. SWAL-QOL
Chen (20)	China	61 (32/29)	61 (33/28)	53.12 ± 3.43	53.20 ± 3.21	NMES + ST	ST	4	1. SSA 2. SWAL-QOL
Cui et al. (21)	China	63 (38/25)	63 (39/24)	64.12 ± 5.47	64.53 ± 5.36	NMES + ST	ST	2	1. SWAL-QOL 2. VFSS 3. WST
Du and Shao (22)	China	50 (26/24)	50 (27/23)	60.36 ± 2.74	59.25 ± 2.37	NMES + ST	ST	4	1. SSA 2. VFSS 3. WST
Geng (23)	China	71 (38/33)	71 (35/36)	46.78 ± 3.31	46.52 ± 3.26	NMES + ST	ST	4	1. SSA 2. WST
Gong (24)	China	45 (29/16)	45 (28/17)	54.06 ± 17.62	53.06 ± 17.24	NMES + ST	ST	4	1. VFSS
Gu and Shu (25)	China	40 (25/15)	40 (21/19)	71.36 ± 9.23	70.25 ± 8.42	NMES + ST	ST	12	1. SSA 2. SWAL-QOL
Lei et al. (26)	China	56 (30/26)	55 (21/34)	56.15 ± 9.71	54.30 ± 11.34	NMES + ST	ST	2	1. SSA 2. SWAL-QOL
Li (27)	China	40 (22/18)	40 (25/15)	65.72 ± 3.14	66.07 ± 3.27	NMES + ST	ST	8	1. SSA 2. SWAL-QOL 3. UMHB 4. FMHB 5. CR
Liang et al. (28)	China	50 (26/24)	50 (28/22)	62.8 ± 3.2	63.2 ± 2.8	NMES + ST	ST	2	1. SSA 2. WST
Mo et al. (29)	China	41 (31/10)	39 (28/11)	67.13 ± 9.64	65.89 ± 9.23	NMES + ST	ST	4	1. SSA 2. SWAL-QOL 3. CR
Shi et al. (30)	China	60 (33/27)	59 (32/27)	64.98 ± 5.18	65.12 ± 5.14	NMES + ST	ST	4	1. SSA 2. SWAL-QOL 3. VFSS
Tian et al. (31)	China	31 (14/17)	31 (17/14)	51.2 ± 2.3	52.1 ± 3.1	NMES + ST	ST	4	1. SSA

(Continued)

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TABLE 1 (Continued)

Study	Location	Sample size (gender)		Age (year)		Intervention		Period of treatment (week)	Outcome measure
		T (male/female)	C (male/female)	T	C	T	C		
Wang et al. (32)	China	42 (NA)	40 (NA)	NA	NA	NMES + ST	ST	3	3. VFSS
Wang (33)	China	41 (24/17)	41 (23/18)	59.34 ± 8.12	59.52 ± 7.60	NMES + ST	ST	4	1. SSA 2. SWAL-QOL 3. UMHB 4. FMHB
Wang and Ye (34)	China	30 (15/15)	30 (16/14)	67.28 ± 4.75	67.17 ± 4.79	NMES + ST	ST	4	3. VFSS
Wang (35)	China	37 (20/17)	37 (19/18)	61.8 ± 6.5	63.0 ± 7.1	NMES + ST	ST	4	1. SSA 2. SWAL-QOL
Wang et al. (36)	China	30 (17/13)	30 (18/12)	63.6 ± 11.6	62.8 ± 11.3	NMES + ST	ST	4	1. SSA 2. SWAL-QOL
Wen and Wu (37)	China	41 (20/21)	41 (22/19)	68.13 ± 6.74	67.45 ± 7.12	NMES + ST	ST	4	1. SWAL-QOL 2. WST
Zhan et al. (38)	China	24 (13/11)	24 (15/9)	64.3 ± 2.9	65.6 ± 3.1	NMES + ST	ST	2	1. UMHB 2. FMHB
Zhang et al. (39)	China	27 (14/13)	28 (11/17)	63.7 ± 6.3	62.3 ± 8.1	NMES + ST	ST	6	1. CR
Zhang et al. (40)	China	64 (34/30)	64 (35/29)	64.78 ± 5.34	63.91 ± 5.52	NMES + ST	ST	4	1. VFSS
Guo and Zhang (41)	China	50 (28/22)	50 (33/17)	69.30 ± 12.18	67.00 ± 11.26	NMES + ST	ST	2	1. SSA 2. SWAL-QOL 3. WST 4. CR
Zheng et al. (42)	China	50 (26/24)	50 (25/25)	65.65 ± 15.53	65.16 ± 15.21	NMES + ST	ST	4	1. SSA 2. VFSS
Zhou et al. (43)	China	45 (25/20)	45 (23/22)	62.87 ± 3.57	63.18 ± 3.92	NMES + ST	ST	9	1. VFSS 2. WST
Zhu et al. (44)	China	20 (11/9)	20 (13/7)	56.6	56.1	NMES + ST	ST	2	1. VFSS
Dong (45)	China	50 (28/22)	50 (26/24)	48.25 ± 1.47	48.31 ± 1.44	NMES + ST	ST	3	1. SSA 2. SWAL-QO 3. WST
Liu (46)	China	28 (19/9)	28 (20/8)	58.9 ± 11.7	56.4 ± 10.3	NMES + ST	ST	8	1. UMHB 2. FMHB
Wu and Zhang (47)	China	20 (14/6)	20 (15/5)	57.6 ± 15.4	59.5 ± 17.6	NMES + ST	ST	3	1. WST
Xu et al. (48)	China	10 (6/4)	10 (4/6)	NA	NA	NMES + ST	ST	4	1. VFSS
Deng (49)	China	45 (25/20)	45 (24/21)	61.6 ± 4.9	61.8 ± 4.2	NMES + ST	ST	8	1. CR

(Continued)

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TABLE 1 (Continued)

Study	Location	Sample size (gender)		Age (year)		Intervention		Period of treatment (week)	Outcome measure
		T (male/female)	C (male/female)	T	C	T	C		
Zhang (50)	China	52 (39/13)	52 (36/16)	65.90 ± 10.88	67.61 ± 10.44	NMES + ST	ST	2	1. CR
Li et al. (51)	China	45 (24/21)	45 (23/22)	66.7 ± 14.6	66.1 ± 13.1	NMES + ST	ST	4	1. SSA
Sproson et al. (52)	Britain	15 (10/5)	15 (9/6)	73 ± 15.3	81 ± 11.0	NMES + ST	ST	4	1. FOIS 2. PAS 3. SWAL-QOL
Simonelli et al. (53)	Italy	16 (10/6)	16 (6/10)	67.2 ± 16.2	72.4 ± 12.3	NMES + ST	ST	8	1. FOIS 2. PAS
Meng et al. (54)	China	10 (7/3)	10 (7/3)	65.2 ± 10.73	64.4 ± 9.03	NMES + ST	ST	2	1. WST 2. UMHB 3. FMHB
Park et al. (55)	South Korea	25 (12/13)	25 (14/11)	54 ± 11.93	55.8 ± 12.23	NMES + ST	Sham NMES + ST	6	1. PAS 2. FDS 3. UMHB 4. FMHB
Arreola et al. (56)	Spain	30 (19/11)	29 (19/10)	70.7 ± 12.91	73.52 ± 11.56	NMES + ST	ST	2	1. PAS
Carnaby et al. (57)	America	18 (10/8)	18 (8/10)	62.7 ± 12.2	70.6 ± 11.8	NMES + ST	Sham NMES + ST	3	1. CR
Huang et al. (58)	China	10 (9/1)	11 (6/5)	68.9 ± 16.9	67 ± 17.1	NMES + ST	ST	3	1. FOIS 2. PAS 3. FDS
Lee et al. (59)	South Korea	31 (22/9)	26 (20/6)	63.4 ± 11.4	66.7 ± 9.5	NMES + ST	ST	3	1. FOIS
Lim et al. (60)	South Korea	18 (12/6)	15 (10/5)	66.3 ± 15.4	62.5 ± 8.2	NMES + ST	ST	2	1. PAS 2. FDS
Zhang et al. (61)	China	27 (13/14)	28 (14/14)	63.72 ± 6.29	63.14 ± 6.56	NMES + ST	ST	6	1. CR
Guillén-Solà et al. (62)	Spain	21 (10/11)	21 (12/9)	70.3 ± 8.4	68.9 ± 7.0	NMES + ST	ST	3	1. CR
Zhang et al. (63)	China	28 (16/12)	27 (17/10)	61.3 ± 7.1	62.6 ± 8.7	NMES + ST	ST	4	1. FOIS 2. SSA 3. WST

NMES, transcutaneous neuromuscular electrical stimulation; ST, the swallowing rehabilitation training; T, treatment group; C, control group; NA, not available; SSA, the standardized swallowing assessment; SWAL-QOL, the swallowing quality of life questionnaire; WST, the water swallow test; VFSS, the videofluoroscopic swallow study; CR, complication rate; FMHB, forward movement distance of hyoid bone; UMHB, upward movement distance of hyoid bone; FOIS, functional oral intake scale; PAS, penetration-aspiration scale; FDS, functional dysphagia scale.

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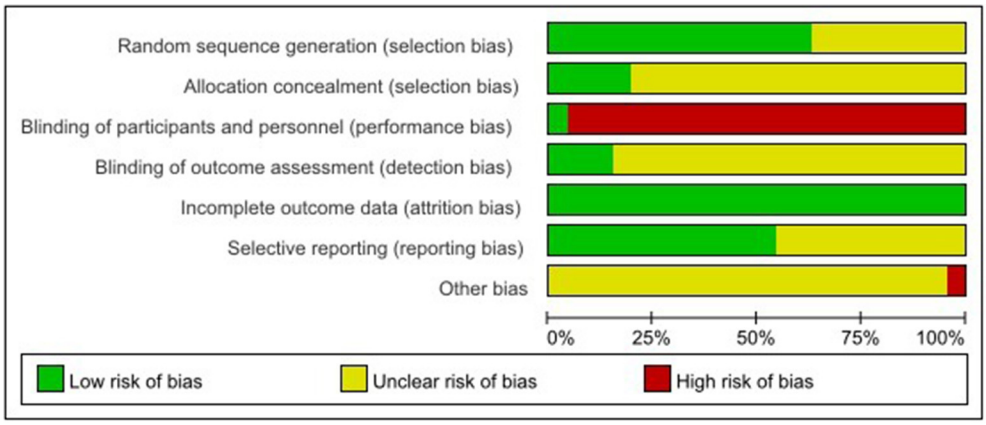

FIGURE 2
Risk of bias graph.

so the risk of bias was low. The remaining 21 studies were identified as having an unclear risk of bias.

3.3.7. Other bias sources

Because there were high drop-out rates in two (52, 60) studies, we rated them as high risk. In the remaining 44 studies, we did not observe any potential study bias, so they were identified as the unclear risk of bias.

3.4. Results of the meta-analysis

3.4.1. Standardized swallowing assessment

A total of 21 studies reported changes in SSA in patients with post-stroke dysphagia after NMES + ST. The effect of NMES + ST on the improvement of swallowing function in patients with post-stroke dysphagia was better than single ST, and the difference was statistically significant [MD = −6.39, 95% CI (−6.56, −6.22), $P < 0.00001$, $I^2 = 92\%$], but there was heterogeneity as shown in Figure 4.

3.4.2. Videofluoroscopic swallow study

A total of 11 studies reported changes in VFSS after treatment, and NMES + ST was more effective [MD = 1.42, 95% CI (1.28, 1.57), $P < 0.00001$, $I^2 = 98\%$], but there was a high heterogeneity as shown in Figure 5.

3.4.3. The swallowing quality of life questionnaire

A total of 16 studies reported changes in SWAL-QOL scores after treatment. Compared with ST, NMES + ST improved the quality of life of patients with dysphagia more significantly [MD = 11.90, 95% CI (11.10, 12.70), $P < 0.00001$, $I^2 = 98\%$]. Nevertheless, there was heterogeneity as shown in Figure 6.

3.4.4. Water swallow test

A total of 11 studies used the water swallow test to evaluate the swallowing function of patients. The efficacy of NMES + ST was better than that of single ST, with the statistical difference [MD = −0.78, 95% CI (−0.84, −0.73), $P < 0.00001$, $I^2 = 39\%$], as shown in Figure 7.

3.4.5. Forward movement distance of the hyoid bone

Seven studies reported changes in the forward movement distance of the hyoid bone after treatment. NMES + ST increased the forward movement distance of hyoid bone compared with single ST [MD = 4.28, 95% CI (3.93, 4.64), $P < 0.00001$, $I^2 = 97\%$], but there was heterogeneity, as shown in Figure 8.

3.4.6. Upward movement distance of the hyoid bone

Seven studies reported changes in the upward movement distance of the hyoid bone after treatment. NMES + ST significantly increased the upward movement distance of the hyoid bone compared with ST [MD = 2.84, 95% CI (2.28, 3.40), $P < 0.00001$, $I^2 = 0\%$], as shown in Figure 9.

3.4.7. Complication rate

Nine studies evaluated and recorded the rate of complications in patients with dysphagia. The results showed that NMES + ST could significantly reduce the rate of complications such as pneumonia and malnutrition compared with single ST (OR = 0.37 95% CI [0.24, 0.57], $P < 0.00001$, $I^2 = 22\%$), as shown in Figure 10.

3.4.8. Penetration-aspiration scale

Six studies reported changes in PAS after treatment, with NMES + ST achieving better clinical efficacy than ST [MD = −0.63, 95% CI (−1.15, −0.12), $P = 0.01$, $I^2 = 14\%$; as shown in the Supplementary material].

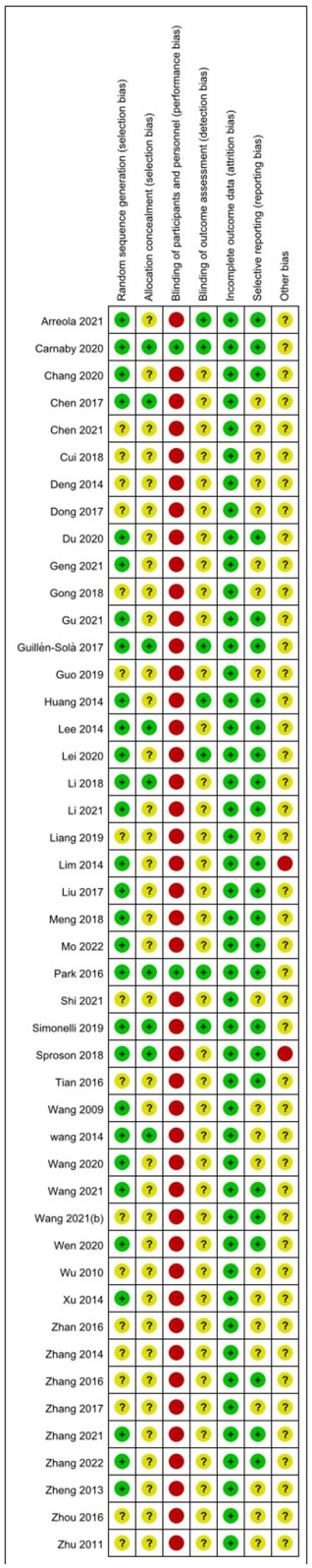

FIGURE 3
Risk of bias summary.

3.4.9. Functional oral intake scale

Five studies reported changes in FOIS after treatment, and NMES + ST was better than ST [MD = 1.32, 95% CI (0.81, 1.83), $P < 0.00001$, $I^2 = 18\%$; as shown in the Supplementary material].

3.4.10. Functional dysphagia scale

Three studies evaluated swallowing function according to FDS, and the clinical effect of NMES + ST may be more positive [MD = −8.81, 95% CI (−16.48, −1.15), $P = 0.02$, $I^2 = 57\%$; as shown in the Supplementary material].

3.5. Subgroup analysis

3.5.1. Subgroup analysis of SSA

A subgroup analysis showed that 25 Hz electrical stimulation [MD = −7.00, 95% CI (−12.20, −1.80), $P = 0.008$] had a more positive clinical effect on dysphagia after stroke than 10–50 Hz electrical stimulation [MD = −6.17, 95% CI (−7.09, −5.25), $P < 0.00001$], 30–80 Hz electrical stimulation [MD = −5.62, 95% CI (−8.18, −3.06), $P < 0.0001$], 40–80 Hz electrical stimulation [MD = −3.02, 95% CI (−4.80, −1.24), $P = 0.0009$], 80 Hz electrical stimulation [MD = −5.13, 95% CI (−7.68, −2.59), $P < 0.0001$]. In the study, 7 mA electrical stimulation [MD = −11.20, 95% CI (−12.82, −9.58), $P < 0.00001$] was better than 0–25 mA [MD = −5.83, 95% CI (−7.48, −4.19), $P < 0.00001$], 0–15 mA [MD = −8.08, 95% CI (−11.80, −4.37), $P < 0.0001$], 5–11 mA [MD = −3.85, 95% CI (−6.53, −1.16), $P = 0.005$], 5–25 mA [MD = −6.37, 95% CI (−6.99, −5.75), $P < 0.00001$], 0–30 mA [MD = −4.28, 95% CI (−6.14, −2.42), $P < 0.00001$]. A 4-week treatment course [MD = −6.29, 95% CI (−7.16, −5.42), $P < 0.00001$] might have better clinical efficacy, and older patients (age > 60 years old; MD = −6.33, 95% CI [−7.10, −5.56], $P < 0.00001$) may have a more significant positive effect on post-stroke dysphagia than younger patients (age <60 years old; MD = −4.58, 95% CI [−6.03, −3.14], $P < 0.00001$). However, in the duration of each treatment and course of the disease, there is no statistical difference between subgroups (as shown in the Supplementary material).

3.5.2. Subgroup analysis of VFSS

The subgroup analysis showed that the treatment group within 4 weeks [MD = 2.24, 95% CI (1.62, 2.86), $P < 0.00001$] was better than the 4-week treatment group [MD = 2.09, 95% CI (1.46, 2.71), $P < 0.00001$] and the treatment group over 4 weeks [MD = −2.39, 95% CI (−2.73, −2.05), $P < 0.00001$]. There was no significant difference in clinical efficacy between subgroups in age, course of the disease, duration of each treatment, intensity of electrical stimulation, and frequency of electrical stimulation (as shown in the Supplementary material).

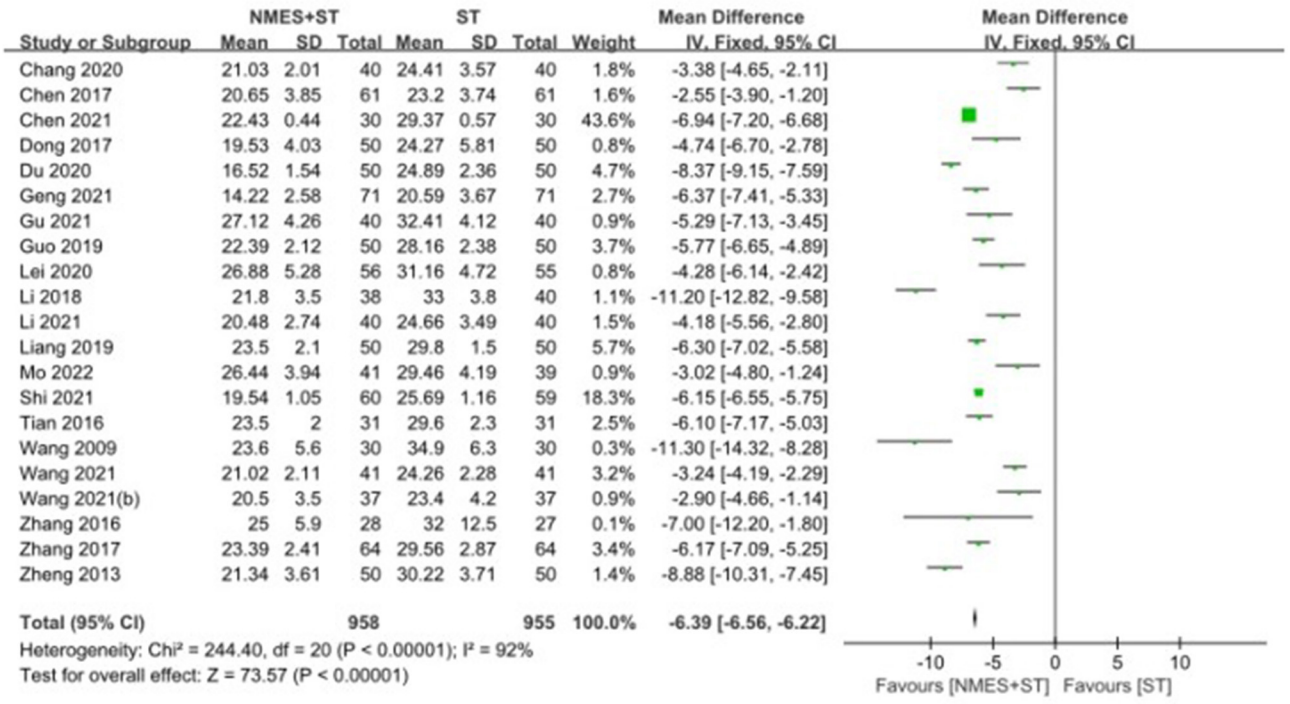

FIGURE 4
Forest plot for the standardized swallowing assessment.

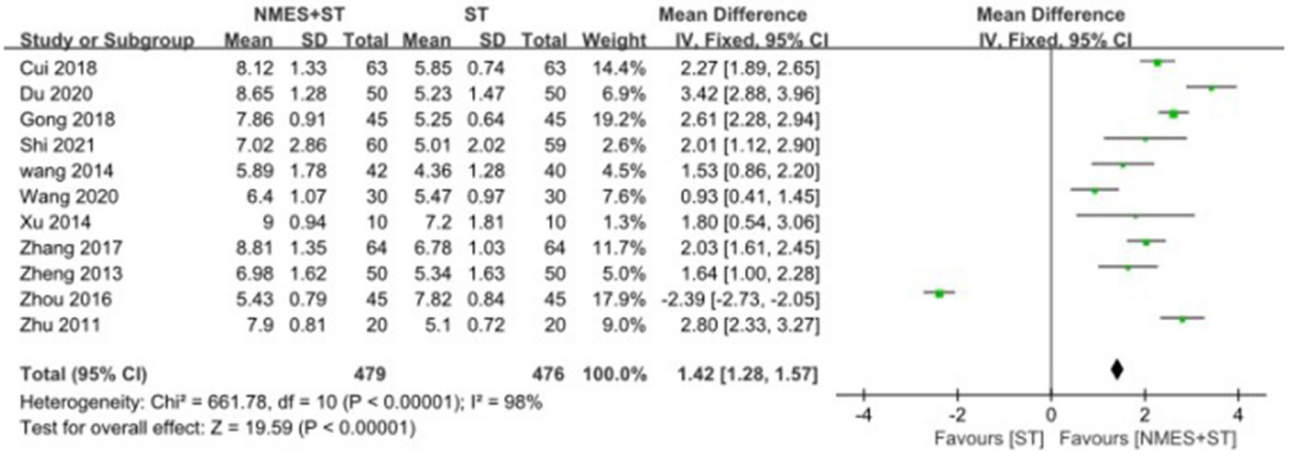

FIGURE 5
Forest plot for videofluoroscopic swallow study.

3.5.3. Subgroup analysis of SWAL-QOL

Subgroup analysis showed that 0–15 mA electrical stimulation [MD = 94.92, 95% CI (85.33, 104.51), $P < 0.00001$] was compared with 0–25mA [MD = 21.00, 95% CI (10.04, 31.96), $P = 0.0002$], 5–11 mA [MD = 27.68, 95% CI (−3.73, 59.09), $P = 0.08$], 0–30 mA [MD = 24.63, 95% CI (19.44, 29.82), $P < 0.00001$], 14–20 mA [MD = 29.19, 95% CI (19.23, 39.15), $P < 0.00001$] might produce better influence. Patients [the day from onset < 20 days; MD = 30.32, 95% CI (12.27, 48.37), $P = 0.001$] may have better clinical efficacy, and older patients (age > 60 years old; MD = 27.50, 95% CI [18.58, 36.42], $P < 0.00001$) was better than younger patients (age < 60 years old; MD = 13.25, 95% CI [5.67, 20.84], $P = 0.0006$). However, there were no statistical differences between subgroups in electrical stimulation frequency, course of treatment, and duration of each treatment (as shown in the Supplementary material).

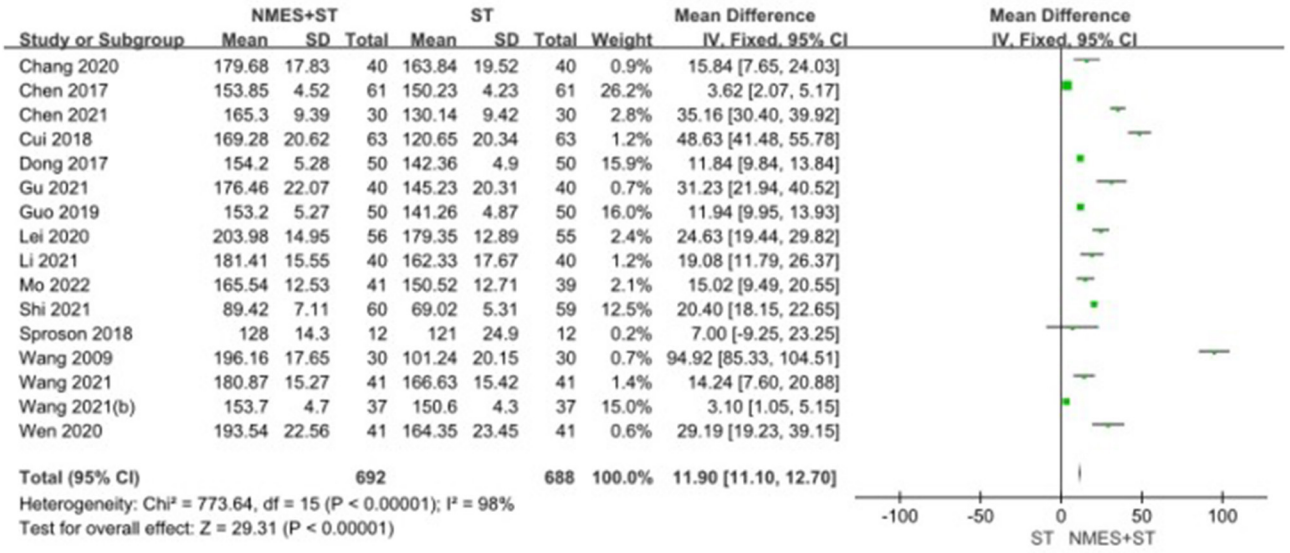

FIGURE 6
Forest plot for the swallowing quality of life questionnaire.

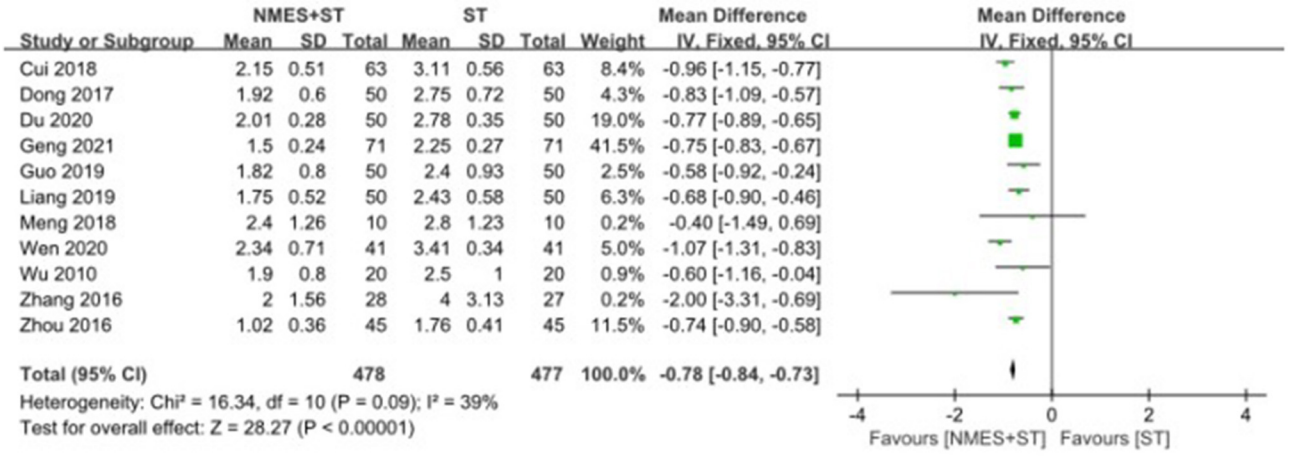

FIGURE 7
Forest plot for water swallow test.

3.6. Publication bias

We used funnel plots to evaluate the publication bias of SSA, VFSS, SWAL-QOL, and WST, respectively. The results showed that the funnel plots of SSA and WST were relatively symmetric, and they might not have publication bias, while the funnel plots of VFSS and SWAL-QOL were asymmetric. It might have publication bias, as shown in Figures 11–13, Supplementary material.

3.7. Sensitivity analysis

Sensitivity analysis was performed because I^2 of SSA (92%), VFSS (98%), SWAL-QOL (98%), FMHB (97%), and FDS (57%) were >50%. After sensitivity analysis of FDS, we excluded one study that could have led to high heterogeneity. FDS analysis showed the disappearance of high heterogeneity ($I^2 = 0$; Supplementary material). However, after sensitivity analysis of other relevant literature data, the responsible articles leading to high heterogeneity were not determined. During the analysis, we found that some subgroups still had high heterogeneity. Subsequently, sensitivity analysis was conducted again for each subgroup, but the source of heterogeneity was still not identified. Therefore, meta-regression analysis was used to explain the high heterogeneity. However, it was not performed due to the small number of studies included in FMHB (as shown in the Supplementary material).

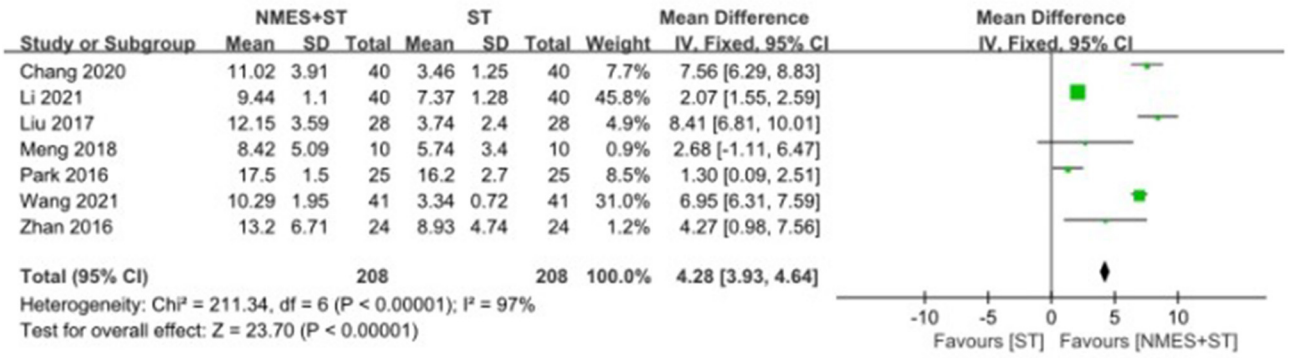

FIGURE 8
Forest plot for forward movement distance of hyoid bone.

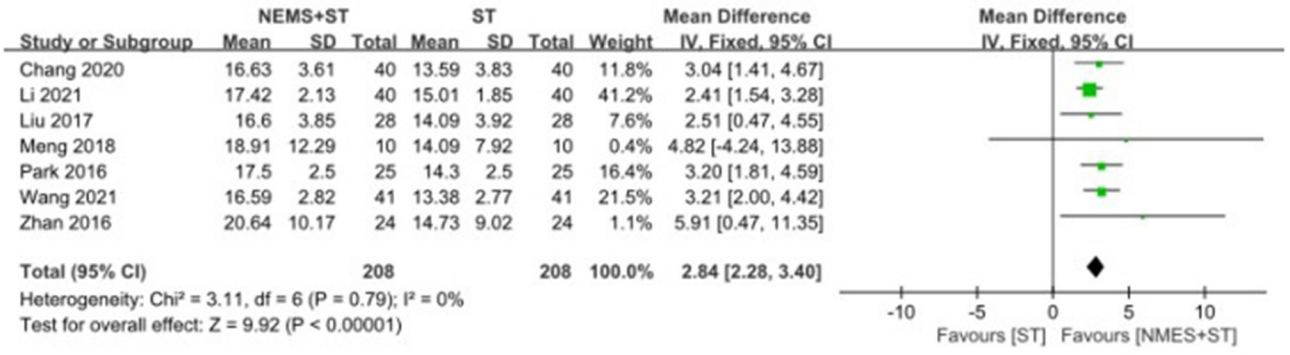

FIGURE 9
Forest plot for upward movement distance of hyoid bone.

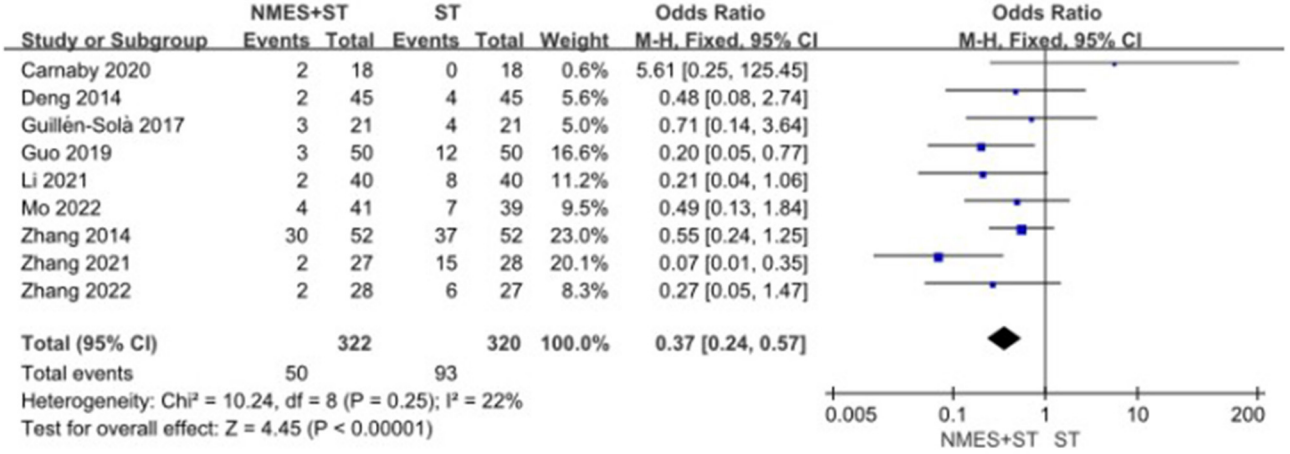

FIGURE 10
Forest plot for complication rate.

3.7.1. Heterogeneity of SSA

According to the results of the meta-regression analysis, the high heterogeneity of SSA may be related to age ($P = 0.032$), but there was not significantly associated with the course of treatment ($P = 0.160$), course of disease ($P = 0.091$), duration of each treatment ($P = 0.096$), the intensity of electrical

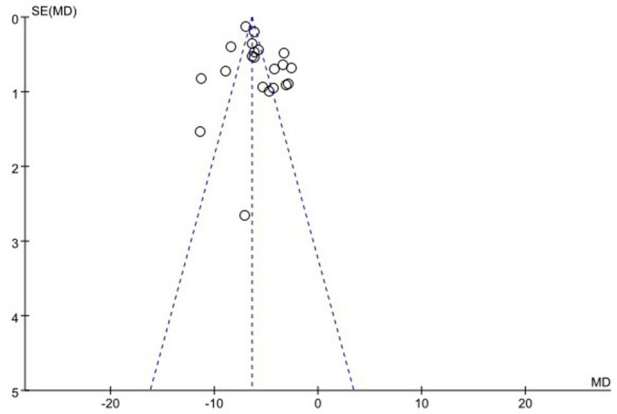

FIGURE 11
Funnel plot for standardized swallowing assessment.

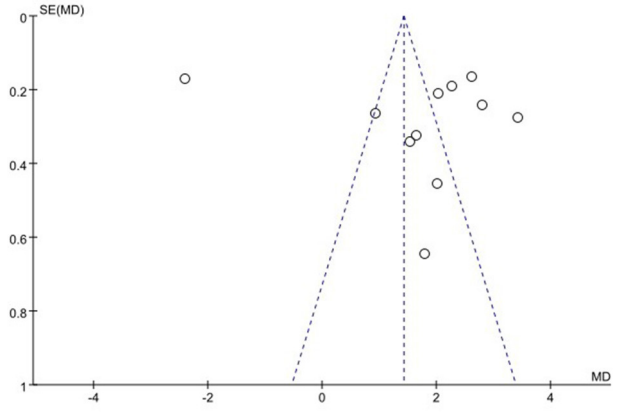

FIGURE 12
Funnel plot for videofluoroscopic swallow study.

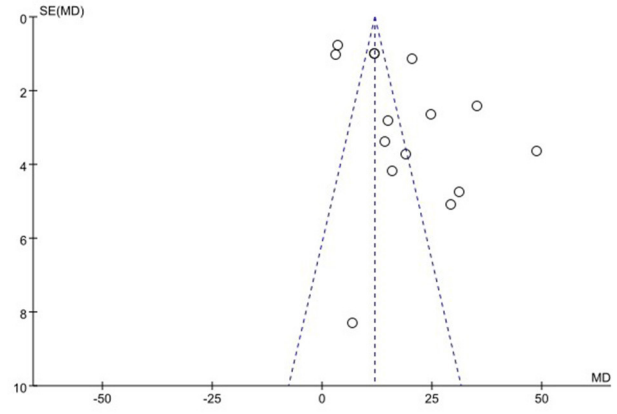

FIGURE 13
Funnel plot for the swallowing quality of life questionnaire.

stimulation ($P = 0.320$), and frequency of electrical stimulation ($P = 0.802$).

3.7.2. Heterogeneity of SWAL-QOL

The heterogeneity of SWAL-QOL results might be due to the age ($P = 0.024$), course of treatment ($P = 0.003$), course of disease ($P = 0.002$), and duration of each treatment ($P = 0.003$), but there was no significant correlation with frequency of electrical stimulation ($P = 0.782$) and intensity of electrical stimulation ($P = 0.287$).

3.7.3. Heterogeneity of VFSS

The heterogeneity of VFSS results might be due to the course of treatment ($P = 0.022$), but it might not be related to age ($P = 0.147$), course of disease ($P = 0.345$), treatment time ($P = 0.124$), the intensity of electrical stimulation ($P = 0.459$), and frequency of electrical stimulation ($P = 0.542$).

3.8. Quality of evidence

After the GRADE evaluation, the quality of evidence: WST and UMHB were rated as moderate quality. VFSS, CR, FMHB, and FOIS were rated as low quality. PAS, FDS, SSA, and SWAL-QOL were rated as very low quality. The low quality included the high risk of bias in the included studies, insufficient sample size, high heterogeneity, indirect comparison of trial results, and inconsistency as shown in Table 2.

3.9. Adverse events

Nine studies reported adverse events. Five studies (50–53, 62) reported that during the study period, patients in the experimental group did not report any adverse events, while Wang et al. (33) reported that one patient had a skin allergy to the electrode patch; one patient had a peculiar smell in the mouth, and the adverse reactions disappeared after stopping treatment. Arreola (56) and Lim (60) show that two patients reported skin tingling, which disappeared after electrical stimulation was stopped. Zhang et al. (63) reported that seven patients had localized skin redness or allergic reactions in the area of electrode placement, and the adverse reactions disappeared after the treatment was stopped, and no one withdrew because of skin reactions.

4. Discussion

This meta-analysis showed that NMES + ST could effectively increase the forward and upward movement distance of the hyoid bone, improve the quality of life of patients with dysphagia, reduce the rate of complications, and improve the swallowing function of patients.

In addition, subgroup analysis based on the course of the disease found that NMES + ST may have a more significant clinical influence on patients (the day from onset < 20 days). This subgroup results emphasize the importance of early treatment of dysphagia after stroke, which may be related to the fact that NMES can enhance pharyngeal sensory feedback pathways, promote cortical reorganization, and increase pharyngeal motor performance in the

TABLE 2 Summary of GRADE recommendations.

Quality assessment								No. of patients		Effect		Quality
Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NMES + ST	ST	Relative (95% CI)	Absolute	
Standardized swallowing assessment	21	Randomized trials	Serious[1]	Serious[2]	Serious[3]	None	None	958	955		MD 6.39 lower (6.56–6.22 lower)	Very low
The swallowing quality of life questionnaire	16	Randomized trials	Serious[1]	Serious[2]	Serious[3]	None	None	692	688		MD 11.90 higher (11.10–12.70 higher)	very low
Penetration-aspiration scale	6	Randomized trials	Serious[1]	Serious[4]	None	Serious[4]	None	111	107		MD 0.63 lower (1.15–0.12 lower)	Very low
Water swallow test	11	Randomized trials	Serious[1]	None	None	None	None	478	477		MD 0.78 lower (0.84–0.73 lower)	Moderate
Functional dysphagia scale	3	Randomized trials	Serious[1]	Serious[2]	None	Serious[4]	None	53	51		MD 8.81 lower (16.48–1.15 lower)	Very low
Functional Oral Intake Scale	5	Randomized trials	Serious[1]	None	None	Serious[4]	None	97	93		MD 1.32 higher (0.81–1.83 higher)	Low
Videofluoroscopic Swallow Study	11	Randomized trials	Serious[1]	Serious[2]	None	None	None	479	476		MD 1.42 higher (1.28–1.57 higher)	Low
Forward movement distance of hyoid bone	7	Randomized trials	Serious[1]	Serious[2]	None	None	None	208	208		MD 4.28 higher (3.93–4.64 higher)	Low
Upward movement distance of hyoid bone	7	Randomized trials	Serious[1]	None	None	None	None	208	208		MD 2.84 higher (2.28–3.40 higher)	Moderate
Quality assessment								No. of patients		Effect		Quality
Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NMES + ST	ST	Relative (95% CI)	Absolute	
Complication rate	9	Randomized trials	Serious[1]	Serious[4]	None	None	None	50/322 (15.5%)	93/320 (29.1%)	OR 0.37 (0.24 to 0.57)	159 fewer per 1,000 (from 101 to 201 fewer)	Low
									20%		115 fewer per 1,000 (from 75 to 143 fewer)	

Supplement: 1. High risk of bias; 2. High heterogeneity; 3. Indirect comparison; 4. The number of the patient included is small; 4. Inconsistent results.

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contralateral motor cortex (64–66). Early treatment may be more effective in promoting cortical reorganization.

The subgroup analysis based on the course of treatment showed that 4 weeks or less might achieve more satisfactory clinical efficacy than the course of more than 4 weeks. The study (67) found that electrical stimulation may have a cumulative effect on brain activity, which is associated with the recovery of behavioral function. Therefore, we wondered if there was an upper threshold for the cumulative effect of electrical stimulation on the plasticity of the cerebral cortex, resulting in the limited recovery of swallowing function from excessive electrical stimulation.

In the subgroup analysis based on the frequency and intensity of electrical stimulation, the results of SSA as the outcome index showed that 25 Hz electrical stimulation and 7 mA electrical stimulation seemed to have a more positive effect. In contrast, the results of SWAL-QOL showed that the clinical efficacy of 0–15 mA electrical stimulation was more prominent. However, there was no statistical difference between the subgroups of electrical stimulation at different frequencies ($P > 0.05$). Studies (63, 68) confirmed that there were specific differences in clinical efficacy in different intensities and frequencies of electrical stimulation, which might be related to the different degrees of motor-evoked potentials (MEPs) induced by different frequencies and intensities of stimulation on the pharyngeal muscle. Pharyngeal muscle MEPs were closely related to the excitability of the swallowing cortex-medulla oblongata (69, 70) and could have a long-term effect on the reorganization of the cerebral cortex through nerve conduction, thereby promoting the recovery of swallowing function.

In age-based subgroup analysis, it appeared to be more clinically positive in patients (age > 60 years old) than in patients (age < 60 years old). As people grow older, the human physiological function will also decrease (71), which may lead to the fact that routine ST does not provide the same recovery effect for older patients as for younger patients. In the control group, patients (age > 60 years old) achieved worse clinical efficacy in conventional ST than patients (age < 60 years old). However, patients in the experimental group received NMES + ST. The addition of electrical stimulation can enhance the contraction of swallowing muscles, promote the repair of damaged nerves and the remodeling of the cerebral cortex, which may make it possible that patients (age > 60 years old) in the experimental group can obtain the same benefits as other patients (age<60 years old). For this reason, the relative benefit is more significant in patients over 60 than in patients under 60.

Swallowing is a complex neuromuscular reflex activity involving the cortical center, brainstem swallowing center, peripheral nerve, and other aspects. Stroke can cause damage to the cortical swallowing center, corticobulbar tract, brainstem swallowing center, cranial nerves (V, IX, X, XI, and XII), and spinal nerves (C1, C2, and C3), which leads to symptoms of swallowing disorder such as drinking cough, eating difficulties, dysarthria. Research (72, 73) has proved that specific intensity of electrical stimulation on the glossopharyngeal muscle group can enhance muscle contraction ability, increase the degree of activation, and prevent disuse muscle atrophy. Swallowing-related muscles are mainly composed of type I muscle fibers and type II muscle fibers. Type II muscle fibers are smaller than type I and are not easily polarized (73). When NMES stimulates muscle, type II muscle fibers that constitute swallowing muscles are preferentially activated. Traditional rehabilitation training activates type I muscle fibers (72). When simultaneous treatment is performed, type I and type II muscle fibers are simultaneously activated, and the glossopharyngeal muscle group can produce a stronger contraction. In addition, electrical stimulation can produce vasoactive peptides to cause local vasodilation, which can improve the blood circulation of the injured part (74), accelerate the regeneration and repair of the nerve to correctly project the regeneration track of the target organ, promote the regeneration of the axon and the maturation of the myelin sheath (75), and further promote the functional recovery and reorganization of the cerebral cortex and related neural connections and pathways (76, 77). The sufficient movement of the hyoid-laryngeal complex is the key to ensuring the effective and safe completion of swallowing activities (78, 79). At present, the range of motion of the hyoid bone is often used to measure the movement of the hyoid-laryngeal complex of patients with dysphagia. Furthermore, the upward and forward movement distance of the hyoid bone in patients with dysphagia is significantly lower than that of ordinary people (80–82). This study also shows that while the swallowing function of patients is improved, the distance of upward and forward movement of the hyoid bone is significantly increased, which is consistent with previous studies.

However, in the subgroup analysis of the frequency and intensity of electrical stimulation, there was high heterogeneity within subgroups possibly due to the different placement of NMES in different studies. Studies had found that when electrodes were placed on the suprahyoid muscle (83), thyrohyoid muscle (53), orbicularis oculi muscle (84), and masseter muscle (85), the swallowing functions were improved. Furthermore, a meta-analysis study showed that horizontal electrodes placed in the suprahyoid muscle or suprahyoid muscle and thyrohyoid muscle seem to have the best effect (11), so the electrode placement site is related to clinical efficacy. The heterogeneity of the treatment course subgroup may be related to the differences in the intensity and frequency of electrical stimulation, pulse duration, and swallowing rehabilitation. One study (86) proposed that the shorter the pulse duration, the greater the stimulation intensity needed to obtain a muscle response. The pulse duration is inversely proportional to the specificity of the stimulus applied, which may be responsible for the high heterogeneity in subgroups. In addition, the high heterogeneity of age and disease course subgroups may be related to the inconsistency of stroke type, disease severity, frequency of electrical stimulation, and electrical stimulation intensity among patients included in different studies, which still needs further exploration.

4.1. Strengths and weaknesses

This study included more clinical randomized controlled trials (46 RCTs) and case numbers (3,346 patients) than previous meta-analysis studies on NMES in treating post-stroke dysphagia. It evaluated the clinical efficacy of NMES + ST from 10 different

outcome indicators, such as SSA, SWAL-QOL, and VFSS. In addition, subgroup analysis found that the clinical efficacy of NMES + ST in patients with a disease course of fewer than 20 days appeared to be more significant than that in patients with a disease course of more than 20 days, which provided evidence support for early intervention treatment. A treatment course of 4 weeks or less appears to be better than a course of more than 4 weeks, which will help reduce the cost of treatment and improve the potential cost-effectiveness of the intervention; Electrical stimulation with a frequency of 25 Hz and intensity of 7 mA or 0–15 mA appears to work better. This finding could help develop optimal stimulation parameters. The effect of electrical stimulation in patients over 60 years old is noticeable, promoting further attention to the treatment of swallowing disorders in the elderly. This study also has some limitations: (1) The majority of the 46 RCTs included in this study are from China, which may lead to regional bias. (2) Most of the included clinical trials do not report the blinding method used, which reduced the quality of the methodological study. There may be some placebo effect and observer bias, which may reduce the credibility of the clinical trial results. (3) Among 46 RCTs, only six studies followed-up visited with the patients, so the long-term clinical efficacy of NMES + ST on post-stroke dysphagia still needs to be further explored. (4) Adverse events were reported in only some studies, which resulted in insufficient evidence to support the safety of NMES + ST treatment. Future studies still need to strengthen the recording and reporting of adverse events. (5) Due to the high heterogeneity, some results' reliability in the study has been somewhat affected. (6) The use of multiple types of ST in different studies led to the fact that this study did not perform a subgroup analysis based on the type of ST received by the control group. We look forward to further exploration in subsequent studies.

5. Conclusion

Our study showed that NMES + ST could effectively increase the forward and upward movement distance of the hyoid bone, improve the quality of life of patients with post-stroke dysphagia, reduce the rate of complications, and promote the recovery of swallowing function. NMES with a frequency of 25 Hz, an intensity of 0–15 mA, and a treatment course of 4 weeks or less may have better results. Patients with an onset of fewer than 20 days and over 60 years old appear more effective with NMES + ST. However, there is insufficient evidence on the safety of NMES + ST for post-stroke dysphagia. Moreover, due to the small number of included literature and the low quality of evidence, more large-sample, high-quality, multi-center RCT studies are needed to prove the clinical efficacy of NMES + ST in the treatment of post-stroke dysphagia.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YW conceived the study and drafted the protocol. YW, LX, and LZ participated in literature screening, data extraction, and bias risk assessment. YW, LW, MJ, and LX are responsible for statistical analysis and manuscript writing. LZ was responsible for the planning and guidance of this article. All authors participated in the study and approved the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1163045/full#supplementary-material

References

1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* (2017) 390:1151–210. doi: 10.1016/S0140-6736(17)32152-9

2. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

3. Martino R, Foley N, Bhogal S, Diamant N, Speechley M,Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke*. (2005) 36:2756–63. doi: 10.1161/01.STR.0000190056.76543.eb

4. Foley NC, Martin RE, Salter KL, Teasell RW. A review of the relationship between dysphagia and malnutrition following stroke. *J Rehabil Med*. (2009) 41:707–13. doi: 10.2340/16501977-0415

5. Eslick GD, Talley NJ. Dysphagia: epidemiology, risk factors and impact on quality of life–a population-based study. *Aliment Pharmacol Ther*. (2008) 27:971–9. doi: 10.1111/j.1365-2036.2008.03664.x

6. Doeltgen SH, Bradnam LV, Young JA, Fong E. Transcranial non-invasive brain stimulation in swallowing rehabilitation following stroke—a review of the literature. *Physiol Behav*. (2015) 143:1–9. doi: 10.1016/j.physbeh.2015.02.025

7. Jongprasitkul H, Kitisomprayoonkul W. Effectiveness of conventional swallowing therapy in acute stroke patients with dysphagia. *Rehabil Res Pract*. (2020) 2020:1–5. doi: 10.1155/2020/2907293

8. Smithard DG, O'Neill PA, Martin DF, England R. Aspiration following stroke: is it related to the side of the stroke? *Clin. Rehabil*. (1997) 11:73–6. doi: 10.1177/026921559701100111

9. Steele CM. Electrical stimulation of the pharyngeal swallow: does the evidence support application in clinical practice? *J Speech Lang Pathol Audiol*. (2004) 28:77–83.

10. Chen YW, Chang KH, Chen HC, Liang WM, Wang YH, Lin YN. The effects of surface neuromuscular electrical stimulation on post-stroke dysphagia: a systemic review and meta-analysis. *Clin Rehabil*. (2016) 30:24–35. doi: 10.1177/0269215515571681

11. Doan TN, Ho WC, Wang LH, Chang FC, Tran TTQ, Chou LW. Therapeutic effect and optimal electrode placement of transcutaneous neuromuscular electrical stimulation in patients with post-stroke dysphagia: a systematic review and meta-analysis of randomized controlled trials. *Life*. (2022) 12:875. doi: 10.3390/life12060875

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

13. Cumpston M, Li T, Page MJ, Chandler J, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. *Cohrane Database Syst Rev*. (2019) 10. doi: 10.1002/14651858.ED000142

14. Tan SW, Wu A, Cheng LJ, Wong SH, Lau Y, Lau ST. The effectiveness of transcranial stimulation in improving swallowing outcomes in adults with poststroke dysphagia: a systematic review and meta-analysis. *Dysphagia*. (2022) 37:1796–813. doi: 10.1007/s00455-022-10424-6

15. Li SH, Hu WS, Wu QF, Sun JG. The efficacy of bloodletting therapy in patients with acute gouty arthritis: a systematic review and meta-analysis. *Complement Ther Clin Pract*. (2022) 46:101503. doi: 10.1016/j.ctcp.2021.101503

16. Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Interpreting results and drawing conclusions. In: Chandler J, Thomas J, Higgins JPT, Page MJ, Cumpston M, Li T, et al. editors. *Cochrane Handbook for Systematic Reviews of Interventions*. New York, NY: Wiley (2019), p. 403–31. doi: 10.1002/9781119536604.ch15

17. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin. Epidemiol*. (2013) 66:719–25. doi: 10.1016/j.jclinepi.2012.03.013

18. Chang E. Effect of neuromuscular electrical stimulation combined with feeding training on patients with dysphagia after stroke. *Chin J Integr Med Cardio-Cerebrovasc Dis*. (2020) 18:337–40. doi: 10.12102/j.issn.1672-1349.2020.02.038

19. Chen XX, Chen QG, Gu LH, Zhao YL, Cui T, Lin L, et al. Clinical observation of percutaneous acupoint electrical stimulation combined with swallowing training on patients with swallowing dysfunction after stroke. *Chin Man Rehabil Med*. (2021) 12:49–50+52. doi: 10.19787/j.issn.1008-1879.2021.01.016

20. Chen XX. Effect of neuromuscular electrical stimulation combined with swallowing train on the survival quality of patients with dysphagia after cerebral infarction. *Clin Res Pract*. (2017) 2:19–20. doi: 10.19347/j.cnki.2096-1413.201736008

21. Cui YQ, Song QQ, Ye HM, Mo JM, Lu HY. Influence of nerve and muscle electrical stimulation on swallowing function and living quality in stroke patients with dysphagia. *Tianjin J Nurs*. (2018) 26:421–4. doi: 10.3969/j.issn.1006-9143.2018.04.013

22. Du YB, Shao K. To study and analyze the feasibility and effectiveness of neuromuscular electrical stimulation combined with rehabilitation therapy in the treatment of swallowing dysfunction after stroke. *Reflexol Rehabil Med*. (2020) 29:129–31.

23. Geng XZ. Effects of neuromuscular electrical stimulation combined with early swallowing management on swallowing function and nerve function in patients with swallowing disorder after craniocerebral injury. *Reflexol Rehabil Med*. (2021) 2:163–5.

24. Gong XQ. Efficacy of neuromuscular electrical stimulation combined with swallowing training for dysphagia after stroke. *Clin Res Pract*. (2018) 3:34–5. doi: 10.19347/j.cnki.2096-1413.201807016

25. Gu YW, Shu J. Effects of surface electromyogram biofeedback and neuromuscular electrical stimulation on dysphagia after stroke and quality of life. *Chin J Rehabil*. (2021) 36:599–603. doi: 10.3870/zgkf.2021.10.005

26. Lei C, Sun ZM, Wang YF, Ming WW, Li HY. Application of pharyngeal ice stimulation combined with low-frequency pulsed electrical stimulation in patients with post-stroke swallowing disorders. *J Clin Pathol*. (2020) 40:116–23. doi: 10.3978/j.issn.2095-6959.2020.01.020

27. Li Q. Effect of neuromuscular electrical stimulation combined with swallowing rehabilitation training on swallowing function in patients with dysphagia after stroke. *Reflexol Rehabil Med*. (2021) 2:154–6.

28. Liang ZL, Huang L, Huang TZ. Observation on treating dysphagia by low-frequency electrical stimulation plus swallowing training. *Clin J Chin Med*. (2019) 11:75–7. doi: 10.3969/j.issn.1674-7860.2019.29.029

29. Mo SJ, Chen SY, Tan YH. Application of pharyngeal muscle electrical stimulation combined with direct feeding training in swallowing function rehabilitation of patients with indwelling gastric tube in stroke. *J Qilu Nurs*. (2022) 28:110–3.

30. Shi XW, Yang WL, Jie WJ. Effect of neuromuscular electrical stimulation in the treatment of neurological dysphagia after stroke. *Pract Clin J Integr Tradit Chin West Med*. (2021) 21:53–5. doi: 10.13638/j.issn.1671-4040.2021.10.024

31. Tian T, Li JR, Li SH. Observation of curative effect of low frequency electric stimulation swallowing disorder training instrument on swallowing dysfunction after stroke. *J Clin Neurol*. (2016) 29:378–80.

32. Wang JL, Ding DQ, Tan F, Wang SY, Wu HK, Huang T, et al. Clinical study of neuromuscular electrical stimulation combined with electroacupuncture in the treatment of acute cerebral infarction pharyngeal disorder. *Chongqing Med*. (2014) 43:4071–3. doi: 10.3969/j.issn.1671-8348.2014.30.030

33. Wang L. Effects of neuromuscular electrical stimulation combined with swallowing training on swallowing function and quality of life in patients with dysphagia after acute cerebral infarction. *Reflexol Rehabil Med*. (2021) 2:125–7.

34. Wang L, Ye FL. Observation on curative effects of lemone ice stimulation in combination with low frequency electrical stimulation in the treatment of SD after stroke. *West J Tradit Chin Med*. (2020) 33:131–5. doi: 10.12174/j.issn.1004-6852.2020.05.37

35. Wang XJ. Observation of the effect of neuromuscular electrical stimulation combined with swallowing function training on swallowing function and quality of survival after cerebral infarction. *Reflexol Rehabili Med*. (2021) 2:119–21, 162.

36. Wang YC, Luo L, Li P, Wen XM, Xiang T, Wu J. Effect of early comprehensive rehabilitation therapy on dysphagia in stroke patients. *Chin J Phys Med Rehabil*. (2009) 31:839–42. doi: 10.3760/cma.j.issn.0254-1424.2009.12.016

37. Wen JY, Wu GH. Effect of neuromuscular electrical stimulation therapy combined with rehabilitation exercise on the recovery of swallowing function in patients with dysphagia after cerebral infarction. *Med Theory Pract*. (2020) 33:3738–40. doi: 10.19381/j.issn.1001-7585.2020.22.017

38. Zhan Y, Liu YY, Wang SS, Xun YJ, Zhai HY, Zhang X, et al. Efficacy of neuromuscular electrical stimulation on the rehabilitation of post-stroke pharyngeal dysphagia. *Chin J Rehabil*. (2016) 31:372–4. doi: 10.3870/zgkf.2016.05.016

39. Zhang Q, Wu S, Zhou TF, Chen Y, Shi YM. Effects of synchronous neuromuscular electrical stimulation in feeding training in patients with post-stroke swallowing disorders. *Chin J Phys Med Rehabil*. (2022) 44:415–8. doi: 10.3760/cma.j.issn.0254-1424.2022.05.007

40. Zhang T, Fu Y, Yu SH. Analysis of the effect of neuromuscular electrical stimulation on dysphagia in patients with cerebral infarction. *Chin Community Doctors*. (2017) 33:152–3. doi: 10.3969/j.issn.1007-614x.2017.23.92

41. Guo YX, Zhang Y. Clinical study of the treatment for swallowing dysfunction following acute cerebral infarction by neuromuscular electrical stimulation combined with swallowing training. *Chin J Pract Intern Med*. (2019) 39:1084–7. doi: 10.19538/j.nk2019120115

42. Zheng CJ, Xia WG, Zhang YP, Hua Q, Xu T. Neuromuscular electrical stimulation combined with swallowing training for dysphagia after stroke. *Chin J Phys Med Rehabil*. (2013) 35:201–4. doi: 10.3760/cma.j.issn.0254-1424.2013.03.011

43. Zhou WZ, Wang HB, Yang SH. Efficacy of NMES therapy and swallowing training alone for dysphagia after stroke. *J Brain Nerv Dis*. (2016) 24:75–8.

44. Zhu SW, Jiang PY, Dang HM, Zhang JL, Zhu YL. Effect of neuromuscular electrical stimulation and swallowing training on dysphasia after stroke. *Chin J Rehabil Theory Pract*. (2011) 17:730–2. doi: 10.3969/j.issn.1006-9771.2011.08.010

45. Dong JZ. Efficacy of neuromuscular electrical stimulation therapy in patients with swallowing disorders after cerebral infarction. *Chin J Pract Nerv Dis*. (2017) 20:49–51. doi: 10.3969/j.issn.1673-5110.2017.10.016

46. Liu YS. Effect of neuromuscular electrical stimulation combined with swallowing rehabilitation training on post-stroke dysphagia and its effect on movement of the hyolaryngeal complex. *Chin J Gen Med*. (2017) 15:1782–5. doi: 10.16766/j.cnki.issn.1674-4152.2017.10.042

47. Wu AC, Zhang ZH. Neuromuscular electrical stimulation combined with swallowing function training for the treatment of post-stroke swallowing dysfunction. *Chin J Rehabil*. (2010) 25:453–4. doi: 10.3870/zgkf.2010.06.022

48. Xu MX, Wang Q, Meng PP, Jiang L. Electrical stimulation and swallowing training in treating post-stroke dysphagia. *Chin J Phys Med Rehabil.* (2014) 36:274–7. doi: 10.3760/cma.j.issn.0254-1424.2014.04.008

49. Deng HQ. *Study on Acute Ischemic Stroke Patients with Swallowing Disorder Treated by Early Combinational Stimulations Therapy* [Dissertation/master's thesis]. Jinan, Shandong: Taishan Medical University (2014).

50. Zhang XL. *The Study of Efficacy of Vitalstim Electrical Stimulation-swallowing Training on Dysphagia After Stroke* [Dissertation/master's thesis]. Jinan, Shandong: Taishan Medical University (2014).

51. Li LJ, Li YM, Wu XH, Wang GH, Yi XJ, Zhao YC, et al. The value of adding transcutaneous neuromuscular electrical stimulation (VitalStim) to traditional therapy for poststroke dysphagia: a randomized controlled trial. *Top Geriatr Rehabil.* (2018) 34:200–6. doi: 10.1097/TGR.0000000000000195

52. Sproson L, Pownall S, Enderby P, Freeman J. Combined electrical stimulation and exercise for swallow rehabilitation post-stroke: a pilot randomized control trial. *Int J Lang Commun Disord.* (2018) 53:405-17. doi: 10.1111/1460-6984.12359

53. Simonelli M, Ruoppolo G, Iosa M, Morone G, Fusco A, Grasso MG, et al. A stimulus for eating. The use of neuromuscular transcutaneous electrical stimulation in patients affected by severe dysphagia after subacute stroke: a pilot randomized controlled trial. *NeuroRehabilitation.* (2019) 44:103–10. doi: 10.3233/NRE-182526

54. Meng P, Zhang S, Wang Q, Wang P, Han C, Gao J, et al. The effect of surface neuromuscular electrical stimulation on patients with post-stroke dysphagia. *J Back Musculoskelet Rehabil.* (2018) 31:363–70. doi: 10.3233/BMR-170788

55. Park JS, Oh DH, Hwang NK, Lee JH. Effects of neuromuscular electrical stimulation combined with effortful swallowing on post-stroke oropharyngeal dysphagia: a randomised controlled trial. *J Oral Rehabil.* (2016) 43:426–34. doi: 10.1111/joor.12390

56. Arreola V, Ortega O, Álvarez-Berdugo D, Rofes L, Tomsen N, Cabib C, et al. Effect of transcutaneous electrical stimulation in chronic poststroke patients with oropharyngeal dysphagia: 1-year results of a randomized controlled trial. *Neurorehabil Neural Repair.* (2021) 35:778–89. doi: 10.1177/15459683211023187

57. Carnaby GD, LaGorio L, Silliman S, Crary M. Exercise-based swallowing intervention (McNeill Dysphagia Therapy) with adjunctive NMES to treat dysphagia post-stroke: a double-blind placebo-controlled trial. *J Oral Rehabil.* (2020) 47:501–10. doi: 10.1111/joor.12928

58. Huang KL, Liu TY, Huang YC, Leong CP, Lin WC, Pong YP. Functional outcome in acute stroke patients with oropharyngeal dysphagia after swallowing therapy. *J Stroke Cerebrovasc Dis.* (2014) 23:2547–53. doi: 10.1016/j.jstrokecerebrovasdis.2014.05.031

59. Lee KW, Kim SB, Lee JH, Lee SJ, Ri JW, Park JG. The effect of early neuromuscular electrical stimulation therapy in acute/subacute ischemic stroke patients with dysphagia. *Ann Rehabil Med.* (2014) 38:153–9. doi: 10.5535/arm.2014.38.2.153

60. Lim KB, Lee HJ, Yoo J, Kwon YG. Effect of low-frequency rTMS and NMES on subacute unilateral hemispheric stroke with dysphagia. *Ann Rehabil Med.* (2014) 38:592–602. doi: 10.5535/arm.2014.38.5.592

61. Zhang Q, Wu S. Effects of synchronized neuromuscular electrical stimulation (NMES) on the submental muscles during ingestion of a specified volume of soft food in patients with mild-to-moderate dysphagia following stroke. *Med Sci Monit Int Med J Exp Clin Res.* (2021) 27:e928988–1. doi: 10.12659/MSM.928988

62. Guillén-Solà A, Messagi Sartor M, Bofill Soler N, Duarte E, Barrera MC, Marco E. Respiratory muscle strength training and neuromuscular electrical stimulation in subacute dysphagic stroke patients: a randomized controlled trial. *Clin Rehabil.* (2017) 31:761–71. doi: 10.1177/0269215516652446

63. Zhang M, Tao T, Zhang ZB, Zhu X, Fan WG, Pu LJ, et al. Effectiveness of neuromuscular electrical stimulation on patients with dysphagia with medullary infarction. *Arch Phys Med Rehabil.* (2016) 97:355–62. doi: 10.1016/j.apmr.2015.10.104

64. Hamdy S, Rothwell JC, Aziz Q, Thompson DG. Organization and reorganization of human swallowing motor cortex: implications for recovery after stroke. *Clin Sci.* (2000) 99:151–7. doi: 10.1042/cs0990151

65. Hamdy S, Aziz Q, Rothwell JC, Power M, Thompson DG. Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. *Gastroenterology.* (1998) 115:1104–12. doi: 10.1016/S0016-5085(98)70081-2

66. Steele CM, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. *Dysphagia.* (2010) 25:323–33. doi: 10.1007/s00455-010-9301-5

67. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restor Neurol Neurosci.* (2007) 25:123–9.

68. Doeltgen SH, Dalrymple-Alford J, Ridding MC, Huckabee ML. Differential effects of neuromuscular electrical stimulation parameters on submental motor-evoked potentials. *Neurorehabil Neural Repair.* (2010) 24:519–27. doi: 10.1177/1545968309360417

69. Fraser C, Power M, Hamdy S, Rothwell J, Hobday D, Hollander I, et al. Driving plasticity in human adult motor cortex is associated with improved motor function after brain injury. *Neuron.* (2002) 34:831–40. doi: 10.1016/S0896-6273(02)00705-5

70. Hamdy S, Rothwell JC, Aziz Q, Singh KD, Thompson DG. Long-term reorganization of human motor cortex driven by short-term sensory stimulation. *Nat Neurosci.* (1998) 1:64–8. doi: 10.1038/264

71. Wirth R, Dziewas R, Beck AM, Clavé P, Hamdy S, Heppner HJ, et al. Oropharyngeal dysphagia in older persons–from pathophysiology to adequate intervention: a review and summary of an international expert meeting. *Clin Interv Aging.* (2016) 11:189–208. doi: 10.2147/CIA.S97481

72. Kletzien H, Russell JA, Leverson G, Connor NP. Effect of neuromuscular electrical stimulation frequency on muscles of the tongue. *Muscle Nerve.* (2018) 58:441–8. doi: 10.1002/mus.26173

73. Blumenfeld L, Hahn Y, LePage A, Leonard R, Belafsky PC. Transcutaneous electrical stimulation versus traditional dysphagia therapy: a nonconcurrent cohort study. *Otolaryngol Head Neck Surg.* (2006) 135:754–7. doi: 10.1016/j.otohns.2006.04.016

74. Ahlborn P, Schachner M, Irintchev A. One hour electrical stimulation accelerates functional recovery after femoral nerve repair. *Exp Neurol.* (2007) 208:137–44. doi: 10.1016/j.expneurol.2007.08.005

75. Haastert-Talini K, Schmitte R, Korte N, Klode D, Ratzka A, Grothe C. Electrical stimulation accelerates axonal and functional peripheral nerve regeneration across long gaps. *J Neurotrauma.* (2011) 28:661–74. doi: 10.1089/neu.2010.1637

76. Johnson AM, Connor NP. Effects of electrical stimulation on neuromuscular junction morphology in the aging rat tongue. *Muscle Nerve.* (2011) 43:203–11. doi: 10.1002/mus.21819

77. Langdon PC, Lee AH, Binns CW. High incidence of respiratory infections in 'nil by mouth' tube-fed acute ischemic stroke patients. *Neuroepidemiology.* (2009) 32:107–13. doi: 10.1159/000177036

78. Ishida R, Palmer JB, Hiiemae KM. Hyoid motion during swallowing: factors affecting forward and upward displacement. *Dysphagia.* (2002) 17:262–72. doi: 10.1007/s00455-002-0064-5

79. Kim Y, McCullough GH. Maximum hyoid displacement in normal swallowing. *Dysphagia.* (2008) 23:274–9. doi: 10.1007/s00455-007-9135-y

80. Paik NJ, Kim SJ, Lee HJ, Jeon JY, Lim JY, Han TR. Movement of the hyoid bone and the epiglottis during swallowing in patients with dysphagia from different etiologies. *J Electromyogr Kinesiol.* (2008) 18:329–35. doi: 10.1016/j.jelekin.2006.09.011

81. Ueda N, Nohara K, Kotani Y, Tanaka N, Okuno K, Sakai T. Effects of the bolus volume on hyoid movements in normal individuals. *J Oral Rehabil.* (2013) 40:491–9. doi: 10.1111/joor.12060

82. van der Kruis JG, Baijens LW, Speyer R, Zwijnenberg I. Biomechanical analysis of hyoid bone displacement in videofluoroscopy: a systematic review of intervention effects. *Dysphagia.* (2011) 26:171–82. doi: 10.1007/s00455-010-9318-9

83. Byeon H. Combined effects of NMES and Mendelsohn maneuver on the swallowing function and swallowing–Quality of life of patients with stroke-induced sub-acute swallowing disorders. *Biomedicines.* (2020) 8:12. doi: 10.3390/biomedicines8010012

84. Oh DH, Park JS, Kim WJ. Effect of neuromuscular electrical stimulation on lip strength and closure function in patients with dysphagia after stroke. *J Phys Ther Sci.* (2017) 29:1974–5. doi: 10.1589/jpts.29.1974

85. Lee KW, Kim SB, Lee JH, Lee SJ, Park JG, Jang KW. Effects of neuromuscular electrical stimulation for masseter muscle on oral dysfunction after stroke. *Ann Rehabil Med.* (2019) 43:11–8. doi: 10.5535/arm.2019.43.1.11

86. Grill WM, Mortimer JT. The effect of stimulus pulse duration on selectivity of neural stimulation. *IEEE Trans Biomed Eng.* (1996) 43:161–6. doi: 10.1109/10.481985

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Evidence-based management and motor rehabilitation of cerebral palsy children and adolescents: a systematic review

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Background: Evidence regarding the management of several aspects of cerebral palsy improved in recent years. Still, discrepancies are reported in clinical practice. Italian professionals and stakeholders expressed the need of setting up updated, evidenced-based, shared statements, to address clinical practice in cerebral palsy rehabilitation. The objective of the present study was to provide an updated overview of the state of knowledge, regarding the management and motor rehabilitation of children and young people with cerebral palsy, as the framework to develop evidence-based recommendations on this topic.

Methods: Guidelines and systematic reviews were searched, relative to evidence-based management and motor treatment, aimed at improving gross motor and manual function and activities, in subjects with cerebral palsy, aged 2–18 years. A systematic search according to the Patients Intervention Control Outcome framework was executed on multiple sites. Independent evaluators provided selection and quality assessment of the studies and extraction of data.

Results: Four guidelines, 43 systematic reviews, and three primary studies were included. Agreement among guidelines was reported relative to the general requirements of management and motor treatment. Considering the subject's multidimensional profile, age and developmentally appropriate activities were recommended to set individual goals and interventions. Only a few approaches were supported by high-level evidence (i.e., bimanual therapy and constraint-induced movement therapy to enhance manual performance). Several task-specific active approaches, to improve gross motor function and gait, were reported (mobility and gait training, cycling, backward gait, and treadmill), based on low-level evidence. Increasing daily physical activity and countering sedentary behavior were advised. Based on the available evidence, non-invasive brain stimulation, virtual reality, action-observation therapy, hydrotherapy, and hippotherapy might be complementary to task or goal-oriented physical therapy programs.

Conclusion: A multiple-disciplinary family-centered evidence-based management is recommended. All motor rehabilitation approaches to minors affected by cerebral palsy must share the following fundamental characteristics: engaging active involvement of the subject, individualized, age and developmentally appropriate, goal-directed, skill-based, and preferably intensive and time-limited, but suitable for the needs and preferences of the child or young person and their family, and feasible considering the implications for themselves and possible contextual limitations.

KEYWORDS

cerebral palsy, rehabilitation, physical therapy modalities, occupational therapy, patient participation, learning, exercise, play and playthings

1. Introduction

Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; epilepsy; and secondary musculoskeletal problems (1). It is the most common motor disability in childhood, affecting 2–2.5 per 1,000 live births (2). Although in CP the causative brain damage is static, the secondary musculoskeletal problems and motor manifestations change over time. Pathological movements and postures manifest during infancy or early childhood, and secondary disability may be progressive and may involve different aspects of the subject's life. Therefore, several specialists and experts are involved in the management of cerebral palsy, and their engagement may change over time. Recommendations were published in the past predominantly covering specific aspects (e.g., botulinum injections and osteoporosis management), then national institutes started promoting clinical practice guidelines, to orient clinical choices and health policies. Italian guidelines for CP were first published in 2005 (3) and then revised in 2012–2014 (4). They provided a comprehensive approach to the complexity of the child's disability profile. Nonetheless, general criteria were reported to guide and coordinate professionals, without specifying proven effective interventions. Evidence regarding the rehabilitation of several aspects of cerebral palsy dramatically improved in recent years. Still, discrepancies are reported in clinical practice, partially due to organizational characteristics and resources of service providers. Guidelines must define what is currently regarded as a safe and appropriate approach. Therefore, Italian stakeholders expressed the need of setting up updated, evidenced-based, shared statements, to address clinical practice in CP rehabilitation. The objective of the present study was to provide an updated overview of the state of knowledge, regarding the management and motor rehabilitation of children and young people with CP, as a framework to develop evidence-based recommendations on this topic.

Abbreviations: AGREE, Appraisal of Guidelines Research and Evaluation; AHA, Assistive Hand Assessment; AMSTAR, Assessing the Methodological Quality of Systematic Reviews; AOT, Action observation therapy; BBS, Berg Balance Scale; BBT, Box and Block test; CFCS, Communicative Function Classification System; CIMT, Constraint-induced movement therapy; CNS, Central nervous system; COPM, Canadian Occupational Performance Measure; CP, Cerebral palsy; CPG(s), Clinical practice guideline(s); CPT, Conventional Physical Therapy; DF, Dorsiflexion; EDACS, Eating and Drinking Function Classification System; FES, Functional electric stimulation; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HABIT, Hand–Arm Bimanual Intensive Therapy; HABIT-ILE, Hand and Arm Bimanual Intensive Training Including Lower Extremity; HAS Haute Autorité de Santé; JBI, Joanna Briggs Institute; JTHFT, Jebsen-Taylor Hand Function Test; MACS, Manual Ability Classification System; MAS, Modified Ashworth Scale; MUUL, Melbourne Assessment of Unilateral Upper Limb function; NDT, Neurodevelopmental treatment; NIBS, Non-invasive brain stimulation; NICE, National Institute for Health and Care Excellence; NMES, Neuromuscular electrical stimulation; NSCA, National Strength and Conditioning Association; NSW, New South Wales; NWT, Nintendo WII Balance; PBS, Pediatric Balance Scale; PEDI, Pediatric Evaluation of Disability Inventory; PICO, Patients, intervention, control, outcome; PROM, Passive range of motion; QUEST, Quality of Upper Extremity Skills Test; RAS, Rhythmic auditory stimulation; RCT, Randomized controlled trial; rTMS, Repetitive transcranial magnetic stimulation; SR(s), Systematic review(s); tDCS, Transcranial direct current stimulation; VFCS, Visual Function Classification System; VR, Virtual reality.

2. Materials and methods

2.1. Search and selection

The scope of the systematic review was structured in research questions, according to the Patients, Intervention, Control, and Outcome (PICO) framework. The following queries were considered:

1. Which are the general principles to provide comprehensive management of CP subjects under the age of 18 years?
2. Which are the most effective motor rehabilitation approaches to improve gross motor or upper limb performance, in CP subjects aged 2–18 years?

Query 2 was deliberately maintained inclusive, rather than providing separated queries for gross motor or manual functions and activities because several studies involved both aspects as outcomes.

Available evidence on each question was systematically enquired. Search and selection procedures are described in the Supplementary material 1.

Clinical practice guidelines (CPGs) were first searched, relative to CP management and rehabilitation. In case of missing or incomplete evidence, to answer the identified queries, the search was extended to systematic reviews (SRs). Screening and selection were independently executed by two evaluators (SG and SS), by first assessing titles and abstracts and then full texts. Any discrepancies among the evaluators were resolved through discussion. A few studies were included from manual search, relative to uncovered topics.

2.2. Quality assessment

Two evaluators for each study independently provided the quality assessment of the included documents (SF, SG, SP, and SS). Any discrepancy among the evaluators was resolved through discussion. CPGs were assessed using the Appraisal of Guidelines Research and Evaluation (AGREE) 2 tool (5). Three qualitative levels were identified based on the AGREE 2 scores: "high", "moderate", and "low" (6). SRs were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 tool (7). While computing the total score, the reviewers agreed in considering "yes partially" as "yes" and item 11 (relative to the meta-analysis) as a non-critical item, because just a minority of studies included a meta-analysis. GRADE's (Grading of Recommendations, Assessment, Development, and Evaluation) evidence profiles were implemented including the few meta-analyses available (8, 9). Observational primary studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for case series (10).

2.3. Data extraction

All authors, in numbers of two for each study, independently provided data extraction, resolving any discrepancy through discussion. Recommendations relevant to the queries were extracted from each selected CPG and reported verbatim. Relevant contents were extracted from the included SRs: population (type of CP and age), characteristics of the intervention, outcome measures, and conclusion of the authors about the effectiveness with adverse events whenever reported. In most cases, studies presented mixed neuromotor treatments, addressing manual or gross motor performances and mixed outcome measures. The extracted contents were synthetized and ordered considering first the essential requirements shared by the child-focused therapies, then considering the individual approaches and addressing manual or gross motor function and activities.

3. Results

Based on the search on organizational websites, four CPGs were found: two from the National Institute for Health and Care Excellence (NICE) site (11, 12) and one from the New South Wales (NSW) Ministry of Health site (13), which were included concerning both queries; one report from Haute Autorité de Santé (HAS) site (14) was excluded because only general information was given, irrelevant with respect to the queries.

Concerning the Pubmed search for CPGs, a first selection, based on title and abstract, excluded 363 studies as non-pertinent. Seven were selected and examined on full text, with the exclusion of five as non-pertinent relative to the intervention (15–19). Shaunak et al. (20) reported about NICE CPG, without reporting any further information: therefore, it was finally excluded. Only one CPG by Castelli et al. (4) was finally selected.

In total, four CPGs were included. They provided exhaustive information relative to query 1. Nonetheless, three primary studies were manually retrieved and included (21–23) to disclose the reference developmental trajectories relative to the functional classifications recommended by the CPGs. Figure 1 represents the PRISMA flowchart relative to Query 1.

Based on the search on databases for query 2, a total of 145 SRs were retrieved, and after the removal of 21 duplicates, SRs were screened: 65 were excluded on abstracts, three were not retrieved as full text, and 15 were excluded on full text (24–38). Further two SRs were considered from individual search (39, 40). Therefore, 43 SRs (39–81) were finally included, concerning query 2. Figure 2 represents the PRISMA flowchart relative to Query 2.

The quality and risk of bias analysis of included studies are represented in Table 1 for CPGs, Table 2 for observational studies, and Supplementary Table 3 for SRs.

3.1. Evidence synthesis relative to query 1

Evidence synthesis concerning query 1 is reported in Supplementary Table 4.

NICE CPG (12) recommended providing a management program developed and implemented in partnership with the child or young person and their parents or careers, individualized and goal-focused. Considering the impact on the individual child or young person and their family was advised. Assessments and goals should be identified, as age and developmentally appropriate, in agreement with the subjects and their parents or careers, focusing on the following domains of the World Health Organization's International Classification of Functioning, Disability, and Health: body functions and structures, activities and participation, environmental factors. The physical therapy (physiotherapy and/or occupational therapy) program had to be tailored to the child or young person's individual needs and aimed at specific goals, such as: enhancing skill development, function, and ability to participate in everyday activities; and preventing consequences such as pain or contractures. The likelihood of achieving the treatment goals, possible difficulties in implementing the program, and implications for the person and their careers had to be considered. Moreover, the CPG recommended reassessing the

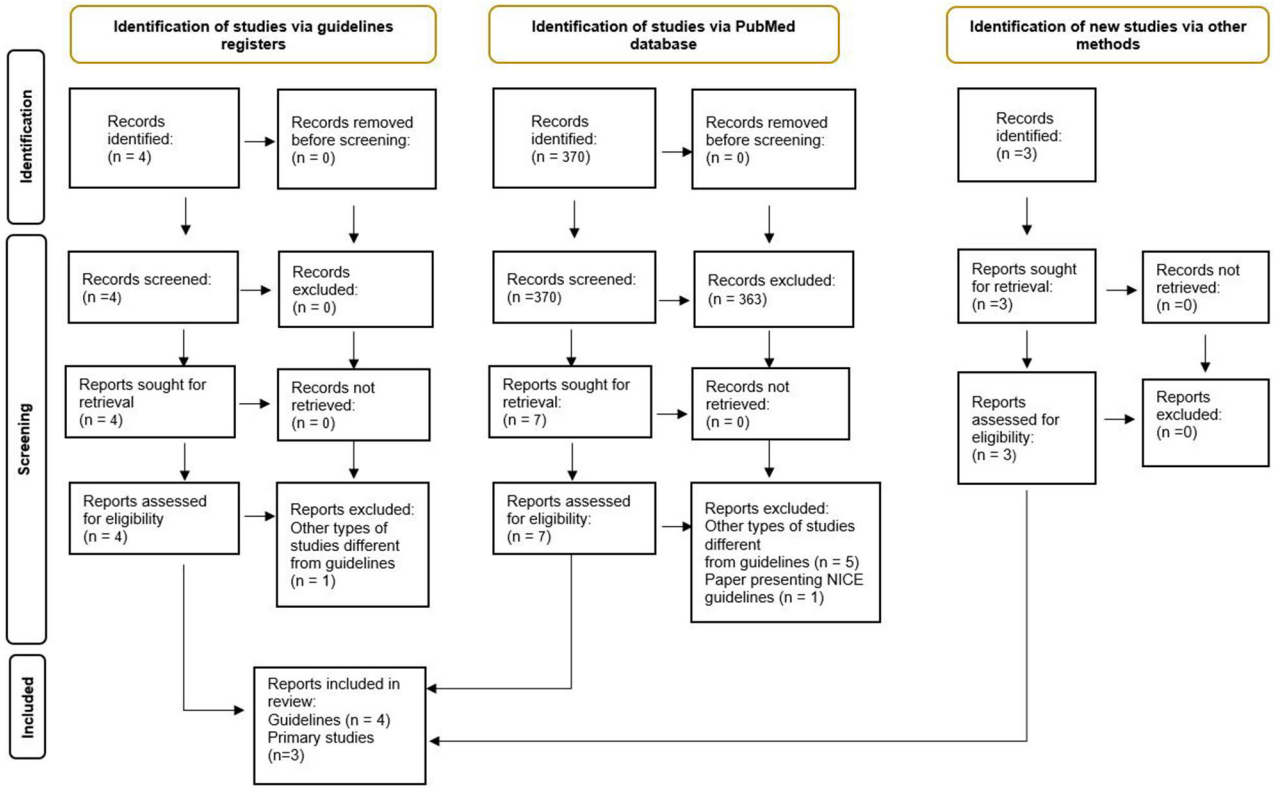

FIGURE 1
PRISMA flow diagram relative to query 1.

physical therapy program at regular intervals to ensure the goals are achieved and the program remains appropriate to the child or young person's needs. Finally, ensuring access to adults' services nearby, with expertise in managing cerebral palsy, was reported as a minimum standard of care (11).

The Australian CPG (13) outlined the need to develop individually tailored treatment plans and to provide a multiple-disciplinary team approach (whether in a format of multidisciplinary, interdisciplinary, or transdisciplinary). This was supposed to be locally implemented whenever possible or seeking multidisciplinary support from tertiary institutions or specialist services, to facilitate the provision of a holistic approach. The team was recommended to include all professionals involved in the child's care, as well as the teachers. Australian CPG (13) advocated particular attention to times of transition, with early forward planning to be essential for positive outcomes. Finally, the authors recommended using functional motor ability classification scales to guide assessment, goal setting, and intervention:

- Gross Motor Function Classification System (GMFCS) for the posture-kinetic organization (82).
- Manual Ability Classification System (MACS) relative to praxis manual function (83).
- Communicative Function Classification System (CFCS) for communicative skills (84).
- Eating and Drinking Function Classification System (EDACS) relative to feeding (85).
- Visual Function Classification System (VFCS) concerning visual impairment (86).

Previous Italian recommendations (4) described rehabilitation as a complex process focusing on the person in all his/her dimensions, physical, mental, emotional, communicative, and relational (holistic approach), and involving the child's family and social and environmental context (ecological approach). Interventions were supposed to be tailored based on the patient's profile, considering his/her functioning in the area of autonomic control, personal autonomy, locomotion, manipulation and praxis, sensation/perception, cognition, communication, and relationships; the architecture of the main functions (activities/abilities); and age and developmentally appropriate goals. While assessing the patient, the authors recommended taking into account not only the single functional area involved but also its relationship with the other areas, to be able to define the overall level of development attained and the reciprocal impact between areas. It was considered important to provide not just a mere description of the skills (i.e., present, absent, or emerging) but also to state whether and in what way the child implemented adaptive, compensatory, or additional strategies, not least because these could serve as a crucial guide for the proposed therapy.

Considering the recommendation by the Australian CPG (13) to refer to functional classifications, the authors agreed on the relevance of integrating with the developmental curves based on the cited classifications. They appeared particularly important to focus

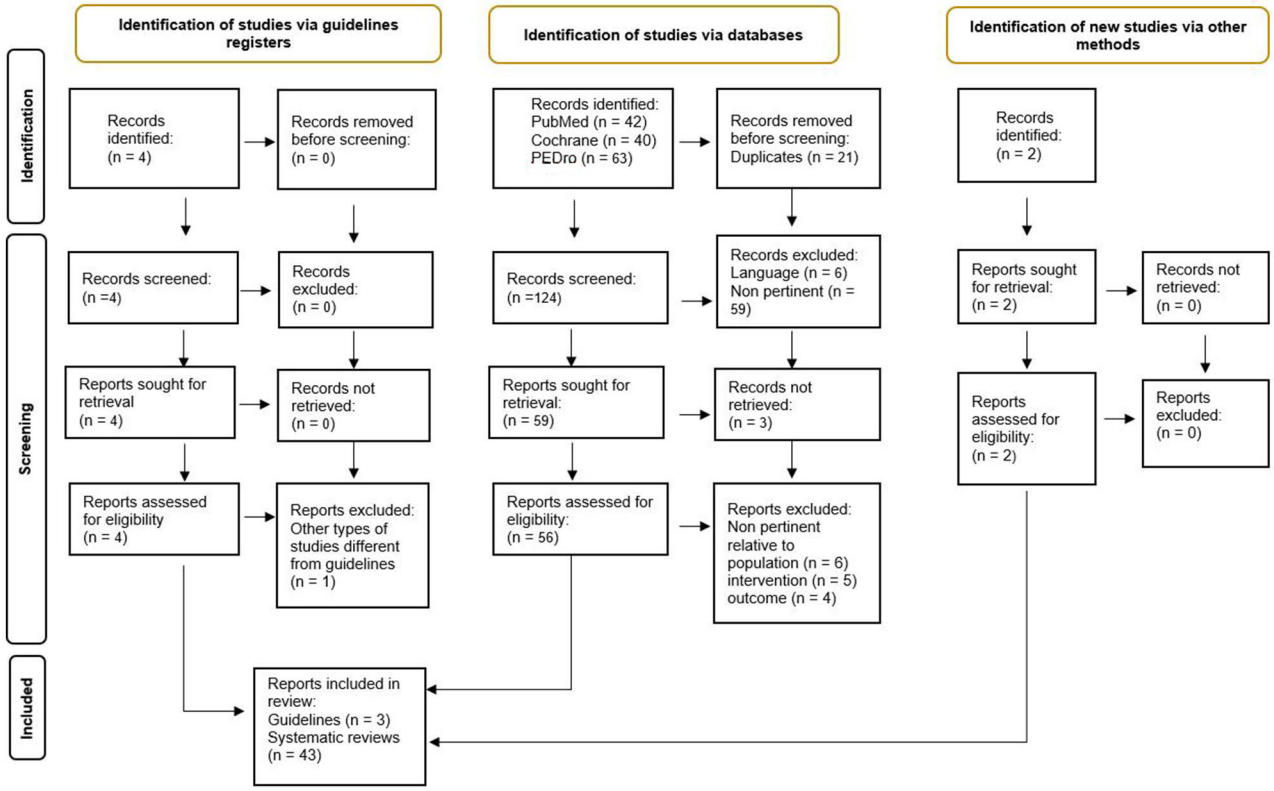

FIGURE 2
PRISMA flow diagram relative to query 2.

on the critical periods and to define the limits of rehabilitation. Rosenbaum et al. (21) reported the gross motor development curves of 657 uni- and bilateral CPs, of mixed subtypes, describing average development predicted by the Gross Motor Classification System. The age range was 1–13 years at first assessment and the follow-up lasted 4 years. Higher ability levels reached their limit of development in a longer period than lower ability levels, though all levels reached their developmental limit by the age of 7 years.

Klevberg et al. (22) described the bimanual performance of 60 unilateral and 42 bilateral CP of mixed subtypes, MACS I–III. The mean age at the first assessment was 25 months for unilateral and 35 months for bilateral CP. The mean follow-up was 4.5 months. Children with bilateral CP seemed to reach their developmental limits around 30 months of age, regardless of MACS level, and to change their performance over time to a smaller extent than those with unilateral CP.

Eliasson et al. (23) confirmed that the Assistive Hand Assessment (AHA) score at 18 months together with the MACS levels resulted in the prediction of future development, based on data from 171 unilateral spastic CP, with an age range of 18 months—18 years and mean follow-up of 8 years. Children classified as having higher ability (MACS level I) had both a higher rate and limit of development and a shorter period of development than those having a lower ability (MACS level II). Children functioning in MACS level III had the lowest limit, and development occurred for the longest time. The stable performance lasted throughout adolescence for participants in all MACS levels, from approximately 7 years. Nonetheless, on an individual level, a large variation in development was seen; therefore, regular follow-up for children in all MACS levels was recommended.

3.2. Evidence synthesis relative to query 2

Evidence synthesis concerning query 2 is reported in Supplementary Table 5.

Considering the few meta-analysis available, separate evidence profiles were implemented for the following outcome: gross motor function measured by Gross Motor Function Measure (GMFM) and gait speed; balance measured by Pediatric Balance Scale (PBS), Berg Balance Scale (BBS), or mixed outcome measures; and upper limb performance by AHA, Melbourne assessment of Unilateral Upper Limb function (MUUL), ABILHAND-Kids, or mixed outcome measures (Supplementary Tables 6A–D). The evidence level according to GRADE was overall at low to very low.

Most studies were systematic reviews, without meta-analysis, considering mixed outcome measures and in many cases also mixed characteristics concerning population and treatments. Therefore, a statistical synthesis was not feasible, and a description of the main contents is provided below and in Supplementary Table 5.

TABLE 1 Quality assessment through AGREE II of included guidelines.

AGREE II									
References	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	TOT	Quality*
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence		
Spasticity in under 19s: management National Institute for Health and Care Excellence *(NICE guidelines, 2012-2016)*	97.92%	91.67%	97.92%	97.22%	93.75%	87.50%	95.29%	High quality
Managing cerebral palsy in under 25s *(NICE guidelines, 2021)*	100%	91.67%	98.96%	77.78%	83.33%	87.50%	91.67%	High quality
Management Of Cerebral Palsy In Children: A Guide For Allied Health Professionals *(NSW Ministry of Health guidelines, 2018)*	100%	94.44%	86.46%	97.22%	87.50%	87.50%	90.94%	High quality
SIMFER-SINPIA Intersociety Commission. Recommendations for the rehabilitation of children with cerebral palsy *(Eur J Phys Rehabil Med, 2016)*	91.67%	80.56%	28.13%	58.33%	18.75%	45.83%	47.10%	Low quality

*High quality, CPGs that scored ≥60% in at least three of six AGREE II domains, including Domain 3; Moderate quality, CPGs with three AGREE II domains assessed a score of ≥60%, except Domain 3; Low quality, CPGs that scored <60% in two or more domains and scored <50% in Domain 3.

3.2.1. Child-focused therapy (goal and task-oriented training) and context-focused therapy

CPGs and SRs agreed in recommending child or context-focused approaches: distinctive features, with time-related references, were discussed.

As previously reported, NICE CPG (12) recommended setting individually tailored goals and interventions, considering age and developmentally appropriate activities, preferences, and impact on the child or young person and their careers. Task-focused active-use therapy, such as constraint-induced movement therapy followed by bimanual therapy, was recommended, to enhance manual skills. An intensive program over a short time (for example, 4–8 weeks) was considered preferable.

The Australian CPG (13) recommended both goal-directed and context-focused therapy to improve function. The first required goals to be age and developmentally appropriate and child-focused to increase motivation. The task should then be analyzed, considering the child's skills as well as environmental limitations, to identify the goal-limiting factor(s). The intervention should be structured and involve repetitive practice, appropriate adaptations to the task or the environment, and outcomes evaluated using validated tools. The context-focused therapy consisted of changing the task or the environment (but not the underlying body structure and function of the child) to promote successful task performance.

Jackman et al. (41) analyzed 74 randomized controlled trials (RCTs) or quasi-RCT, involving CP or high-risk CP subjects, aged 0–18 years. Authors examined the effectiveness of several types of active interventions, classified as "goal-directed", "functional or part-task", or "non-functional". Outcome measures were AHA and Canadian Occupational Performance Measure (COPM). Differently from non-functional approaches, both goal-directed and functional training were presented as effective, but a difference in the "dose" of practice was reported. Interventions that set functional goals and involved the actual practice of those goals led to goal achievement at a lower dose than general upper limb motor training. According to the authors, children were likely to achieve individual goals, if they had set their own goals and had practiced those goals for more than 14 to 25 h, combining face-to-face therapy with home practice. To improve motor ability, a higher dose of practice was needed, likely 30 to 40 h of practice. Moreover, where the outcome was measured on the AHA, logistic regression showed that children under 8 years of age were two times more likely to succeed. On the COPM, results were similar regardless of age, although children over 8 years were 1.46 times more likely to succeed.

Novak et al. (42) updated the previous SR (87) which included five RCTs, with one SR, involving CP subjects of 4–18 years of age, at GMFCS levels I–III. The authors confirmed the effectiveness of goal-oriented training in improving goal achievement of functional tasks involving gross motor, hand function, and self-care. Relative to task-oriented training, the authors included in the analysis only two small RCTs (GMFCS levels I–III, age 4–18 years) that conferred improved gross motor skills compared to control non-task-based therapy. Finally, based on three RCTs (GMFCS levels I–IV, 11 months−4 years), the authors reported no between-group differences for context-focused vs. child-focused to improve

TABLE 2 Quality assessment of included primary studies through JBI critical appraisal checklist for case series.

Primary studies	Items										Quality
	1	2	3	4	5	6	7	8	9	10	
Rosenbaum et al. (21)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Klevberg et al. (22)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Eliasson et al. (23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

self-care. Therefore, they recommended using both approaches simultaneously and letting the family select the preferred one.

Inamdar et al. (43) examined 12 RCTs, involving uni-bilateral CP, at GMFCS levels I–V, and the age range of 18 months–puberty. They concluded that task-specific, intensive, and child-initiated intervention components showed promise for improving sitting in young infants at risk for CP. And components of impairment remediation combined with functional balance training should be explored to improve sitting in children diagnosed with CP.

Hsu et al. (44) included 13 RCTs (GMFCS levels I–III, 1–17 years). The meta-regression analysis revealed that the improvement in GMFM scores was positively associated with the number of daily training hours and program duration.

Das et al. (45) based on 34 SRs, involving mostly hemiplegic CP (0–18 years), confirmed the effectiveness of intensive activity-based, goal-directed interventions. Conversely, the ability of manual stretching to increase the range of motion and reduce spasticity was limited.

3.2.2. Bimanual therapy and hand-arm bimanual intensive therapy

NICE CPG (12) simply recommended considering task-focused active-use therapy, such as constraint-induced movement therapy (CIMT, temporary restraint of an unaffected arm to encourage use of the other arm) followed by bimanual therapy (unrestrained use of both arms) to enhance manual skills.

The Australian CPG (13) recommended bimanual training as an increased opportunity to practice bilateral activities to improve the use of both hands during activity. Bimanual training should provide practicing the specific task or goal, or parts of the task, rather than focusing on the underlying body structure and functional deficits. The best candidates for bimanual training were considered to be older than 12 months, have spontaneous use of affected hand and selective motor control, have basic skills such as grasp and hold, and have the cognitive skills to respond to cues. The effectiveness of bimanual therapy was equal to that of CIMT when the same amount of therapy was provided.

Alahmari et al. (46) considered four RCTs, about bimanual therapy (duration of intervention 60–90 h for 2–4 weeks) in hemiplegic subjects. A meta-analysis on the efficacy (measured using the Jebsen-Taylor Hand Function Test—JTHFT) of HABIT vs. CIMT or structured and unstructured bimanual therapies was conducted: HABIT showed a trivial effect compared to the other interventions, with an effect size of 0.06. Both groups performed functional tasks improving hand function within enjoyable and playful activities.

Ouyang et al. (47) included a SR of 11 RCTs, one quasi-RCT, one retrospective, and two longitudinal studies. The treatments were individualized training, group-based training, or both, mostly in daily camp settings, for hemiplegic subjects aged 3–18 years. The outcome measures were mixed: AHA, JTHFT, Quality of Upper Extremity Skills Test (QUEST), ABILHAND-Kids, Box and Block test (BBT), COPM, and Pediatric Evaluation of Disability Inventory (PEDI). HABIT in the form of 6 h a day for 3 consecutive weeks (totaling 90 h) led to the improvement of bimanual ability, unilateral dexterity, self-care function, and functional goals, and the improvements were mostly maintained during the follow-up period (duration not specified).

Novak et al. (42), based on three RCTs in hemiplegic children aged 2–10 years, reported that CIMT (total duration of intervention 90 hours) was equally effective for improving bimanual performance and unimanual capacity as dose-matched occupational therapy or HABIT (bimanual training). Then, recommended using both approaches and selecting one according to the family's preferences.

3.2.3. Constraint-induced movement therapy

NICE CPG (12), as previously reported, recommended combining CIMT and bimanual therapy into an intensive program over a short time (for example, 4–8 weeks), to enhance manual skills.

The Australian CPG (13) reported that the modified model of CIMT (mCIMT) involving the use of slings, mitts, and splints for up to 2 h a day, but for a longer overall duration, was as effective as traditional CIMT (restraint applied for most of the waking day). Modified CIMT was recommended with an age-dependent model: shorter periods of daily practice at home and/or preschool over an 8–10-week period, under the age of 4 years; and intensive 2–3-week camps or group-based intervention, over 4 years of age. The CPG declared that higher intensity did not always bring better outcomes and CIMT did not result in age-dependent outcomes, although children with poorer hand function tended to make greater improvements.

Hoare et al. (48) conducted a SR with meta-analysis including 36 RCTs, in unilateral CP subjects with a mean age of 5.96 years (3 months−19.8 years). The most common constraint devices were a mitt/glove or a sling (11 studies each); the frequency was 2–7 days/week and the duration of intervention sessions was 0.5–8 h per day, for 1–10 weeks. The mixed outcome measures are as follows: AHA, QUEST, MUUL, BBT, and ABILHAND-Kids. CIMT appeared no more effective than another upper-limb therapy that was carried out intensively (most comparisons were with intensive

bimanual therapist-led interventions). CIMT did not appear to impact body structure and function outcomes, such as grip strength, muscle stiffness, and spasticity. It had no consistent effect on quality of life and there was minimal research on participation outcomes. Two key ingredients across all models of CIMT were maintained: (1) restraint of the well-functioning upper limb (irrespective of device/type); and (2) intensive, structured training (irrespective of type). CIMT appeared to be a safe intervention for children with unilateral CP. The authors were not able to identify the characteristics of children who could be advised to participate in one or the other of CIMT or bimanual interventions. Therefore, they recommended to choose considering the developmental needs, child and family characteristics and preferences, therapist expertise, costs of implementing the intervention, funding and service delivery models, and resource availability.

Novak et al. (42) reported data from two SRs including hemiplegic children aged 3 months−19 years. The authors recommended CIMT to improve bimanual performance, unimanual capacity, activity, and participation in hemiplegic CP. CIMT conferred better activity and participation gains than no therapy, with large effect sizes, but it was equally effective to dose-matched occupational therapy.

Finally, also the SR by Das et al. (45), involving mostly hemiplegic patients, aged 0–18 years, confirmed the use of CIMT to improve upper-extremity functioning.

3.2.4. Home programs

NICE CPG (12) recommended considering the following items when deciding who should deliver physical therapy:

- whether the child or young person and their parents or careers were able to deliver the specific therapy.
- what training the child or young person, or their parents or careers might need.
- the wishes of the child or young person and their parents or careers.

The Australian CPG (13) recommended home programs aimed at improving the performance of functional activities when based on the following five-step model:

- Establish collaborative relationships between parents and therapist.
- Set mutually agreed upon family and child goals.
- Select therapeutic activities that focus on achieving family and child goals, supported by the best available evidence.
- Support implementation of the home program through parent education, home visits, and program updates to sustain motivation.
- Evaluate outcomes.

The use of appropriate outcome measures for evaluation was recommended. The authors concluded that there was insufficient evidence to support the use of home programs aimed at improving participation.

Beckers et al. (49) reviewed 26 RCTs and four single-subject studies, involving uni/bilateral CP subjects, aged 4 months−19 years, at GMFCS levels I–V. The authors reported that no conclusions could be drawn due to the large variability in the study, patient and intervention characteristics, comparators, and outcome measures used in the included studies. Even within the same treatment approach, the frequency and duration of the interventions varied. Training intensity confirmed to be an important predictor of treatment success.

Novak et al. (42) based on two RCTs (GMFCS I–V, age 4–13 years) reported that home programs conferred improved function compared to no therapy and were an effective way to increase the dose of therapy.

3.2.5. Action observation therapy

No recommendation was available on this topic in the included CPGs.

Abdelhaleem et al. (50) conducted a SR with meta-analysis, including 12 RCTs, with uni-bilateral CP subjects aged 5–15 years. No evidence of benefit had been found to draw a firm conclusion regarding the effectiveness of AOT, due to limitations in methodological quality and variations between studies.

The SR by Alamer et al. (51) included nine RCTs, with hemiplegic subjects aged 3–12 years, at GMFCS levels I–IV. The authors suggested that AOT is more effective than simple motor training, to improve physical function and structure, activities, and participation. However, the authors recalled particular attention when applying AOT for CP children with severe motor and cognitive impairment, and recommended further studies to determine the optimal frequency, intensity, and time of AOT.

The SR by Novak et al. (42) included only two RCTs, with ambulatory spastic unilateral CP subjects aged 5–15 years. The duration of intervention was 1 h a day for 15 days−3 weeks. Upper limb action observation training conferred better bimanual performance compared to watching videos but with a small effect size.

3.2.6. Hand and arm bimanual intensive training including lower extremity

No recommendations were found on this topic. Only one SR by Novak et al. (42) was available on databases, including two RCTs, with uni-bilateral CP subjects aged 6–16 years, at GMFCS levels I–IV. The intervention lasted 90 h and was in a camp setting. The authors reported low evidence of improved motor function in both lower and upper limbs, compared to usual care.

3.2.7. Adapted physical therapy and physical activity

An adapted physical therapy program was recommended by NICE CPG (12), following treatment with botulinum toxin type A, continuous pump-administered intrathecal baclofen, orthopedic surgery, or selective dorsal rhizotomy. Furthermore, the authors recommended considering muscle-strengthening therapy where the assessment indicated that muscle weakness was contributing to the loss of function or postural difficulties, using progressive repetitive exercises performed against resistance.

The Australian CPG (13) promoted gait training, defining it as the process of first learning or re-learning how to walk, after

an intervention such as orthopedic surgery. It could be achieved in several ways, but repetition of the actual motions/gait pattern performed during walking was reported as the most important factor. Depending on the severity of the person's impairment, one or more physiotherapists, parallel bars, and high- or low-support assistive mobility devices might be involved to facilitate the gait pattern. Furthermore, the authors stated that strength-training in the lower limbs could be an accepted intervention for children with cerebral palsy, despite the lack of evidence regarding the effects on activity and participation. No adverse increase in spasticity was reported. The authors suggested setting the strengthening programs relying on the guidelines published by The American Academy of Pediatrics and the National Strength and Conditioning Association (NSCA), and complying with the following requirements:

- To perform a small number of repetitions until fatigue.
- To allow sufficient rest between exercises for recovery.
- Not to be performed frequently or for long durations.
- To increase the resistance as the ability to generate force increases.

The strength training should be combined with other activity-based programs such as treadmill training or cycling, involving other aspects of function such as endurance and coordination. Finally, the Australian CPG (13) recommended fitness training, defined as "planned structured activities involving repeated movement of skeletal muscles that result in energy expenditure to improve or maintain levels of physical fitness". Aerobic fitness training provided short-term benefits for clients with sufficient motor skills to be able to undertake training, which was not maintained when training stopped. The frequency and intensity of interventions varied across the literature and generally focused on structured moderate to vigorous exercise. Attention was shifted recognizing the importance of reducing sedentary behavior and encouraging light-intensity activities throughout the day. It was recommended that fitness training to improve aerobic fitness, muscle strength, and the general health of children with cerebral palsy should be integrated into the child's daily life on an ongoing basis.

The SR by Corsi et al. (52) included 13 RCTs about gait or strength training, with uni-bilateral CP subjects, aged 7–18 years, at GMFCS levels I–III. Vibratory platform, gait training, electrical stimulation, and transcranial stimulation were effective to improve spatiotemporal gait parameters, especially velocity. Conversely, isolated strength training was not effective to improve gait parameters in CP.

Liang et al. (53) conducted a SR and meta-analysis, including 27 RCTs, in uni-bilateral CP, at GMFCS levels I–III, with a mean age of 1.8–16 years. Exercise interventions (resistance or aerobic or mixed training) showed beneficial effects on gait speed and muscle strength, but no significant effect on gross motor function in children with CP.

Merino-Andres et al. (54) conducted a SR with meta-analysis, including 27 RCTs [most studies had been analyzed also by Ryan et al. (60)]. Uni-bilateral CP subjects involved were aged 3–22 years, at GMFCS levels I–IV. The authors reported improvements after strength training programs, compared to other physical therapy techniques or untreated control groups, for muscle strength at the knee flexors, at the knee extensors, at the plantar flexors, maximum resistance, balance, gait speed, GMFM (global, D and E dimension), and spasticity.

Bania et al. (55) conducted a SR and meta-analysis including nine RCTs, with CP subjects aged 2–18 years (most were over 6 years), at GMFCS levels I–III. Activity training on the ground (whole-body self-initiated activities such as sitting, turning, sit-to-stand, walking, stepping, stair climbing, or other similar activities people use to transfer independently or with handheld support at home or outdoor settings) compared to no treatment or usual treatment (Neurodevelopmental treatment—NDT—or strengthening) showed no statistically significant difference.

The SR and meta-analysis by Armstrong et al. (56) about cycling, analyzed five RCTs, one quasi-RCT, one comparison trial, one pre-post study with a control group, and one single-group study with a control period. Uni-bilateral CP subjects at GMFCS levels I–V, mean age 10.4 years (SD 2.3), were involved. The authors concluded that cycling could improve aerobic fitness, muscle strength, balance, and gross motor function in children with CP; however, evidence was limited by small sample sizes, inconsistent outcome measures, and a lack of follow-up testing.

The SR by Lopez et al. (57) enquired about dance and Rhythmic Auditory Stimulation (RAS), selecting one case study, 10 clinical trials (three RCTs), and three pilot studies, involving either children or adults. The authors reported a positive impact on body functions, emotional expression, social participation, and attitudinal change as areas for consideration in future research. Nonetheless, the level of evidence was very low.

Das et al. (45) analyzed 34 SRs, involving mostly hemiplegic subjects aged 0–18 years. Intensive activity-based, goal-directed interventions resulted to be more effective than passive non-functional approaches, such as manual stretching, whose ability to increase range of motion and reduce spasticity was limited.

Collado-Garrido et al. (58) conducted a SR including 12 RCTs and three non-RCTs, with uni-bilateral CP subjects aged 4–18 years, at GMFCS levels I–V. The authors reported a statistically significant positive effect on muscle strength and motor function following resistance therapy, though they also declared limitations due to publication bias.

The SR (17 RCTs and 17 non-RCTs) by Clutterbuck et al. (59) enquired about several active exercise interventions (gross motor activity training alone or with progressive resistance exercise plus additional physiotherapy, physical fitness training, modified sport, and non-immersive virtual reality), in subjects affected by CP mixed types, aged 3–18 years, at GMFCS I–IV (mostly I–III). The authors reported an improvement in gross motor function of ambulant/semi-ambulant children, in particular, following gross motor activity training. They also indicated that practice variability is essential to improve gross motor function.

The SR by Novak et al. (42) enquired about several approaches: mobility training, strength training, aerobic exercise, physical activity, and modified sports.

The mobility training studies (six SRs) examined an eclectic group of interventions including Nintendo, wall climbing, sit-to-stand, circuit training of functional tasks, and overground or

treadmill walking. Subjects aged 3–21 years, at GMFCS levels I–IV, were involved. The authors reported low- to moderate-level evidence of improving gait speed and gross motor function.

The strength training studies (four SRs), involved mixed CP subjects, aged 3.4–20 years, GMFCS levels I–III, and confirmed improved muscle strength and gait.

Moderate-based evidence [including Ryan et al. (60)] supported aerobic exercise (including cycling and treadmill) in children of GMFCS I–II who could move fast enough to train in aerobic fitness, to improve gross motor function in the short and intermediate term, without affecting gait speed.

Concerning physical activity, the authors reported low-level evidence (four SRs) and conflicting results on improving gross motor function, gait, and fitness, in subjects aged <25 years, affected by CP mixed types, GMFCS levels I–V.

Very low-level evidence (observational studies in CP mixed types, GMFCS I–III, 4–16 years) supported modified sports, to improve gross motor skills, gait speed, and aerobic fitness.

The SR with the meta-analysis by Ryan et al. (60) was older (2017) than previous studies, but of higher quality and was included in the SRs by Novak et al. (42) and Merino-Andres et al. (54). It analyzed 29 RCTs (eight compared aerobic exercise to usual care, 15 compared resistance training to either usual care or no treatment, four compared mixed training to usual care or no treatment, and two compared aerobic exercise to resistance training) evaluated as low- to very low-level evidence. Samples were CP mixed types, GMFCS I–V, of ages <19 years. Aerobic exercise improved motor function (activity level) but did not improve gait speed, walking endurance, participation, or aerobic fitness among children with CP in the short or intermediate term. There was no research regarding the effect of aerobic exercise on participation or quality of life. Resistance training did not improve motor function, gait speed, or participation in the short or intermediate term, or quality of life in the short term, in children and adolescents with CP but improved muscle strength. Mixed training did not improve motor function or gait speed but appeared to improve participation in children and adolescents with CP in the short term. No difference was evidenced between aerobic and resistance training on motor function, but a difference in muscle strength in the short term. Although the evidence suggested that exercise might be safe for people with CP, only 16 trials (55%) included information on adverse events; these trials reported no serious adverse events.

Elnahhas et al. (61) conducted a SR (seven RCTs) on backward gait training, involving uni-bilateral spastic CP, GMFCS levels I–III, of ages 5–14 years. The authors reported moderate evidence that backward gait training improved mobility (gait) and some evidence that it improved balance and gross motor function.

The SR and meta-analysis by Araujo et al. (62) involved uni-bilateral spastic CP subjects aged 5–15 years, at GMFCS levels I–II (incomplete data). Very low-quality evidence suggested that balance-training interventions (i.e., activities that caused unpredicted perturbations, such as unstable or mobile surfaces, in multiple training settings) combined with other interventions enhanced the effect of the other intervention alone on postural control in the short term.

Inamdar et al. (43) conducted a SR with meta-analysis (12 RCTs), enquiring about several approaches to improve sitting in uni-bilateral CP children, aged 18 months–puberty, at GMFCS I–V. The authors suggested that task-specific, intensive, and child-initiated intervention components might improve sitting in young infants at risk for CP, while components of impairment remediation combined with functional balance training should be explored to improve sitting in children diagnosed with CP.

Yardimci-Lokmanoglu et al. (63) conducted a SR including three small RCTs, with spastic CP subjects aged 5–15 years, at GMFCS levels I–III. Different approaches to proprioception (i.e., whole body vibration or integrated intensive proprioceptive and visuomotor training) combined with conventional physical therapy (CPT), showed no superiority in motor performance, compared to CPT alone.

3.2.8. Treadmill and mechanically assisted walking

The Australian CPG (13) described treadmill training among recommended treatments, with or without partial body-weight support. The authors reported low-quality evidence to support treadmill training to improve weight-bearing and improve functional walking, although the practice of overground walking, rather than treadmill training might be more effective.

The SR and meta-analysis by Chiu et al. (64) analyzed 17 RCTs, in uni-bilateral CP subjects, aged 4–14 years, at GMFCS levels I–IV. The duration of the intervention was 4–12 weeks, the intensity of training was 15–40 min, and the frequency was 2–5 days/week. Compared with no walking, mechanically assisted walking training resulted in small improvements in walking speed (with or without body weight support) and gross motor function (with body weight support). Compared with the same dose of overground walking, mechanically assisted walking training with body weight support resulted in little to no difference in walking speed and gross motor function. Two studies found that mechanically assisted walking training without body weight support was probably more effective than the same dose of overground walking training for walking speed and gross motor function. Not many studies reported adverse events, although those that did report appeared to show no differences between groups. The results were largely not clinically significant, sample sizes were small, and the risk of bias and intensity of intervention varied across studies, making it hard to draw robust conclusions.

The SR with the meta-analysis by Han et al. (65) included eight RCTs, with uni-bilateral CP patients, GMFCS levels I–IV, with a mean age of 4.5–16 years. Findings suggested that treadmill training was effective for gait endurance, gait speed, and limb support time. No significant improvement was observed in cadence and step length.

Novak et al. (42) examined three SRs in uni-bilateral CP patients, aged 4–21 years at GMFCS levels I–IV. The authors reported that treadmill training, with or without body weight support, conferred improved walking speed, endurance, and gross motor function.

3.2.9. Virtual reality for upper arm activities

No recommendation was available on this topic in included CPGs.

The SR with the meta-analysis by Johansen et al. (66) included eight RCTs, in CP subjects aged 5–20 years, at GMFCS levels I–V. The results highlighted the potential of video games (task-oriented, motivating, and intensive) as a supplementary method of training arm and hand functions for persons with CP. Nonetheless, they should be interpreted with caution due to the high risk of bias and low level of evidence.

Also, the SR by Plasschaert et al. (67) (two studies in bilateral CP) reported very low-level evidence for improvement in upper limb function.

Rathinam et al. (68) published a SR including six RCTs, in uni/bilateral CP subjects, aged 6–18 years, at GMFCS levels I–V. Four studies reported some improvement in hand function, but only one had a low risk of bias. The authors reported that the available evidence was inconsistent and that VR could not be reliably suggested to improve hand function until further studies had ascertained its therapeutic effect.

Conversely, Novak et al. (42) reported that VR conferred better arm function than NDT or usual care, with large effect sizes, based on a SR (19 RCTs) in CP subjects aged 4–12 years. The duration of the intervention was 20–90 min/day, 1–7 days/week, and over 4–20 weeks. The authors suggested the use of VR as a complement to conventional therapies and not as a substitute.

3.2.10. Virtual reality for gross motor and balance activities

No recommendation was available on this topic in included CPGs.

Montoro-Cardenas et al. (69) enquired about the effectiveness of Nintendo WII Balance (NWT), for improving functional and dynamic balance, in spastic uni-bilateral CP children, at GMFCS levels I–IV. NWT was combined with CPT in 30-min sessions with interventions lasting longer than 3 weeks. Very low-quality evidence was found with a large effect of NWT compared with no intervention and moderate quality evidence for using NWT with CPT vs. CPT for improving dynamic balance.

The SR by Wu et al. (70) included 11 RCTs, in uni-bilateral CP subjects >6 years, at GMFCS I–IV (but data were incomplete). VR games played a positive role in the improvement of balance, but the evidence was limited by the methodological defects of included studies.

Ren et al. (71) analyzed seven RCTs, in uni-bilateral CP subjects >6 years, at GMFCS I–V. The authors reported preliminary evidence that VRGs improved the gross motor skills of children with CP. The single intervention time was 17–40 min and the intervention frequency was >5 times per week, over 12 weeks.

The SR by Pin et al. (72) included 21 studies (10 RCTs) in CP subjects at GMFCS levels I–II, with a mean age of over 4.8 years. ICP (interactive computer play) seemed to be more effective than conventional therapy in improving postural control and balance, with medium to large effect sizes.

Warnier et al. (73) conducted a SR with meta-analysis, including 26 studies (nine RCTs), in CP subjects mostly at GMFCS level I, aged 6–18 years. The meta-analysis confirmed the positive effect of VR, though results should be interpreted with caution due to differences in the interventions used, the lack of randomized controlled trials, and the relatively small groups.

In the SR (14 RCTs) by Ghai et al. (40), 88% of the studies reported significant enhancements in gait performance after training with VR. Meta-analyses revealed positive effects of virtual reality training on gait velocity (Hedge's g = 0.68), stride length (0.30), cadence (0.66), and gross motor function measure (0.44). Subgroup analysis reported a training duration of 20–30 min per session, ≤4 times per week across ≥8 weeks to allow maximum enhancements in gait velocity.

Novak et al. (42) presented results from one observational study, involving subjects aged 4–12 years, and compared VR + biofeedback vs. VR alone: the combination conferred better balance than VR alone. The authors also reviewed one RCT and five observational studies, involving subjects aged 5–18 years, at GMFCS levels I–III. Wii Fit appeared to confer improved balance.

Araujo et al. (62) analyzed just one RCT, in spastic hemiplegic CP, with a mean age of 9.6 years (SD 2.6), at GMFCS I–II. Wii therapy and NDT, compared to NDT, improved balance in terms of PBS in the short term (12 weeks).

3.2.11. Hydrotherapy

The Australian CPG (13) claimed for further research on hydrotherapy, nonetheless, outlined some positive aspects of this approach: the warmth and buoyancy of the water might provide support and pain relief, by assisting relaxation and reducing spasms; walking might be possible without aides; and fitness and endurance might be more easily challenged in a controlled way. Hydrotherapy was also presented as an excellent recreational pursuit that could lead to improved swimming skills and respiratory function.

The SR by Roostaei et al. (39) included 11 studies (two RCTs), with uni-bilateral CP mixed types, GMFCS levels I–V, with ages 3–21 years. The treatment had a frequency of 2–3 days/week and a duration of 6–16 weeks. Evidence was limited. The aquatic exercise was feasible and adverse effects were minimal. However, the authors claimed the need for further research defining dosing parameters across age categories and GMFCS levels, the aquatic setting (type of pool and temperature of the water), and group or individualized treatment.

Novak et al. (42), based on low-quality evidence [including Roostaei et al. (39)], reported that aquatic-based exercises improved vitals and gross motor function.

3.2.12. Non-invasive brain stimulation

The NIBS includes transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS).

Elbanna et al. (74) reported data from 14 RCTs comparing tDCS or rTMS with or without treadmill or VR vs. sham rTMS or placebo or NDT or treadmill training. A mixed population of CP, traumatic brain injury, or pediatric stroke ≤18 years, was considered. The authors concluded that rTMS improved upper limb function and tDCS improved balance and the majority of gait variables, but the level of evidence was low, and no long-term follow-up was provided. No adverse effects were described.

Novak et al. (42) presented results from four SRs, involving spastic or dystonic CP, aged 4–19 years. tDCS combined with treadmill or VR appeared to confer improved gait velocity, stride length, cadence, and balance compared to sham tDCS and rehabilitation. Adverse effects were rare, mild, and transient and included minor tingling, burning, itching, and skin redness.

Corsi et al. (52) reported data from three RCTs, involving uni-bilateral CP, GMFCS I-III, aged 7–18 years. tDCS combined with virtual reality or treadmill was effective to improve spatiotemporal gait parameters, especially velocity compared to sham stimulation. No follow-up was enquired.

3.2.13. Neuromuscular electrical stimulation

The Australian CPG (13) reported emerging evidence to support the use of Functional Electric Stimulation (FES) for children with cerebral palsy in the lower limb and inconclusive evidence for its use in the upper limb.

The SR by Salazar et al. (75) examined six RCTs, in uni-bilateral CP, with a mean age of 1.04–8.6 years. Low-quality of evidence suggested that NMES might be used as an adjuvant therapy to improve gross motor function, particularly the sitting and standing dimensions of the GMFM scale. The evidence was limited due to the small number of studies included and the reduced sample size in each study. Further research with adequate methodological quality, ample sample size, and long-term follow-up was advised.

Corsi et al. (52) published a SR (five RCTs) enquiring about several treatments (vibratory platform, gait training, electrical stimulation, and transcranial stimulation), which all resulted to be effective to improve spatiotemporal gait parameters. The studies involved uni-bilateral CP, aged 7–18 years, at GMFCS levels I–III.

Conversely, the study by Das et al. (45) (34 SRs in uni-bilateral CP, 0–18 years) reported limited functional gain following NMES.

Controversial results about improving gait and low-level evidence about improving standing and sitting were reported by Novak et al. (42) (five SRs, in mixed CP types, GMFCS I–IV, and 1–19 years of age).

3.2.14. Neurodevelopmental therapy

The Australian CPG (13) expressed a strong recommendation against NDT, because it considered the child as a relatively passive recipient of the treatment, and the approach was embedded into the context of normal developmental sequence.

Recent SRs (42, 45, 76, 87) all agreed reporting a lack of evidence to support the use of NDT in current practice.

3.2.15. Hippotherapy

The Australian CPG (13) accounted for hippotherapy among adjunct interventions for children with CP, as it might have positive effects on balance and gross motor function, although evidence was limited.

The SR with the meta-analysis by Guindos-Sanchez et al. (77) (10 RCTs with mixed age subjects, GMFCS I-V) reported improvements in GMFM-66 total scores and GMFM-88 dimensions A, B, and E, balance recovery, and muscle spasticity reduction.

Novak et al. (42) (five SRs and three RCTs, in uni-bilateral CP subjects, aged 3–16 years, GMFCS levels I–V) attributed low level and conflicting evidence relative to gross motor function, but some positive effects on trunk position and arm function in GMFCS I–IV.

The SR by Araujo et al. (62) included just one low-level study dealing with hippotherapy (missing data about GMFCS, mean age 7 years, and uni-bilateral CP). A large additional effect on postural control was found when balance-training interventions (including hippotherapy) were combined with NDT at short-term (standardized mean difference of 1.3; 95% confidence interval 0.5, 2.0, $p = 0.001$). Nonetheless, the quality of the evidence was very low due to publication bias, imprecision, and inconsistency.

3.2.16. Suit therapy

The Australian CPG (13) stated that there is conflicting and limited evidence on the benefits of suit therapy and claimed further research.

Novak et al. (42) (three SRs with CP mixed type, 3–17 years) reported that the suit might act on hip and shoulder stability and movement, given the suit was located over the hips and shoulders, whereas there was no effect on distal kinematics as the suit could not act on regions of the body not covered by the suit. Some children disliked wearing the suits and experienced adverse events including respiratory compromise, overheating, and peripheral cyanosis. The suits also impeded functions such as independent toileting and dressing.

The SR by Karadag-Saygi et al. (78) included 29 studies (nine RCTs) heterogenous in design, type of suit, size, study population, and outcomes measured. Some improvements were reported in proximal stability and gross motor function but with low evidence and several adverse effects.

3.2.17. Taping

No recommendation was found in included CPGs on this topic.

The SR with the meta-analysis by Inamdar et al. (43) included 12 RCTs, in uni-bilateral subjects, aged 18 months–puberty, at GMFCS levels I–V. The authors reported that kinesio-taping might be an effective adjunct to conventional physical therapy in improving sitting ability in children with spastic bilateral CP.

Similarly, Novak et al. (42) (seven SRs, uni-bilateral CP, <18 years, and GMFCS I–V) considered taping as an adjunct to therapy, not a stand-alone intervention, to improve gross motor and upper limb function. It was found to be most beneficial with GMFCS I–II, i.e., children with better selective motor control. Children had more active movement in the upper limbs when the tape was elasticized compared to rigid tape. A small number of children had a skin allergy to the tape, which was considered a contraindication.

3.2.18. Orthoses

The Australian CPG (13) recommended the use of functional and positional orthoses, as common practice, even though the evidence was limited. Functional orthoses (e.g., ankle foot orthoses,

wrist extension orthoses, neoprene wrist, and thumb orthoses) generally position joints in a biomechanically advantageous position to either enable or improve function. Positional orthoses (e.g., spinal braces, leg or elbow wraparounds, and hip abduction orthoses) aimed to maintain corrected anatomical alignment of the joint and maintain range of motion around that joint, to reduce the need for future orthopedic surgery and in some cases to maintain healthy skin integrity.

The SR by Betancourt et al. (79), including three RCTs and 14 prospective cohort studies (uni-bilateral CP, GMFCS I–IV, 3–18 years), reported that CP children using ankle-foot orthoses had improved stride length and dorsiflexion angle during gait.

3.2.18. Serial casting

The Australian CPG (13) recommended casting (one cast or a series) to gain/restore muscle length and provide soft tissue elongation, in the short term, in the lower limb. While no evidence was reported to support upper limb casting. Casting was indicated when soft tissue contracture was interfering with function or causing potential biomechanical misalignment, not in the case of bony changes occurring at a joint. It was reported as particularly effective following botulinum toxin injections.

The SR by Milne et al. (80) analyzed 25 studies (mixed type, mostly had poor methodological quality) with a mixed population in two studies. Lower limb serial casting was found to be effective for improving ankle dorsiflexion (DF) passive range of motion (PROM) in the immediate to short term, decreasing hypertonicity measured by the Modified Ashworth Scale (MAS) in the short term. Serial casting with or without botulinum toxin did not significantly affect gross motor capacity measured by Gross Motor Function Measure. Serial casting with botulinum toxin achieved significantly more DF PROM than serial casting alone.

3.2.19. Massage

The Australian CPG (13) accounted massage as one of the complementary and alternative medicines to relax a child after a bath, before sleeping, to relieve muscle pain, or to prepare for a therapy session. The authors reported the existence of a wide variety of massage techniques, from gentle effleurage to deep tissue massage or myofascial release, supported by little evidence of benefits in children with cerebral palsy.

Also, the SR by Guchan et al. (81) (11 studies including seven RCTs, in subjects aged 0–18 years, missing data relative to GMFCS level) suggested massage as an adjunct to traditional therapies to reduce muscle tone in spastic-type CP, but the evidence was at a very low level.

4. Discussion

4.1. Query 1

Relative to query 1, the selected CPGs (4, 11–13) presented recurrent shared issues, that may be synthetized as follows.

The management program needs to be aimed at specific goals, such as enhancing skill development, function, and ability to participate in everyday activities. It must be individually tailored, considering:

- needs and preferences of the child or young person and their parents or careers.
- the multidimensional profile of the child (holistic approach), including physical, mental, emotional, communicative, and relational features.
- age and developmentally appropriate activities as interventions and goals.
- functional ability scales (GMFCS, MACS, CFCS, VFCS, and EDACS) (82–86).
- Evidence-based interventions.
- implications (including emotional implications) for the individual child or young person and their parents or careers, including the time and effort involved and potential individual barriers.
- contextual barriers and possible difficulties in implementing the program.

In particular, the Australian CPG (13) recommended using functional motor ability classification scales (82–86) to guide assessment and intervention. High-quality observational studies (21–23) demonstrated the prognostic value of such classification scales and presented reference prognostic curves for gross motor and manual function. This frame helps to acknowledge the critical periods in which the intervention must focus on the limits of rehabilitation itself, to define the individualized realistic programs. Furthermore, the stabilizing of trajectories allows shifting from capacity-related intervention to goal-directed training and participation interventions, to promote new skills acquisition (23). All CPGs agree on the importance of providing baseline and regular assessment of the child or young person's functioning, using validated and specific tools, to ensure realistic goal setting, provide a baseline for therapy, and verify whether the goals are being achieved and/or the program remains appropriate to the child or young person's needs. A multiple-disciplinary (multidisciplinary, interdisciplinary, or transdisciplinary) team approach is advisable, including all child care professionals with expertise in CP management (pediatrician, neuropsychiatrist, physiatrist, physiotherapist, neuro-psychomotor therapist, occupational therapist, speech therapist, psychologist, orthopedic surgeon, nurse, orthotist, etc.), who may work within the same organization or as a network within the geographical area closest to the child, or at tertiary institutions or specialist services, together with educational professionals, to facilitate the provision of a holistic service (4). Finally, it is recommended to ensure the young person has access to adult services, both locally and regionally, that include healthcare professionals with an understanding of managing cerebral palsy (11, 13).

4.2. Query 2

Concerning query 2, the CPGs (12, 13) established the essential requirements merging all motor rehabilitation approaches in CP, which are synthetized as follows:

- individualized active use interventions.
- child-focused and age and developmentally appropriate goals to enhance motivation (i.e., playful activity or daily activity).
- the task should be analyzed considering the child's skills as well as environmental limitations.
- consider not only motor skills but the child's multidimensional profile.
- consider the impact of the intervention on the child and the family.
- intervention might be structured with adaptations of the task and/or of the context (objects and environment), based on the analysis of the child's skills, to support motivation and avoid frustration.
- intervention should involve the repetitive practice of a task or part of it, without incurring burnout in the child.
- intensive interventions over a brief period, in general, resulted to be more effective, but compliance of the child and the family is to be considered.

Therefore, passive interventions such as stretching (13, 45) or NDT (13, 42, 45, 76, 87) are considered ineffective in improving functions and activities. Nonetheless, stretching might have a role after botulinum injections are limited to improve PROM.

Previous issues on task-oriented, active-use, intensive treatment are mostly based on studies regarding manual performances (88), though CPGs (12, 13) and two selected SRs (43, 44) have extended them to gross motor function interventions. They all rely on the motor learning theory (89), which views movement emerging from the interaction of three systems: the person, the task, and the environment. Practice and experience alter the development of movement patterns through interaction with the environment and the demands of the task (90). Then, motor rehabilitation is not inhibition of primitive reflexes or normalization of movement but maximizing the efficiency of the damaged central nervous system (CNS), in response to the environment and demands of the task, leading to relatively permanent changes in the capability for movement and task performance (91).

The NICE CPG (12) generally talked about task-oriented active-use interventions aimed at individualized goals, while the Australian CPG (13) and the SR by Novak et al. (42) discussed child-oriented vs. context-oriented approaches and task-focused vs. goal-directed training, as alternatives, although they concluded they are all effective. It seems that these distinctions mostly respond to the need of categorizing the interventions for research studies and are based on underlying the predominant aspect. Nonetheless, in clinical practice, an overlap of these issues is often observed, and even in research studies, the distinction is not always so clear. From a more inclusive and general perspective, both issues may be considered components of the rehabilitation approach. In a child-oriented rehabilitation setting, the context (objects and environment) may be adapted to facilitate emerging skills and supporting motivation (92). Based on the performance and limitations of the child and young person, adaptations of the environment or of the objects may need to be transferred into the life contexts. Even the contraposition of task vs. goal-oriented approaches should be dampened, considering that any intervention to be effective must aim for goals that fit the subject in terms of being realistic and motivating (92–94). Then, also task-oriented interventions are expected to be set on individualized goals. Nonetheless, the results by Jackman et al. (41) and Eliasson et al. (23) suggested that younger children might be more responsive to task or part-task training, than older subjects, who still may improve on individual goals with goal-directed training. In this case, "goal-directed" is intended in a stricter view, as linked to individual activities, in a developmental stage in which improvement in the underlying functions is no more expected.

Another issue influencing the effectiveness is the intensity of treatment. Nonetheless, all CPGs (12, 13) are recommended considering the impact of treatment on CP child or young person and their family, and this may limit the frequency of the intervention. Jackman et al. (41) tried to define the minimal doses to reach success, in terms of the total amount of hours of treatment. The authors demonstrated that the interventions that set functional goals and involve the actual practice of those goals led to goal achievement at a lower dose than general upper limb motor training. Nonetheless, indicating the precise amount of training in terms of hours and risks to overcome the need for individualizing the intervention is based on the characteristics of the subjects, which is a priority. Furthermore, the evidence is limited because of heterogeneity and the absence or short follow-up of the included studies. The home programs (12, 13, 42, 49) may be considered to increase the dose of therapy, depending on family and child compliance. In this case, the requirements of the Australian CPG model (13) appear realistic and shareable:

- Establish collaborative relationships between parents and therapist.
- Set mutually agreed upon family and child goals.
- Select therapeutic activities that focus on achieving family and child goals that are supported by the best available evidence.
- Support implementation of the home program through parent education, home visits, and program updates to sustain motivation.
- Evaluate outcomes.

Beyond setting the general characteristics required by any motor rehabilitation approach, CPGs, in particular the Australian CPG, and the included SRs, reported a list of interventions that resulted effective in improving function and activities in children and young persons with CP. The individual interventions will be analyzed, distinguishing them as focusing on manual vs. gross motor performance.

4.2.1. Manual function and activities

Two interventions were demonstrated to be effective for children with unilateral cerebral palsy, based on high-level evidence: bimanual therapy and constraint-induced movement therapy. Both provide time-limited, goal-directed, skills-based, intensive blocks of self-initiated movement practice based on motor learning theory (91). The evidence (12, 13, 42, 48) concludes that both can be used because they are equally effective at the same dose, and the choice must rely on the preferences of the family,

the therapist's expertise, funding and service delivery models, and resource availability. Nonetheless, they are not the same.

Bimanual therapy is a process of learning bimanual hand skills through the repetitive use of carefully chosen, goal-related, two-handed activities that provoke specific bimanual actions and behaviors (91). It targets explicit learning or procedural knowledge through a mediated learning experience (95). The bimanual performance involves perceptual and cognitive processes underlying the movement response, based on the interaction among the child, the object, and the task. According to the action–perception theory, in a reciprocal and dynamic relationship, perception guides action, and action in turn allows for a more precise perception of future actions (88, 96).

CIMT involves placing a restraint on a child's less impaired upper limb to facilitate spontaneous and repetitive use of the impaired limb in a range of unimanual activities, specifically targeted to the child's individual ability and developmental level. Improvements are achieved by implicit learning (91), which is the ability to acquire a new skill without a corresponding increase in knowledge about the skill (97). It generally requires minimal attention and is not dependent on age and IQ (97). Typically, the type of tasks practiced in a CIMT program is discrete, while more complex tasks most often require two hands to perform. Furthermore, in the absence of a constraint device, these unimanual tasks would typically be performed using the dominant hand as it would be more effective with minimal effort (98). Then, CIMT does not allow practice and learning of how to use the more impaired hand for assisting hand actions, in complex bimanual activities. CIMT is effective for the development of unimanual actions brought about by implicit learning; however, it is not possible to target the cognitive and perceptual skills or explicit learning required for using two hands together to complete a task (91). As Hoare et al. (91) suggested, CIMT and bimanual should be viewed as complementary. CIMT could be used to target unimanual actions. Once these actions are established, bimanual therapy could be used for children to learn how to use these actions for bimanual skill development and learning how to perform daily activities with two hands (91).

The Australian CPG (13) reported that children with poorer function do tend to make greater improvement following CIMT. Nonetheless, possible frustration due to difficulties in performing functional tasks might affect the compliance of these subjects, and compliance is one of the basic requirements to be considered.

The evidence supporting the other approaches addressing manual performance is still limited.

The rationale for AOT is strong (99, 100), though results of available SRs are inconclusive (42, 50, 51) and future research is needed to verify the optimal frequency and intensity of AOT programs and characteristics of children that better fit the AOT approach, with particular attention to the severity of motor impairment and cognitive status as possible limitations.

VR as videogames (42, 66, 68) involving the upper limb might sustain engagement based on playful activities and releasing feedback to the subject's activation. Furthermore, it gives the possibility of controlling, reproducing, and measuring aspects of the activity enhancing its therapeutic potential. Some devices used in the studies are commonly recoverable and low-cost. Nonetheless, advances are required to define the type and parameters of the activity, and the evidence remains at a low level.

Based on the emerging literature, rTMS combined with active approaches might have a role in improving upper limb function (42, 52, 74), though further research is needed.

Inconclusive evidence was reported about the use of NMES to improve upper limb functions (13, 42, 45, 52, 75).

Orthoses (either functional or positional) (13, 79) and taping (42, 43) are extensively used by professionals to improve manual function and activities and prevent secondary deformities, even though the evidence supporting them is at a low level.

4.2.2. Gross motor function and activities

All approaches addressing gross motor function and activities are supported by an overall low level of evidence.

Nonetheless, the CPGs recommend an adapted physical therapy program to acquire gross motor skills (i.e., learn for the first time) or recover them after an intervention (i.e., surgery or spasticity or dystonia treatment). Several approaches are described in the SRs to improve balance (62), sitting (43), mobility, and gait, based on low- to very low-level evidence: gross motor activity training (59), mobility training (42), balance training (62), sit-to-stand or other activity training on the ground (55), and gait training (52, 59, 61). NDT is excluded (13, 42, 45, 76). Devices, taping, and the aid of the therapist may be used to facilitate the activities. In general, it may be assumed that an adapted physical therapy program should include self-initiated task-specific activities, complying with the essential requirements previously established. It is worth recalling that this program should also comply with the GMFCS trajectories (21) and the individual developmental stage, in terms of realistic goals and appropriate activities. Further research is needed to better define the characteristics of such adapted physical training, which is anyway reported as advisable, to facilitate learning or re-learning gross motor skills after an intervention.

In the past, strength training was considered to be contraindicated in people with CP because it was thought to enhance muscle stiffness, then result in increased spasticity and decreased range of motion. The CPGs stated that resistance training is accepted, but the objective is just to improve muscle strength (53, 54, 58, 60), having no evidence of effectiveness on the activity and participation dimensions (60). It is not meant to be performed frequently, and for long durations, a small number of repetitions should be performed until fatigue and sufficient rest must be allowed between exercises for recovery. Strength training might be included either in adapted physical programs or in fitness training, though it is recommended to be combined with other activity-based programs, focusing on coordination and endurance.

Concerning gait, both overground and treadmill walking resulted effective (42, 60, 64) at the same dosage, in improving spatial-temporal parameters of gait and gross motor skills connected to gait, in the short to intermediate term, compared to no treatment (60). The treadmill may not replace an adapted physical therapy intervention overground, which implies the possibility to introduce devices and contextual aids to facilitate a child while learning to walk or distractors and obstacles to climb over to

enhance the child's skills. Nonetheless, contextual factors may limit the possibility of exercising overground walking, while a treadmill might be accessible, to ensure either intensive treatment after surgery or daily physical activity to address fitness. Finally, it is advisable to consider the resources and preferences of subjects, their families, and service providers in the choice. The evidence regarding devices ensuring weight relief is inconclusive. Further research is needed to define the effectiveness, indications, and parameters of more complex and performing devices that may provide mechanically assisted walking and weight relief.

As an innovative issue, the CPGs recommended implementing physical activity, in terms of fitness training integrated into the child's daily life, to counteract the decline in mobility which is observed among young adults with CP. Adapted sports (42, 59), but also strength training, aerobic training, and mixed type are described, limited to clients with sufficient motor skills to be able to undertake training. Aerobic training included overground or treadmill walking (13, 42, 60) and cycling (56). The most effective dose of exercise for people with CP is currently unknown. Short-term benefits are reported in gross motor function and activities following aerobic or mixed training, but they are not maintained when the training stops. Many children, adolescents, and adults with CP have low levels of health-related fitness (muscle strength and cardiorespiratory endurance) and reduced habitual physical activity participation, which is well-known to be detrimental to cardiometabolic health (101). As in the general population, CP subjects should reduce sedentary behavior and increase daily physical activity (101). Children and young people with CP might need adaptations and/or aids to facilitate their participation, but these activities are beyond rehabilitation and should be integrated into their daily lives (13).

Immersive VR and VR games (40, 42, 62, 69–73) integrated with a platform or treadmill may help engagement in gross motor exercises, with the advantage of measuring and reproducing the characteristics of the exercise. Nonetheless, the evidence supporting these approaches is limited and their feasibility is linked to service providers' resources, in terms of technologies.

HABIT-ILE (42) is one attempt to encode an intensive self-initiated, mobility training, to improve manual and gross motor function and activities, borrowing from the experience of HABIT. The evidence supporting this approach is still limited.

Hydrotherapy is reported by the Australian CPG (13) among complementary interventions. It may be considered in combination with other task-specific interventions, to recover gross motor function (39, 42), in particular, in the initial phases following orthopedic surgery. Furthermore, mobility training in the water, possibly warm for better comfort, may be an alternative approach to improve fitness. Possible limitations to consider might be open wounds, the child's reduced compliance, contextual barriers, and services' resources.

Low-level evidence suggests that hippotherapy may be considered as one possible complementary approach to improve trunk position and balance (13, 42, 62, 77).

Suit therapy is excluded because of possible adverse events (13, 42, 78), though future research is advisable to verify the positive role of suits as orthoses facilitating trunk control/alignment and upper limb function.

There is controversial evidence (13, 42, 45, 52, 75) to support the use of FES and NMES for children with cerebral palsy in the lower limb and poor data about adverse effects and compliance. Future research is advisable to assess the effectiveness of NMES in GMFCS I–III, in particular, following botulinum injections or orthopedic surgery.

There is emerging evidence (42, 52, 74) that tDCS combined with a motor learning rehabilitation intervention might be more effective in improving gait and balance, compared to the activity training alone. Nonetheless, further studies with longer follow-ups are required to draw conclusions, define parameters, and verify adverse effects.

Orthoses (either functional or positional) (13, 79) and taping (42, 43) are extensively used by professionals to improve gait and gross motor function and activities and prevent secondary deformities, even though the evidence supporting them is at a low level.

Ankle-foot casting (one or a series of casts depending on the desired outcome and the child's tolerance) may be used, following botulinum injection, to provide short-term stretch to improve dorsiflexion passive range of motion (13, 80). It is indicated that initial soft tissue contracture is interfering with function or causing potential biomechanical misalignment. Nonetheless, it is not indicated in the case of advanced contractures or when bony changes are occurring at a joint.

5. Limitations

The present SR reports the general characteristics of the interventions and their effectiveness. More detailed indications are needed regarding which people are more likely to undergo certain treatments, based on individual characteristics, such as age, psychological and cognitive profile, and type of CP. Furthermore, the effectiveness of rehabilitation depends on the plasticity of the nervous system, which may be genetically determined. For example, genetic variation in the dopamine system (102) and polymorphisms of the brain-derived neurotrophic factor (BDNF) gene (103) may influence treatment outcomes in children with cerebral palsy. Nonetheless, based on the studies included in the present systematic review, the evidence appeared too limited to permit defining more specific indications. In the future, a specific search and further research studies would be advisable on these topics.

6. Conclusion

All motor rehabilitation approaches to minors affected by CP must share the following fundamental characteristics: evidence-based, engaging active-involvement of the subject, individualized, age and developmentally appropriate, goal-directed, and skills-based, intensive, and time-limited, suitable for the needs and preferences of the child or young person and their family, feasible considering the implications for themselves and possible contextual limitations.

The following approaches showed evidence of effectiveness in improving manual functions and activities: bimanual therapy and mCIMT with high-level evidence; AOT, VR, and taping with low-level evidence.

All approaches addressing gross motor function and activities are supported by low-level evidence, though an adapted physical therapy, respecting previous requirements, is advisable to acquire gross motor skills to recover them, after an intervention (i.e., surgery or spasticity or dystonia treatment). Among these, several mobility training approaches were reported: balance training, functional tasks on the ground, gait training (overground or with a treadmill), backward walking, and cycling. Resistance training may be combined with them, considering that it may impact muscle strength, rather than gross motor activities.

Finally, as for the general population, it is advisable to increase physical activity integrated into the child's daily life, to maintain or improve fitness, with a possible positive impact on gross motor activities. The benefits recede following the withdrawal of the training. Aerobic activities are included (e.g., overground or treadmill walking, cycling, and dancing) and may be combined with strength training. Nonetheless, this is limited to subjects with sufficient motor skills to be able to undertake training.

Low-level evidence suggests that VR, hippotherapy, and hydrotherapy may be considered as possible complementary approaches in combination with previous interventions.

Future research is needed to demonstrate the effectiveness of NMES and NIBS, as complementary approaches, and to define parameters and indications.

Upper and lower limb orthoses, taping, and ankle-foot casting (following botulinum injections) are supported by low-level evidence, though largely used by professionals.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SF, EP, and SSa: conception and writing—original draft. AF: supervision. SSg and SSa: selection of studies. SF, SSg, SP, and SSa: quality assessment of studies. All authors: acquisition, analysis, and interpretation of the data. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1171224/full#supplementary-material

References

1. Bax MC, Flodmark O, Tydeman C. Definition and classification of cerebral palsy. From syndrome toward disease. *Dev Med Child Neurol Suppl.* (2007) 109:39–41. doi: 10.1111/j.1469-8749.2007.tb12627.x

2. Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev Med Child Neurol.* (2000) 42:816–24. doi: 10.1017/S0012162200001511

3. Ferrari A, Cioni G. Società Italiana di Medicina Fisica e Rehabilitativa-Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza (SIMFER-SINPIA) Intersociety Commission. Guidelines for rehabilitation of children with cerebral palsy. *Eura Medicophys.* (2005) 41:243–60.

4. Castelli E, Fazzi E. SIMFER-SINPIA intersociety commission. Recommendations for the rehabilitation of children with cerebral palsy. *Eur J Phys Rehabil Med.* (2016) 52:691–703.

5. Brouwers MC, Spithoff K, Kerkvliet K, Alonso-Coello P, Burgers J, Cluzeau F, et al. Development and validation of a tool to assess the quality of clinical practice guideline recommendations. *JAMA Netw Open.* (2020) 3:e205535. doi: 10.1001/jamanetworkopen.2020.5535

6. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. *J Clin Epidemiol.* (2019) 108:64–76. doi: 10.1016/j.jclinepi.2018.11.030

7. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* (2017) 358:j4008. doi: 10.1136/bmj.j4008

8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* (2011) 64:383–94. doi: 10.1016/j.jclinepi.2010.04.026

9. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* (2011) 64:401–6. doi: 10.1016/j.jclinepi.2010.07.015

10. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth.* (2020) 18:2127–33. doi: 10.11124/JBISRIR-D-19-00099

11. NICE Guidelines: Managing cerebral palsy in under 25s. (2021). Available online at: http://pathways.nice.org.uk/pathways/cerebral-palsy (accessed August 6, 2021).

12. NICE guidelines: Spasticity in under 19s: management. (2012-2016). Available online at: https://www.nice.org.uk/guidance/cg145 (accessed August 6, 2021).

13. Management of Cerebral Palsy In Children: A Guide For Allied Health Professionals. (2018). Available online at: http://www.health.nsw.gov.au/kidsfamilies/ (accessed August 6, 2021).

14. Rééducation et réadaptation de la fonction motrice des personnes porteuses de paralysie cérébrale. HAS: Haute Autorité de santé (Francia). (2020). Available online at: https://www.has-sante.fr/portail/ (accessed August 6, 2021).

15. Anaby D, Korner-Bitensky N, Steven E, Tremblay S, Snider L, Avery L et al. Current rehabilitation practices for children with cerebral palsy: focus and gaps. *Phys Occup Ther Pediatr.* (2017) 37:1–15. doi: 10.3109/01942638.2015.1126880

16. Graham D, Paget SP, Wimalasundera N. Current thinking in the health care management of children with cerebral palsy. *Med J Aust.* (2019) 210:129–35. doi: 10.5694/mja2.12106

17. Mäenpää H, Autti-Rämö I, Varho T, Forsten W, Haataja L. Multiprofessional evaluation in clinical practice: establishing a core set of outcome measures for children with cerebral palsy. *Dev Med Child Neurol.* (2017) 59:322–8. doi: 10.1111/dmcn.13289

18. Taczała J, Wolińska O, Becher J, Majcher P. An interdisciplinary model of treatment of children with cerebral palsy in Poland. Recommendations of the paediatric rehabilitation section of the polish rehabilitation society. *Ortop Traumatol Rehabil.* (2020) 22:51–9. doi: 10.5604/01.3001.0014.0641

19. Torjesen I, NICE. publishes guideline on diagnosing and managing cerebral palsy in young people. *BMJ.* (2017) 356:j462. doi: 10.1136/bmj.j462

20. Shaunak M, Kelly VB. Cerebral palsy in under 25 s: assessment and management (NICE Guideline NG62). *Arch Dis Child Educ Pract Ed.* (2018) 103:189–93. doi: 10.1136/archdischild-2017-312970

21. Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. *JAMA.* (2002) 288:1357–63. doi: 10.1001/jama.288.11.1357

22. Klevberg GL, Elvrum AG, Zucknick M, Elkjaer S, Østensjø S, Krumlinde-Sundholm L, et al. Development of bimanual performance in young children with cerebral palsy. *Dev Med Child Neurol.* (2018) 60:490–7. doi: 10.1111/dmcn.13680

23. Eliasson AC, Nordstrand L, Backheden M, Holmefur M. Longitudinal development of hand use in children with unilateral spastic cerebral palsy from 18 months to 18 years. *Dev Med Child Neurol.* (2022) 65:376–84. doi: 10.1111/dmcn.15370

24. Hill M, Healy A, Chockalingam N. Effectiveness of therapeutic footwear for children: A systematic review. *J Foot Ankle Res.* (2020) 13:23. doi: 10.1186/s13047-020-00390-3

25. Rozin Kleiner AF, Bellomo A, Pagnussat AS, de Athayde Costa E, Silva A, Sforza C, et al. Wearable sensors, cerebral palsy and gait assessment in everyday environments: is it a reality? A systematic review. *Funct Neurol.* (2019) 34:85–91.

26. Novak I, Honan I. Effectiveness of paediatric occupational therapy for children with disabilities: a systematic review. *Aust Occup Ther J.* (2019) 66:258–73. doi: 10.1111/1440-1630.12573

27. Roostaei M, Raji P, Morone G, Razi B, Khademi-Kalantari K. The effect of dual-task conditions on gait and balance performance in children with cerebral palsy: a systematic review and meta-analysis of observational studies. *J Bodyw Mov Ther.* (2021) 26:448–62. doi: 10.1016/j.jbmt.2020.12.011

28. Saleem GT, Crasta JE, Slomine BS, Cantarero GL, Suskauer SJ. Transcranial direct current stimulation in pediatric motor disorders: a systematic review and meta-analysis. *Arch Phys Med Rehabil.* (2019) 100:724–38. doi: 10.1016/j.apmr.2018.10.011

29. Valentin-Gudiol M, Bagur-Calafat C, Girabent-Farrés M, Hadders-Algra M, Mattern-Baxter K, Angulo-Barroso R. Treadmill interventions with partial body weight support in children under six years of age at risk of neuromotor delay: a report of a Cochrane systematic review and meta-analysis. *Eur J Phys Rehabil Med.* (2013) 49:67–91.

30. Chakraborty S, Nandy A, Kesar TM. Gait deficits and dynamic stability in children and adolescents with cerebral palsy: a systematic review and meta-analysis. *Clin Biomech (Bristol, Avon).* (2020) 71:11–23. doi: 10.1016/j.clinbiomech.2019.09.005

31. Chiu HC Ada L, Chen C. Changes in walking performance between childhood and adulthood in cerebral palsy: a systematic review. *Dev Neurorehabil.* (2020) 23:343–8. doi: 10.1080/17518423.2019.1648579

32. Clutterbuck GL, Auld ML, Johnston LM. High-level motor skills assessment for ambulant children with cerebral palsy: a systematic review and decision tree. *Dev Med Child Neurol.* (2020) 62:693–9. doi: 10.1111/dmcn.14524

33. Huang C, Chen Y, Chen G, Xie Y, Mo J, Li K et al. Efficacy and safety of core stability training on gait of children with cerebral palsy: a protocol for a systematic review and meta-analysis. *Medicine (Baltimore).* (2020) 99:e18609. doi: 10.1097/MD.0000000000018609

34. Tanner K, Schmidt E, Martin K, Bassi M. Interventions within the scope of occupational therapy practice to improve motor performance for children ages 0-5 years: a systematic review. *Am J Occup Ther.* (2020) 74:7402180060p1–7402180060p40. doi: 10.5014/ajot.2020.039644

35. Blumetti FC, Belloti JC, Tamaoki MJ, Pinto JA. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. *Cochrane Database Syst Rev.* (2019) 10:CD001408. doi: 10.1002/14651858.CD001408.pub2

36. Corrado B, Di Luise C, Servodio Iammarrone C. Management of muscle spasticity in children with cerebral palsy by means of extracorporeal shockwave therapy: a systematic review of the literature. *Dev Neurorehabil.* (2021) 24:1–7. doi: 10.1080/17518423.2019.1683908

37. Kim HJ, Park JW, Nam K. Effect of extracorporeal shockwave therapy on muscle spasticity in patients with cerebral palsy: meta-analysis and systematic review. *Eur J Phys Rehabil Med.* (2019) 55:761–71. doi: 10.23736/S1973-9087.19.05888-X

38. Yana M, Tutuola F, Westwater-Wood S, Kavlak E. The efficacy of botulinum toxin A lower limb injections in addition to physiotherapy approaches in children with cerebral palsy: a systematic review. *NeuroRehabilitation.* (2019) 44:175–89. doi: 10.3233/NRE-182581

39. Roostaei M, Baharlouei H, Azadi H, Fragala-Pinkham MA. Effects of aquatic intervention on gross motor skills in children with cerebral palsy: a systematic review. *Phys Occup Ther Pediatr.* (2017) 37:496–515. doi: 10.1080/01942638.2016.1247938

40. Ghai S, Ghai I. Virtual reality enhances gait in cerebral palsy: a training dose-response meta-analysis. *Front Neurol.* (2019) 10:236. doi: 10.3389/fneur.2019.00236

41. Jackman M, Lannin N, Galea C, Sakzewski L, Miller L, Novak I. What is the threshold dose of upper limb training for children with cerebral palsy to improve function? A systematic review. *Aust Occup Ther J.* (2020) 67:269–80. doi: 10.1111/1440-1630.12666

42. Novak I, Morgan C, Fahey M, Finch M, Galea C, Hines A, et al. State of the evidence traffic lights 2019: systematic review of interventions for preventing and treating children with cerebral palsy. *Curr Neurol Neurosci Rep.* (2020) 20:3. doi: 10.1007/s11910-020-1022-z

43. Inamdar K, Molinini RM, Panibatla ST, Chow JC, Dusing SC. Physical therapy interventions to improve sitting ability in children with or at-risk for cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol.* (2021) 63:396–406. doi: 10.1111/dmcn.14772

44. Hsu CW, Kang YN, Tseng SH. Effects of therapeutic exercise intensity on cerebral palsy outcomes: a systematic review with meta-regression of randomized clinical trials. *Front Neurol.* (2019) 10:657. doi: 10.3389/fneur.2019.00657

45. Das SP, Ganesh GS. Evidence-based approach to physical therapy in cerebral palsy. *Indian J Orthop.* (2019) 53:20–34. doi: 10.4103/ortho.IJOrtho_241_17

46. Alahmari K, Tedla JS, Sangadala DR, Mukherjee D, Reddy RS, Bairapareddy KC, et al. Effectiveness of hand-arm bimanual intensive therapy on hand function among children with unilateral spastic cerebral palsy: a meta-analysis. *Eur Neurol.* (2020) 83:131–7. doi: 10.1159/000507325

47. Ouyang RG, Yang CN, Qu YL, Koduri MP, Chien CW. Effectiveness of hand-arm bimanual intensive training on upper extremity function in children with cerebral palsy: A systematic review. *Eur J Paediatr Neurol.* (2020) 25:17–28. doi: 10.1016/j.ejpn.2019.12.017

48. Hoare BJ, Wallen MA, Thorley MN, Jackman ML, Carey LM, Imms C. Constraint-induced movement therapy in children with unilateral cerebral palsy. *Cochrane Database Syst Rev.* (2019) 4:CD004149. doi: 10.1002/14651858.CD004149.pub3

49. Beckers LWME, Geijen MME, Kleijnen J, Ramecker EA, Schnacker M, Smeets R, et al. Feasibility and effectiveness of home-based therapy programs for children with cerebral palsy: a systematic review. *BMJ Open.* (2020) 10: e035454. doi: 10.1136/bmjopen-2019-035454

50. Abdelhaleem N, Taher S, Mahmoud M, Hendawy A, Hamed M, Mortada H, et al. Effect of action observation therapy on motor function in children with cerebral palsy: a systematic review of randomized controlled trials with meta-analysis. *Clin Rehabil.* (2021) 35:51–63. doi: 10.1177/0269215520954345

51. Alamer A, Melese H, Adugna B. Effectiveness of Action Observation Training on Upper Limb Motor Function in Children with Hemiplegic Cerebral Palsy: A Systematic Review of Randomized Controlled Trials. *Pediatric Health Med Ther.* (2020) 11:335–46. doi: 10.2147/PHMT.S266720

52. Corsi C, Santos MM, Moreira RFC, Dos Santos AN, de Campos AC, Galli M, et al. Effect of physical therapy interventions on spatiotemporal gait parameters in children with cerebral palsy: a systematic review. *Disabil Rehabil.* (2021) 43:1507–16. doi: 10.1080/09638288.2019.1671500

53. Liang X, Tan Z, Yun G, Cao J, Wang J, Liu Q, Chen T. Effectiveness of exercise interventions for children with cerebral palsy: a systematic review and meta-analysis of randomized controlled trials. *J Rehabil Med.* (2021) 53:jrm00176. doi: 10.2340/16501977-2772

54. Merino-Andrés J, García de. Mateos-López A, Damiano DL, Sánchez-Sierra A. *Effect of muscle strength training in children and adolescents with spastic cerebral palsy: A systematic review and meta-analysis Clin Rehabil.* (2022) 36:4–14. doi: 10.1177/02692155211040199

55. Bania T, Chiu HC, Billis E. Activity training on the ground in children with cerebral palsy: Systematic review and meta-analysis. *Physiother Theory Pract.* (2019) 35:810–21. doi: 10.1080/09593985.2018.1460647

56. Armstrong EL, Spencer S, Kentish MJ, Horan SA, Carty CP, Boyd RN. Efficacy of cycling interventions to improve function in children and adolescents with cerebral palsy: a systematic review and meta-analysis. *Clin Rehabil.* (2019) 33:1113–29. doi: 10.1177/0269215519837582

57. López-Ortiz C, Gaebler-Spira DJ, Mckeeman SN, Mcnish RN, Green D. Dance and rehabilitation in cerebral palsy: a systematic search and review. *Dev Med Child Neurol.* (2019) 61:393–8. doi: 10.1111/dmcn.14064

58. Collado-Garrido L, Parás-Bravo P, Calvo-Martín P, Santibáñez-Margüello M. Impact of Resistance Therapy on Motor Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health.* (2019) 16:4513. doi: 10.3390/ijerph16224513

59. Clutterbuck G, Auld M, Johnston L. Active exercise interventions improve gross motor function of ambulant/semi-ambulant children with cerebral palsy: a systematic review. *Disabil Rehabil.* (2019) 41:1131–51. doi: 10.1080/09638288.2017.1422035

60. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE. Exercise interventions for cerebral palsy. *Cochrane Database Syst Rev.* (2017) 6:CD011660. doi: 10.1002/14651858.CD011660.pub2

61. Elnahhas AM, Elshennawy S, Aly MG. Effects of backward gait training on balance, gross motor function, and gait in children with cerebral palsy: a systematic review. *Clin Rehabil.* (2019) 33:3–12. doi: 10.1177/0269215518790053

62. Araújo PA, Starling JMP, Oliveira VC, Gontijo APB, Mancini MC. Combining balance-training interventions with other active interventions may enhance effects on postural control in children and adolescents with cerebral palsy: a systematic review and meta-analysis. *Braz J Phys Ther.* (2020) 24:295–305. doi: 10.1016/j.bjpt.2019.04.005

63. Yardimci-Lokmanoglu BN, Bingöl H, Mutlu A. The forgotten sixth sense in cerebral palsy: do we have enough evidence for proprioceptive treatment? *Disabil Rehabil.* (2020) 42:3581–90. doi: 10.1080/09638288.2019.1608321

64. Chiu HC Ada L, Bania TA. Mechanically assisted walking training for walking, participation, and quality of life in children with cerebral palsy. *Cochrane Database Syst Rev.* (2020) 11:CD013114. doi: 10.1002/14651858.CD013114.pub2

65. Han YG, Yun CK. Effectiveness of treadmill training on gait function in children with cerebral palsy: meta-analysis. *J Exerc Rehabil.* (2020) 16:10–9. doi: 10.12965/jer.1938748.374

66. Johansen T, Strøm V, Simic J, Rike PO. Effectiveness of training with motion-controlled commercial video games on hand and arm function in young people with cerebral palsy: A systematic review and meta-analysis. *J Rehabil Med.* (2019) 52:jrm00012. doi: 10.2340/16501977-2633

67. Plasschaert VFP, Vriezekolk JE, Aarts PBM, Geurts ACH, Van den Ende CHM. Interventions to improve upper limb function for children with bilateral cerebral palsy: a systematic review. *Dev Med Child Neurol.* (2019) 61:899–907. doi: 10.1111/dmcn.14141

68. Rathinam C, Mohan V, Peirson J, Skinner J, Nethaji KS, Kuhn I. Effectiveness of virtual reality in the treatment of hand function in children with cerebral palsy: a systematic review. *J Hand Ther.* (2019) 32:426–434.e1. doi: 10.1016/j.jht.2018.01.006

69. Montoro-Cárdenas D, Cortés-Pérez I, Zagalaz-Anula N, Osuna-Pérez MC, Obrero-Gaitán E, Lomas-Vega R. Nintendo Wii Balance Board therapy for postural control in children with cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol.* (2021) 63:1262–75. doi: 10.1111/dmcn.14947

70. Wu J, Loprinzi PD, Ren Z. The rehabilitative effects of virtual reality games on balance performance among children with cerebral palsy: a meta-analysis of randomized controlled trials. *Int J Environ Res Public Health.* (2019) 16:4161. doi: 10.3390/ijerph16214161

71. Ren Z, Wu J. The effect of virtual reality games on the gross motor skills of children with cerebral palsy: a meta-analysis of randomized controlled trials. *Int J Environ Res Public Health.* (2019) 16:3885. doi: 10.3390/ijerph16203885

72. Pin TW. Effectiveness of interactive computer play on balance and postural control for children with cerebral palsy: a systematic review. *Gait Posture.* (2019) 73:126–39. doi: 10.1016/j.gaitpost.2019.07.122

73. Warnier N, Lambregts S, Port IV. Effect of virtual reality therapy on balance and walking in children with cerebral palsy: a systematic review. *Dev Neurorehabil.* (2020) 23:502–18. doi: 10.1080/17518423.2019.1683907

74. Elbanna ST, Elshennawy S, Ayad MN. noninvasive brain stimulation for rehabilitation of pediatric motor disorders following brain injury: systematic review of randomized controlled trials. *Arch Phys Med Rehabil.* (2019) 100:1945–63. doi: 10.1016/j.apmr.2019.04.009

75. Salazar AP, Pagnussat AS, Pereira GA, Scopel G, Lukrafka JL. Neuromuscular electrical stimulation to improve gross motor function in children with cerebral palsy: a meta-analysis. *Braz J Phys Ther.* (2019) 23:378–86. doi: 10.1016/j.bjpt.2019.01.006

76. Zanon MA, Pacheco RL, Latorraca COC, Martimbianco ALC, Pachito DV, Riera R. Neurodevelopmental treatment (Bobath) for children with cerebral palsy: a systematic review. *J Child Neurol.* (2019) 34:679–86. doi: 10.1177/0883073819852237

77. Guindos-Sanchez L, Lucena-Anton D, Moral-Munoz JA, Salazar A, Carmona-Barrientos I. The effectiveness of hippotherapy to recover gross motor function in children with cerebral palsy: a systematic review and meta-analysis. *Children (Basel).* (2020) 7:106. doi: 10.3390/children7090106

78. Karadag-Saygi E, Giray E. The clinical aspects and effectiveness of suit therapies for cerebral palsy: a systematic review. *Turk J Phys Med Rehabil.* (2019) 65:93–110. doi: 10.5606/tftrd.2019.3431

79. Betancourt JP, Eleeh P, Stark S, Jain NB. Impact of ankle-foot orthosis on gait efficiency in ambulatory children with cerebral palsy: a systematic review and meta-analysis. *Am J Phys Med Rehabil.* (2019) 98:759–70. doi: 10.1097/PHM.0000000000001185

80. Milne N, Miao M, Beattie E. The effects of serial casting on lower limb function for children with Cerebral Palsy: a systematic review with meta-analysis. *BMC Pediatr.* (2020) 20:324. doi: 10.1186/s12887-020-02122-9

81. Güçhan Z, Mutlu A. The effectiveness of taping on children with cerebral palsy: a systematic review. *Dev Med Child Neurol.* (2017) 59:26–30. doi: 10.1111/dmcn.13213

82. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* (1997) 39:214–23. doi: 10.1111/j.1469-8749.1997.tb07414.x

83. Eliasson A-C, Krumlinde-Sundholm L, Rösblad B, Beckung E, Arner M, Ohrvall A-M, et al. The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol.* (2006) 48:549–54. doi: 10.1017/S0012162206001162

84. Hidecker MJC, Paneth N, Rosenbaum PL, Kent RD, Lillie J, Eulenberg JB, et al. Developing and validating the communication function classification system for individuals with cerebral palsy. *Dev Med Child Neurol.* (2011) 53:704–10. doi: 10.1111/j.1469-8749.2011.03996.x

85. Sellers D, Mandy A, Pennington L, Hankins M, Morris C. Development and reliability of a system to classify the eating and drinking ability of people with cerebral palsy. *Dev Med Child Neurol.* (2014) 56:245–51. doi: 10.1111/dmcn.12352

86. Baranello G, Signorini S, Tinelli F, Guzzetta A, Pagliano E, Rossi A, et al. VFCS study group. Visual Function Classification System for children with cerebral palsy: development and validation. *Dev Med Child Neurol.* (2020) 62:104–10. doi: 10.1111/dmcn.14270

87. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol.* (2013) 55:885–910. doi: 10.1111/dmcn.12246

88. Greaves S, Imms C, Krumlinde-Sundholm L, Dodd K, Eliasson AC. Bimanual behaviours in children aged 8-18 months: a literature review to select toys that elicit the use of two hands. *Res Dev Disabil.* (2012) 33:240–50. doi: 10.1016/j.ridd.2011.09.012

89. Bernstein NA. The co-ordination and regulation of movements. *Science.* (1968) 158:415–6.

90. Zwicker JG, Harris SR, A. reflection on motor learning theory in pediatric occupational therapy practice. *Can J Occup Ther.* (2009) 76:29–37. doi: 10.1177/000841740907600108

91. Hoare B, Greaves S. Unimanual vs. bimanual therapy in children with unilateral cerebral palsy: Same, same, but different. *J Pediatr Rehabil Med.* (2017) 10:47–59. doi: 10.3233/PRM-170410

92. Borelli G, Neviani R, Sghedoni A, Conti MR, Montanari L, Ovi A. *La fisioterapia nella paralisi cerebrale infantile.* Milan: Springer Verlag Italia. (2013). doi: 10.1007/978-88-470-5277-2

93. Ferrari A. Proposte riabilitative nelle paralisi cerebrali infantile. In: *Edizioni Del Cerro.* (1997).

94. Fedrizzi E. I diversi livelli dell'intervento globale nella riabilitazione del bambino con paralisi cerebrale infantile. In: *Giornale Italiano di Medicina Riabilitativa.* (1987).

95. Feuerstein R, Hoffman MB, Rand Y, Jensen MR, Tzuriel D, Hoffmann DB. Learning to learn: mediated learning experiences and instrumental enrichment. *Special Services in the Schools.* (2010) 3:49–82. doi: 10.1300/J008v03n01_05

96. Ferrari A. From movement to action: a new framework for cerebral palsy. *Eur J Phys Rehabil Med.* (2019) 55:852–61. doi: 10.23736/S1973-9087.19.05845-3

97. Jongbloed-Pereboom M, Janssen AJ, Steenbergen B, Nijhuis-van der Sanden MW. Motor learning and working memory in children born preterm: a systematic review. *Neurosci Biobehav Rev.* (2012) 36:1314–30. doi: 10.1016/j.neubiorev.2012.02.005

98. Krumlinde Sundholm L. On the other hand: About successful use of two hands together. Conference proceedings from the Third International Cerebral Palsy Conference. *Dev Med Child Neur.* (2009) 51:39.

99. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. Cortical mechanisms of human imitation. *Science.* (1999) 286:2526–8. doi: 10.1126/science.286.5449.2526

100. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science.* (2005) 308:662–7. doi: 10.1126/science.1106138

101. Verschuren O, Peterson MD, Balemans AC, Hurvitz EA. Exercise and physical activity recommendations for people with cerebral palsy. *Dev Med Child Neurol.* (2016) 58:798–808. doi: 10.1111/dmcn.13053

102. Diaz Heijtz R, Almeida R, Eliasson AC, Forssberg H. Genetic variation in the dopamine system influences intervention outcome in children with cerebral palsy. *EBioMedicine.* (2018) 28:162–7. doi: 10.1016/j.ebiom.2017.12.028

103. Bagrowski B, Czapracka M, Kraśny J, Prendecki M, Dorszewska J, Józwiak M. Assessment of the relationship between Val66Met BDNF polymorphism and the effectiveness of gait rehabilitation in children and adolescents with cerebral palsy. *Acta Neurobiol Exp (Wars).* (2022) 82:1–11. doi: 10.55782/ane-2022-001

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Evaluation of fMRI activation in post-stroke patients with movement disorders after repetitive transcranial magnetic stimulation: a scoping review

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Background: Movement disorders are one of the most common stroke residual effects, which cause a major stress on their families and society. Repetitive transcranial magnetic stimulation (rTMS) could change neuroplasticity, which has been suggested as an alternative rehabilitative treatment for enhancing stroke recovery. Functional magnetic resonance imaging (fMRI) is a promising tool to explore neural mechanisms underlying rTMS intervention.

Object: Our primary goal is to better understand the neuroplastic mechanisms of rTMS in stroke rehabilitation, this paper provides a scoping review of recent studies, which investigate the alteration of brain activity using fMRI after the application of rTMS over the primary motor area (M1) in movement disorders patients after stroke.

Method: The database PubMed, Embase, Web of Science, WanFang Chinese database, ZhiWang Chinese database from establishment of each database until December 2022 were included. Two researchers reviewed the study, collected the information and the relevant characteristic extracted to a summary table. Two researchers also assessed the quality of literature with the Downs and Black criteria. When the two researchers unable to reach an agreement, a third researcher would have been consulted.

Results: Seven hundred and eleven studies in all were discovered in the databases, and nine were finally enrolled. They were of good quality or fair quality. The literature mainly involved the therapeutic effect and imaging mechanisms of rTMS on improving movement disorders after stroke. In all of them, there was improvement of the motor function post-rTMS treatment. Both high-frequency rTMS (HF-rTMS) and low-frequency rTMS (LF-rTMS) can induce increased functional connectivity, which may not directly correspond to the impact of rTMS on the activation of the stimulated brain areas. Comparing real rTMS with sham group, the neuroplastic effect of real rTMS can lead to better functional connectivity in the brain network in assisting stroke recovery.

Conclusion: rTMS allows the excitation and synchronization of neural activity, promotes the reorganization of brain function, and achieves the motor function recovery. fMRI can observe the influence of rTMS on brain networks and reveal the neuroplasticity mechanism of post-stroke rehabilitation. The scoping review helps us to put forward a series of recommendations that might guide future researchers exploring the effect of motor stroke treatments on brain connectivity.

KEYWORDS

repetitive transcranial magnetic stimulation, functional magnetic resonance imaging, scoping review, stroke, movement disorders

Introduction

According to The Global Burden of Diseases, Injuries, and Risk Factors Study (1), stroke accounted for 101 million prevalent cases, 6.55 million deaths, and 143 million disability-adjusted life-years worldwide in 2019. Ischemic and hemorrhagic stroke are the two main types of stroke. Ischemic stroke was defined as an episode of neurological dysfunction resulting from decreased blood flow to a certain area of the brain. In contrast, hemorrhagic stroke was not brought on by trauma but rather by a weak blood vessel that bursts and bleeds into the surrounding brain tissue (2). Stroke is the principal cause of serious disability globally, and movement disorders are one of the most prevalent sequelae of stroke (3). Meanwhile, the recovery of movement disorders after stroke are often incomplete, which cause a major stress on their families and society (4). Stroke results in neuronal death in the directly damaged brain regions. On the other hand, cortical regions remote from directly damaged areas also undergo secondary degeneration or reorganization, leading to widespread changes in the structure and function of the whole brain network (5). In a word, the direct injury effects of motor neurons and their descending axons, as well as abnormal connections remote from the injured lesion, may be important pathophysiological factors for stroke residual effects (6). These changes are closely related to neurological function deficits and subsequent recovery after stroke (7). It is considered that recovery of motor function following stroke depends on neuroplasticity (8). The nervous system's ability to adjust to pressure from the environment, new experiences, and changes—including brain injury—is known as neuroplasticity (9, 10). The development of our knowledge of the neuroplastic changes has inspired researchers to look into methods of anticipating probable post-stroke recovery.

Repetitive transcranial magnetic stimulation (rTMS) has already aroused increasingly attention as a tool for modulating stroke-induced abnormal brain network activity and functional connections, which allow the brain to change and adapt to injury following stroke (11). rTMS could improve movement disorders by enhancing the neural plasticity of the brain networks (12). Additionally, its long-lasting neuromodulation beyond the stimulation period could make rTMS suitable for the treatment of movement disorders after stroke (13). High-frequency rTMS (HF-rTMS) on the ipsilesional hemisphere can upregulate the excitatory effects of the ipsilesional cortex, while low-frequency rTMS (LF-rTMS) on the contralesional hemisphere can downregulate excitatory effects of the ipsilesional cortex (14) (Figure 1). They have been widely utilized during the acute, subacute, and chronic phases, and have been proven to restore motor function after stroke (15). Despite the benefits associated with rTMS, such as motor recovery, the mechanisms through which rTMS exerts therapeutic effects remain poorly understood.

Functional magnetic resonance imaging (fMRI) measures changes in blood oxygen levels in the brain, and the blood-oxygen-level-dependent (BOLD) signal evaluates brain activity, with better temporal resolution than PET and SPECT, and superior spatial resolution compared to EEG and MEG (16). People can use fluctuations in the BOLD signal to assess functional connectivity, a method identifying correlation patterns between brain regions (17). fMRI is a non-invasive imaging technique to accurately describe the reorganization of the cerebral cortex, changes in inter-hemispheric balance, and activity changes of the hemispheres (18). fMRI includes task-based fMRI and resting-state fMRI(rs-fMRI). Task-based fMRI is a technique that requires subjects to perform specific tasks during scanning. Researchers have used finger-tapping task-based fMRI to investigate changes in the activation of the sensorimotor network pre- and post-rTMS stimulation (19). rs-fMRI is sensitive to changes in deoxyhemoglobin, which can indirectly reflect changes in neuronal activity (20). Thus, rs-fMRI are applicable to stroke survivors with motor dysfunctions. fMRI has been used to explore the underlying mechanisms of rTMS-mediated neuronal modulation and make us better understand the plasticity in the brain network.

The neural response induced by rTMS is not confined to the stimulated brain area, but can also spread to other cortical regions remote from the stimulated area (21). Hence, rTMS can affect extensive brain functional networks and even whole brain activity (22). Researchers and clinicians have harnessed neuromodulatory effects to promote motor recovery in stroke survivors with the aid of rTMS, possibly owing to alterations in the regions below the stimulation site and where sensory-motor networks are connected (23, 24). Most researches used behavioral and neurophysiological measures to evaluated how rTMS affected stroke motor recovery (25). Nevertheless, they were unable to offer information on brain changes with an outstanding spatial resolution. To date, the neural mechanisms associated with rTMS intervention and their influence on functional connections are rather complicated and poorly understood. From a clinical perspective, a profound understanding of the neural mechanisms underlying recovery is helpful for developing efficient therapy in the future. In order to better understand and use the rTMS technology, we did a scoping review to determine the rTMS-induced neural plasticity measured through fMRI in post-stroke patients with movement disorders.

Method

Scoping review

For this scoping review, we use the methodological framework developed by Arksey and O'Malley (26). Arksey and O'Malley suggest that there are five stages to a scoping review: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing, and reporting the results.

Identifying the research question

In this review, we will concentrate on the alteration of brain networks measured by fMRI after rTMS over M1 in stroke patients with movement disorders, and understand the brain mechanisms of rTMS. The scoping review may provide guidance for rTMS use as a therapeutic tool in movement disorders after stroke.

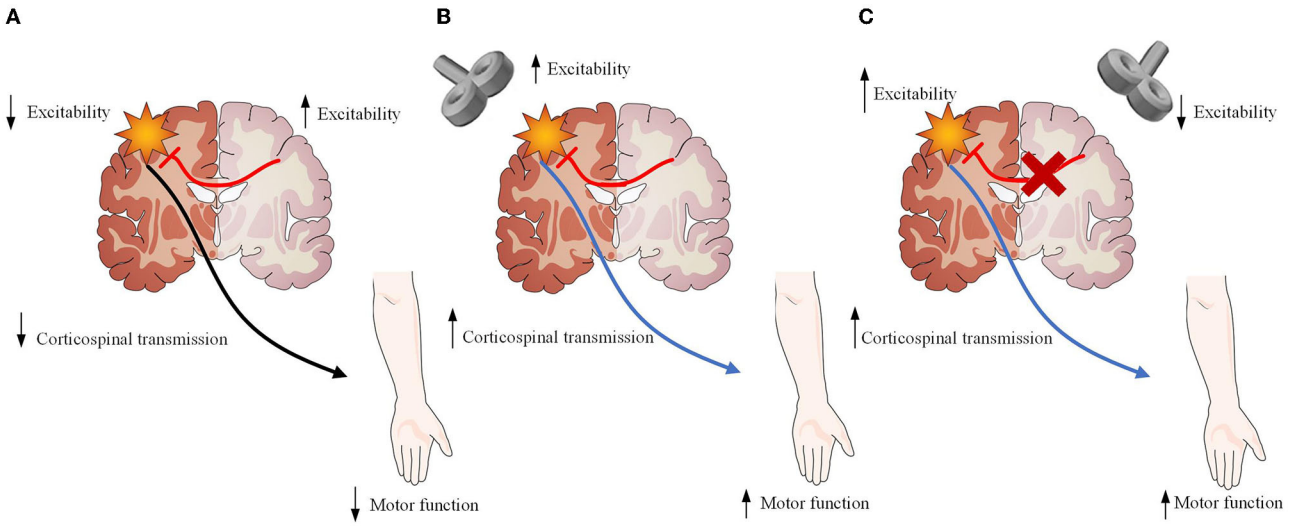

FIGURE 1
Description of the neurobiological model of rTMS as an treatment for stroke recovery. **(A)** Damage to one hemisphere in stroke results not only from neuronal loss within the affected hemisphere but also from the downregulation of remaining neurons within the affected hemisphere resulting in increased inhibition of the affected hemisphere by the unaffected hemisphere. Both are likely involved in lack of functional recovery. **(B)** High-frequency rTMS applied over the ipsilesional hemisphere strengthens the descending motor pathway, facilitating motor recovery. **(C)** Low-frequency rTMS applied over the contralesional hemisphere reduces inhibitory signals from the contralesional motor cortex, promoting beneficial cortical reorganization and motor recovery. Figure was modified from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Common Attribution 3.0 Generic License. (https://creativecommons.org/licenses/by/3.0/) .

TABLE 1 Search strategy for PubMed.

Search	Search term(s)	Results
1	(Stroke OR Cerebral vascular accident OR Ischemic stroke OR hemorrhagic stroke OR Brain vascular accident OR Cerebral stroke)	469,217
2	(Transcranial Magnetic Stimulation OR Repetitive transcranial magnetic stimulation OR Repetitive transcranial magnetic stimulations OR Transcranial Magnetic Stimulations OR Transcranial Magnetic Stimulation, Repetitive OR rTMS OR TMS)	28,275
3	(Functional MRI OR fMRI OR Functional Magnetic Resonance Imaging OR MRI)	730,642
4	(Dyskinesia OR Movement disorder OR Motor dysfunction OR Hemiparesis OR Movement function OR Motor dysfunctions OR Movement disorders)	2,079,800
5	#1 AND #2 AND #3 AND #4	202

Identifying relevant studies

PubMed, Embase, Web of Science, Embase, WanFang Chinese database, and ZhiWang Chinese database were accessed and searched from inception until December 2022. In addition, reference lists of relevant articles were screened to identify key articles that had been missed. The following search terms were entered using the Boolean operators AND/OR: "stroke"; "cerebrovascular accident"; "hemorrhagic stroke"; "ischemic stroke"; "cerebral stroke"; "brain vascular accident"; "transcranial magnetic stimulation"; "transcranial magnetic stimulations"; "repetitive transcranial magnetic stimulations"; "repetitive transcranial magnetic stimulation"; "transcranial magnetic stimulation, repetitive"; "rTMS"; "TMS"; "functional magnetic resonance imaging"; "fMRI"; "Functional MRI"; "fMRI"; "MRI"; "hemiplegia"; "motor deficit"; "dyskinesia"; "movement disorder"; and "motor dysfunction"; "motor deficits"; "movement disorders"; "motor dysfunction." The search method was modified for each database following the example of PubMed (Table 1).

Selecting studies

Inclusion and exclusion criteria

We formulated inclusion and exclusion criteria. The inclusion criteria were: (1) The study population included hemiplegia patients with ischemic or hemorrhagic stroke who performed functional assessment and underwent fMRI that was analyzed; (2) performed rTMS as the treatment; (3) fMRI as a tool to investigate brain activation before rTMS and after rTMS; (4) published in English or Chinese.

Exclusion criteria were: (1) Case studies, conference abstracts, systematic review, and meta-analysis; (2) After proper steps to

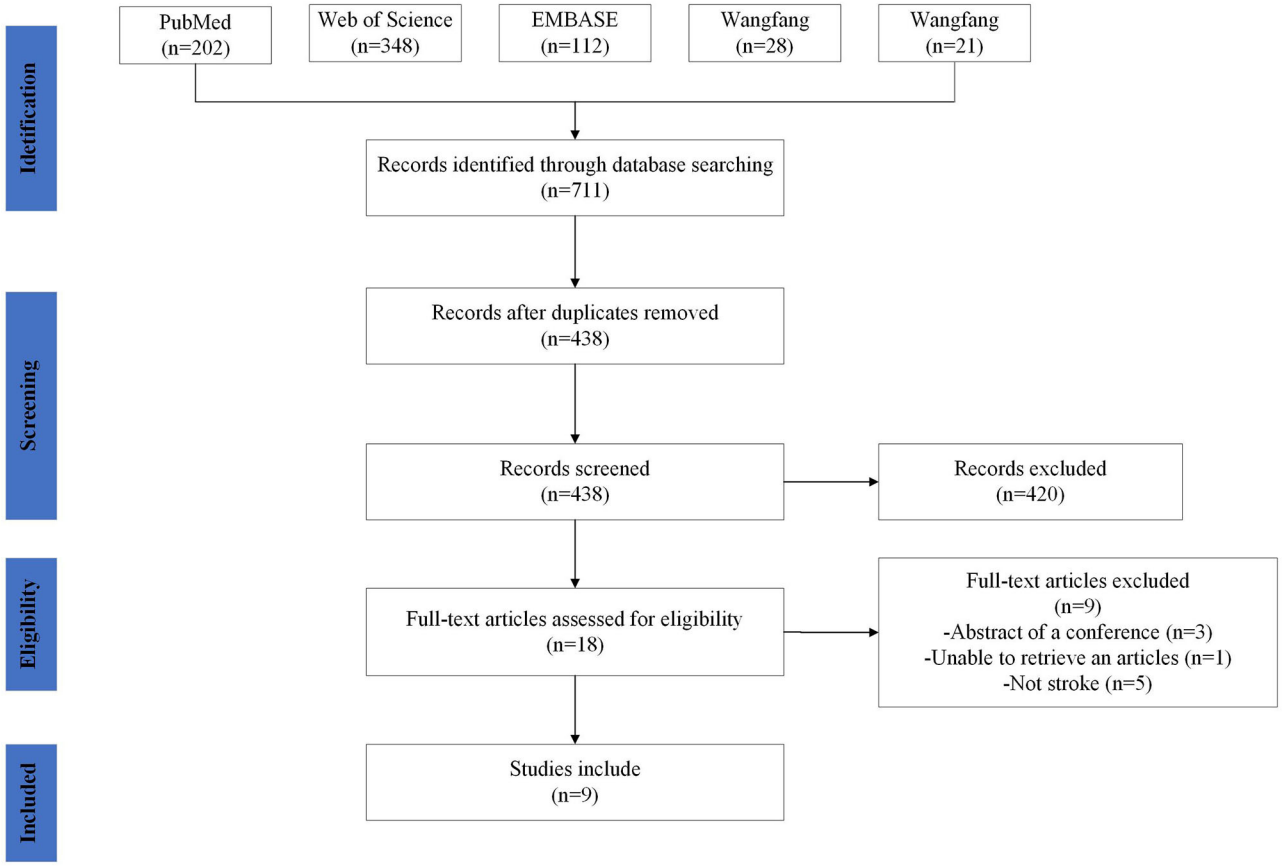

FIGURE 2
Study selection. Flow diagram showing the search strategy, the number of records identified, the excluded articles, and the studies eventually included. A total of nine studies were included.

locate the paper, the article was withdrawn or the complete text was not accessible.

Data management, screening, and extraction

The following phases were involved in study selection: titles and abstracts were reviewed for relevance by two reviewers according to the inclusion and exclusion criteria above. Then Full-texts were then screened. The two authors reached a consensus to determine whether this study should be included or excluded. If the two authors failed to reach consensus, a third author would have been consulted. Included articles were then examined to extract data. The process of identification, screening, eligibility, and inclusion of studies is pictured in Figure 2.

Charting the data

Critical appraisal

Although a critical appraisal is not required by the scoping review, previous studies propose that the quality of evidence is an important part of this type of review (27). We choose the Downs and Black quality assessment checklist (28) to evaluate the level and quality of both randomized and nonrandomized controlled trials. According to the following cut-off points, we categorized the studies as excellent (26–28); good (20–25); fair (15–19); and poor ($\leq$14) (29).

Data collection and synthesis

The data from each study were collected and categorized: each individual study (first author, year, and country of publication), study type, intervention delivered, outcome measurement and population characteristics. Regarding the rTMS protocol, the following stimulus parameters were extracted and recorded: targeted regions, stimulation intensity and frequency, number of TMS pulses per session, number of sessions, course and time. To evaluate whether and how rTMS modulated neural activity, we extracted the changes observed pre- and post-rTMS.

Collating, summarizing, and reporting the results

Seven hundred and eleven records were discovered in the database, 273 duplicate records were removed, and nine records passed the screening procedure' inclusion criteria. Figure 2 displays the screening procedure and the justifications for excluding research. The research contents are summarized in Table 2. In the included studies, the outcome measure was the Fugl–Meyer

TABLE 2 Characterization of studies that used rTMS in stroke.

References	Country	Design: randomization/ blinding/sham	N (C, E) +	Mean Age (Years)	M/F	Disease duration	E/C intervention	rTMS protocol	Task-fMRI/Rs-fMRI	Other outcomes
Ueda et al. (30)	Japan	NO/NO/NO	E: 1 Hz (n = 30)	59.7	19; 11	71.9 ± 47.2 (months)	Contra M1 LF-rTMS + OT	E: 1 Hz; 1,200 pulses; 90% rMT	Task-fMRI	FMA, WMFT
Juan et al. (31)	China	YES/YES/YES	C:Sham (n = 14) E1:LF rTMS (n = 17) E2:HF rTMS (n = 15)	C: 52 E1: 56 E2: 51	C: 12; 3 E1: 14; 3 E2: 12; 3	C: 6 ± 4 (days) E1: 4 ± 2 (days) E2: 4 ± 4 (days)	C: Sham rTMS + PT E1: Contra M1 LF-rTMS + PT E2: Ipsi M1 HF-rTMS + PT	C: the same parameters as E1, but with the coil rotated 90° away from the scalp; E1: 1 Hz; 1,200 pulses; 100% rMT; 5 consecutive days; E2: 10 Hz; 1,200 pulses; 100% rMT; 5 consecutive days	Rs-fMRI	FMA, MRC
Du et al. (32)	China	YES/YES/YES	C:Sham (n = 20) E1:LF rTMS (n = 20) E2:HF rTMS (n = 20)	C: 56 E1: 56 E2: 54	C: 16; 4 E1: 18; 2 E2: 14; 6	C: 4 ± 3 (days) E1: 4 ± 3 (days) E2: 5 ± 4 (days)	C: Sham rTMS+ PT E1: Contra M1 LF-rTMS + PT E2: Ipsi M1 HF-rTMS+ PT	C: the same parameters as E1, but with the coil rotated 90° away from the scalp; E1: 1 Hz; 1,200 pulses; 100% rMT; 5 consecutive days E2: 10 Hz; 1,200 pulses; 100% rMT; 5 consecutive days	Rs-fMRI	FMA, MRC
Guo et al. (33)	China	YES/YES/YES	C: Sham (n = 10) E1:LF rTMS (n = 12) E2:HF rTMS (n = 11)	C: 64.9 E1: 63.58 E2: 65.09	C: 5; 5 E1: 5; 7 E2: 5; 6	C: 5.1 ± 1.79 (days) E1: 5.42 ± 1.93 (days) E2: 6 ± 2.37 (days)	C: Sham rTMS+ PT E1: Contra M1 LF-rTMS + PT E2: Ipsi M1 HF-rTMS+ PT	C: the same parameters as E1 but without real stimulation E1: 1 Hz; 900 pulses; 90% rMT; 10 consecutive days E2: 10 Hz; 1,500 pulses; 90% rMT; 10 consecutive days	Rs-fMRI	FMA, BI
Chen et al. (34)	China	YES/YES/YES	C: Sham (n = 16) E1: HF + LF-rTMS (n =16) E2:HF rTMS (n =15) E3:LF rTMS (n = 16)	C: 59.813 E1: 53.250 E2: 56.800 E3: 59.688	C: 12; 4 E1: 10; 6 E2: 8; 7 E3: 11; 5	C: 7.938 (days) E1: 7.313 (days) E2: 6.667 (days) E3: 8.313 (days)	C: Sham rTMS+ PT E1: Ipsi M1 HF-rTMS+ Contra M1 LF-rTMS+ PT E2: Ipsi M1 HF-rTMS Contra M1 sham rTMS + PT E3: Contra M1 LF-rTMS + Ipsi M1 sham rTMS + PT	HF rTMS: 10 Hz; 600 pulses; 90% rMT; 5 days a week for 4 weeks LF-rTMS: 1 Hz; 600 pulses; 90% rMT; 5 days a week for 4 weeks; Sham rTMS: the same parameters as LF rTMS, but with the coil rotated 90° away from the scalp	Rs-fMRI	FMA, mRS
Wanni et al. (35)	Japan	NO/NO/NO	E:LF rTMS (n =70)	63	46; 24	43.5 ± 18.5 (months)	Contra M1 LF-rTMS + OT	E: 1 Hz; 1,200 pulses; 90% rMT; 12 days	Task-fMRI	FMA, WMFT
Grefkes et al. (36)	Germany	NO/NO/NO	E:LF rTMS (n = 11)	46	9; 2	1–3 (months)	Contra M1 LF-rTMS + OT	E: 1 Hz; 600 pulses; 100% rMT;	Task-fMRI	mRS, MRC, ARAT

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TABLE 2 (Continued)

References	Country	Design: randomization/blinding/sham	N (C, E) +	Mean Age (Years)	M/F	Disease duration	E/C intervention	rTMS protocol	Task-fMRI/Rs-fMRI	Other outcomes
Gottlieb et al. (37)	Germany	YES/YES/YES	C:Sham (n = 14) E: LF rTMS (n = 14)	C: 62 E1: 64	C: 5; 9 E: 3; 11	No mention	C:Sham rTMS+ OT+ PT E: Contra M1 LF- rTMS	E: 1 Hz; 1,200 pulses; 100% rMT; 5 days/week, 2 weeks C: the same parameters as E, the sham coil elicited the pulses in the opposite direction	Rs-fMRI	FMA, MAS
Tosun et al. (38)	Turkey	YES/YES/YES	C:Sham (n = 9) E1:LF rTMS (n = 9) E2:LF rTMS + NMES (n = 7)	C: 61.3 E1: 57.6 E2: 56	C: 5/4 E1: 6/3 E2: 3/4	C: 47.2 ± 41.1 (days) E1: 49.3 ± 43.6 (days) E2: 59.6 ± 58.3 (days)	C:PT E1: Contra M1 LF rTMS + PT E2: Contra M1 LF rTMS + NMES + PT	E: 1 Hz; 1,200 pulses; 90% rMT; 5 days/week, 4 weeks	Task-fMRI	FMA?BI

E, experimental group; C, control group; M, male; F, female; FMA, Fugl-Meyer Assessment scale; WMFT, Wolf Motor Function Test; MI, Motricity Index score; MRC, Medical Research Council; mRS, the modified Rankin scale score; BI, Barthel Index; rTMS, repetitive transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; M1, primary motor cortex; SMA, supplementary motor area; PMA, premotor area; NMES, neuromuscular electrical stimulation; PT, physical therapy; OT, occupational therapy.

Assessment (FMA), Medical Research Council (MRC) scale, Wolf motor function test (WMFT), Motricity Index score (MI), Modified Rankin Scale (mRS) and Barthel Index (BI). The MRC scale has been the common and widely accepted assessment scale for muscle power, which grades muscle power on a scale of 0–5 (39). The WMFT consists of time and quality scales evaluating a set of 15 upper extremity functional tasks (40). As one of the most comprehensive quantitative evaluation indicators following stroke, FMA has been widely used in assessing reflex activity, motor control, and muscle strength, which consists of 33 items related to the motor function and the maximum exercise result is 66 points (41). The Motricity Index (MI) is an effective tool to assess stroke patients with motor dysfunction (42), which assessed muscle power by analyzing movements of all joints of extremities (43). mRS is a single item scale measuring the degree of disability or dependence in the daily activities for patients post-stroke (44). It is a well-designed scale, which is used to classify functionally independent levels with reference to pre-stroke activities. BI was is a frequently-used clinical assessment tool for daily living, thus reflecting motor function (45). As one of the most widely-used assessments of functional independence, BI is much more sensitive to changes in disability than the mRS (46).

Result

Search results

Databases searches identified 711 articles. After screening titles, abstracts, and full texts for eligibility, nine articles were included. Four studies were conducted in China, two in Japan, two in Germany, and one in Turkey. Five studies were RCTs, three were pre-post-test trials, and one was non-randomized controlled trials. A summary of the characteristics of the included papers is summarized in Table 2. Figure 3 shows the findings regarding the effects of rTMS on fMRI and motor performance in stroke survivors.

Quality assessment

Table 3 displayed the outcomes of the quality evaluation of each study. Five studies were rated as having good quality and four as fair according to the Downs and Black criteria. The experimental hypothesis, the primary clinical features of the patients, the intervention techniques, and the key findings were all well reported in the papers under review. However, the studies met the requirements for the reporting section, but none provided the principal confounders in the groups and reported adverse events of intervention. Six studies failed to adhere to the requirement for blinded outcome assessment and participants blinded to treatment.

Rs-fMRI studies of HF-rTMS to the ipsilesional M1

By measuring the effects of the HF-rTMS (10 Hz) applied in the ipsilesional M1 on BOLD signals, Du et al. (32) found that HF-rTMS increased BOLD signal in the ipsilesional motor areas. Motor

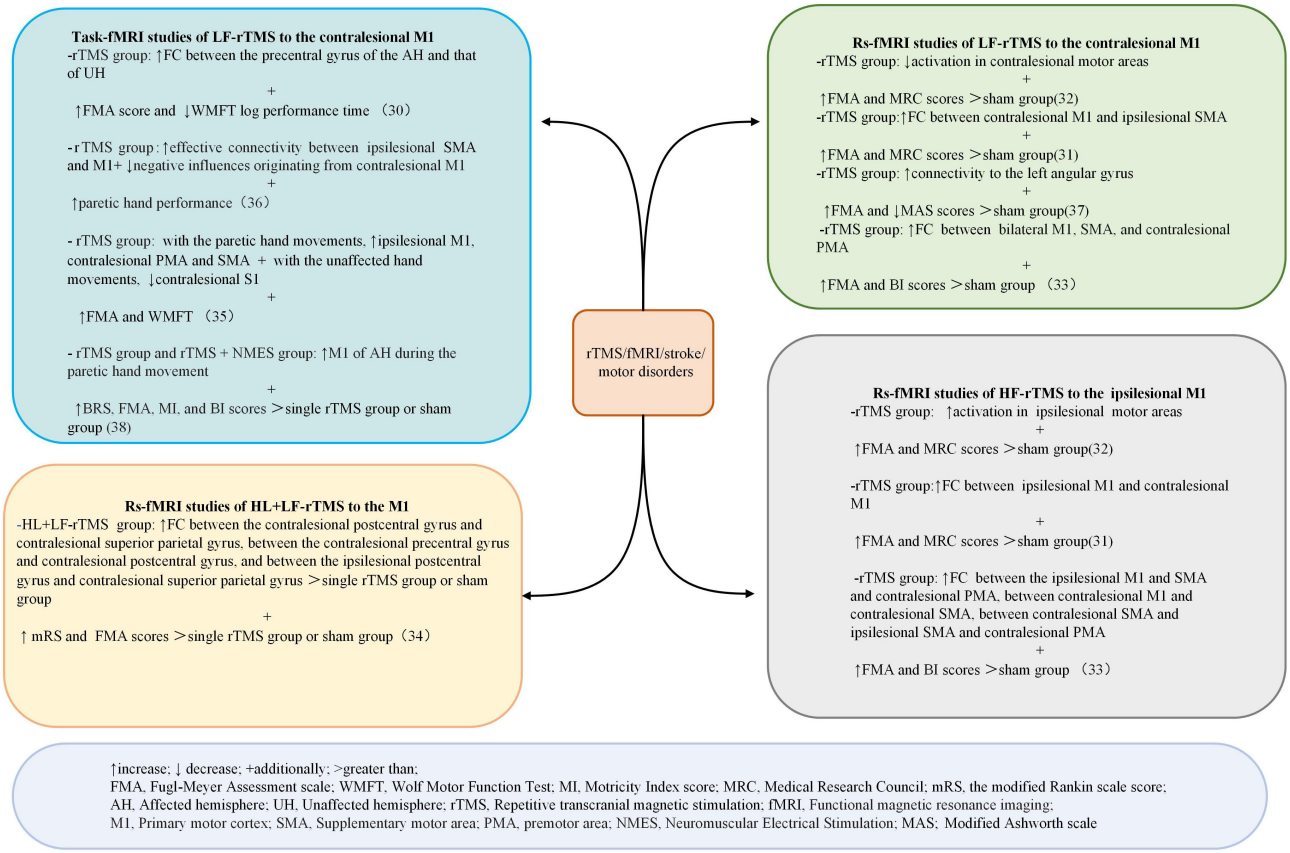

FIGURE 3
Summary of the main results of the included studies regarding the effects of rTMS on fMRI and motor outcomes in patients with stroke. ↑ increase; ↓ decrease; + additionally; >greater than. FMA, Fugl–Meyer Assessment scale; WMFT, Wolf Motor Function Test. MI, Motricitv Index score; MRC, Medical Research Council; mRS, the modified Rankin scale score; AH, affected hemisphere; UH, unaffected hemisphere; rTMS, repetitive transcranial magnetic stimulation: fMRI, functional magnetic resonance imaging; M1, primary motor cortex:; SMA, supp1ementarv motor area; PMA, premotor area; NMES. Neuromuscular Electrical Simulation; MAS, Modified Ashworth scale.

performance was observed in conjunction with fMRI changes. The effects of HF-rTMS (10 Hz) and LF-rTMS (1 Hz) were contrasted by Juan et al. (31). When applied the 10 Hz in the ipsilesional M1 they found an increase in resting-state functional connectivity (FC) between the bilateral M1, which has a positive relationship with motor performance. Guo et al. (33) assessed the effect of functional reorganization following rTMS in stroke survivors as well as the differences between HF-rTMS and LF-rTMS. In the HF-rTMS group, they found higher FC between ipsilesional M1 and contralesional premotor area (PMA), which suggests that HF-rTMS can increase the FC of the ipsilesional motor network and enhance the motor functions. Significant functional connectivity changes after rTMS are summarized in Figure 4. Significant activations of the brain areas after rTMS are summarized in Figure 5.

Rs-fMRI studies of LF-rTMS to the contralesional M1

Du et al. (32) show LF-rTMS reduced brain excitability and fMRI activation in contralesional motor region. These changes were accompanied by improved motor activity. Juan et al. (31) reported 1 Hz rTMS applied to contralesional M1 resulted in enhanced FC between contralesional M1 and ipsilesional SMA. Motor improvement evaluated using the FMA and MRC scale was significantly enhanced in the real rTMS group compared with the sham group. Gottlieb et al. (37) found that connectivity to the left angular gyrus increased after LF-rTMS over M1. The modified Ashworth scale (MAS)score was reduced and the FMA score improved in the LF-rTMS group, suggesting motor improvement. Significant functional connectivity changes after rTMS are summarized in Figure 4. Significant activations of the brain areas after rTMS are summarized in Figure 5.

Rs-fMRI studies of HL + LF-rTMS to the M1

Chen et al. (34) found that inhibitory-facilitatory rTMS treatment induced greater increases in FC between multiple brain regions in comparison to the other groups using single-course or sham rTMS, resulting in great improvements in motor function. Significant functional connectivity changes after rTMS are summarized in Figure 4. Significant activations of the brain areas after rTMS are summarized in Figure 5.

TABLE 3 Downs and Black checklist for quality assessment of included studies.

	Ueda et al.	Du et al.	Juan et al.	Guo et al.	Chen et al.	Wanni et al.	Grefkes et al.	Gottlieb et al.	Tosun et al.
Reporting									
Q1–Hypothesis/aim/objective clearly described	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q2–Main outcomes in Introduction or Methods	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q3–Patient characteristics clearly described	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q4–Interventions of interest clearly described	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q5–Principal confounders clearly described	UTD−0	UTD −0	UTD−0	UTD−0	No−0	No−0	No−0	No−0	No−0
Q6–Main findings clearly described	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q7–Estimates of random variability for main outcomes	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q8–All adverse events of intervention reported	No−0	No−0	No−0	No−0	No−0	No−0	No−0	No−0	No−0
Q9–Characteristics of patients lost to follow-up	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q10–Probability values reported for main outcomes	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
External validity									
Q11–Subjects asked to participate were representative of source population	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0
Q12–Subjects prepared to participate were representative of source population	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0	UTD−0
Q13–Staff/places/facilities study treatment was representative of source population	UTD−0	Yes−1	Yes−1	Yes−1	Yes−1	UTD−0	UTD−0	Yes−1	Yes−1
Internal validity—bias and confounding									
Q14–Study participants blinded to treatment	NO−0	Yes−1	Yes−1	NO−0	NO−0	NO−0	Yes−1	Yes−1	NO−0
Q15–Blinded outcome assessment	No−0	Yes−1	Yes−1	NO−0	UTD−0	NO−0	NO−0	Yes−1	Yes−1
Q16–Any data dredging clearly described	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q17–Analyses adjust for differing lengths of follow-up	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q18–Appropriate statistical tests performed	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q19–Compliance with interventions was reliable	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q20–Outcome measures were reliable and valid	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Q21–All participants recruited from the same source population	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1

(Continued)

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TABLE 3 (Continued)

	Ueda et al.	Du et al.	Juan et al.	Guo et al.	Chen et al.	Wanni et al.	Grefkes et al.	Gottlieb et al.	Tosun et al.
Q22–All participants recruited over the same time period	UTD−0	UTD−0	UTD−0	UTD−0	Yes−1	UTD−0	UTD−0	Yes−1	Yes−1
Q23–Participants randomized to treatment(s)	No−0	Yes−1	Yes−1	No−0	Yes−1	No−0	No−0	Yes−1	Yes−1
Q24–Allocation of treatment concealed from investigators and participants	No−0	Yes−1	Yes−1	No−0	Yes−1	No−0	No−0	Yes−1	Yes−1
Q25–Adequate adjustment for confounding	No−0	No−0	No−0	No−0	No−0	No−0	No−0	No−0	No−0
Q26–Losses to follow-up taken into account	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
Power									
Q27–Power analysis to detect treatment effect at significance level of 0.05	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1	Yes−1
TOTAL	16	21	21	17	20	16	16	22	21
Classification	Fiar	Good	Good	Fair	Good	Fair	Fair	Good	Good

Yes−1; No−0; Unable to determine UTD−0.

Task-fMRI studies of LF-rTMS to the contralesional M1

Ueda et al. (30) found significant FC changes in bilateral cerebral hemispheres after LF-rTMS during task-fMRI. According to Grefkes et al. (36), 1-Hz rTMS has suppressive effects on ipsilesional M1 and facilitates more efficient motor processing in the contralesional hemisphere, as shown by the improved coupling of SMA and M1. Wanni et al. (35) show significant activations were seen in the ipsilesional PMA, M1, and thalamic-cortical regions with the paretic hand movements after rTMS. However, significant activations in the contralesional primary somatosensory cortex (S1), superior parietal cortex, and bilateral cerebellum with unaffected hand movements after the intervention were observed. There was a considerable improvement in FMA and WMFT from pre- to post-rTMS. Tosun et al. (38) reported that greater activation of the affected M1 was observed during the movements of the paretic hand in most patients of the TMS group and TMS + NMES group. Significant functional connectivity changes after rTMS are summarized in Figure 4. Significant activations of the brain areas after rTMS are summarized in Figure 5.

Discussion

Neural plasticity

There is growing evidence to suggest an association of rTMS with the induction of neural plasticity to promote stroke recovery (47). "Neural plasticity" refers to the ability of modification of the nervous system in response to suffering and to adapt following trauma by remodeling its structure, functions, or connections (48). The processes of neural plasticity include altered excitability of neuronal circuits, reorganization by using redundant connections, and formation of new functional connections, which may partly compensate for the lost function. Based on neuroplasticity research, motor function recovery after stroke is related with spontaneous neuroplasticity changes and rTMS-induced plasticity (49). During the post-stroke recovery stage, the spontaneous remodeling neural networks were accompanied by functional recovery (50, 51). It is possible that these spontaneous changes in neuroplasticity are associated with pathophysiological mechanisms, such as salvage ischemic penumbra by revascularization, the release of neurotropic factors and neurotransmitters (52). However, these spontaneous neuroplasticity changes have a limited effect on stroke recovery (53). After stroke, rehabilitation can promote dynamic processes due to increase effective neuronal information input, promote neural repair and functional compensation (54). rTMS was identified to be a successful rehabilitation method for improving stroke recovery by promoting neuroplasticity. The application of fMRI provides a good understanding of the mechanisms involved. Recently, plasticity-induced rTMS was combined with fMRI to map plastic aftereffects (55). The neuroplastic mechanisms of motor function recovery after stroke can see the Figure 6.

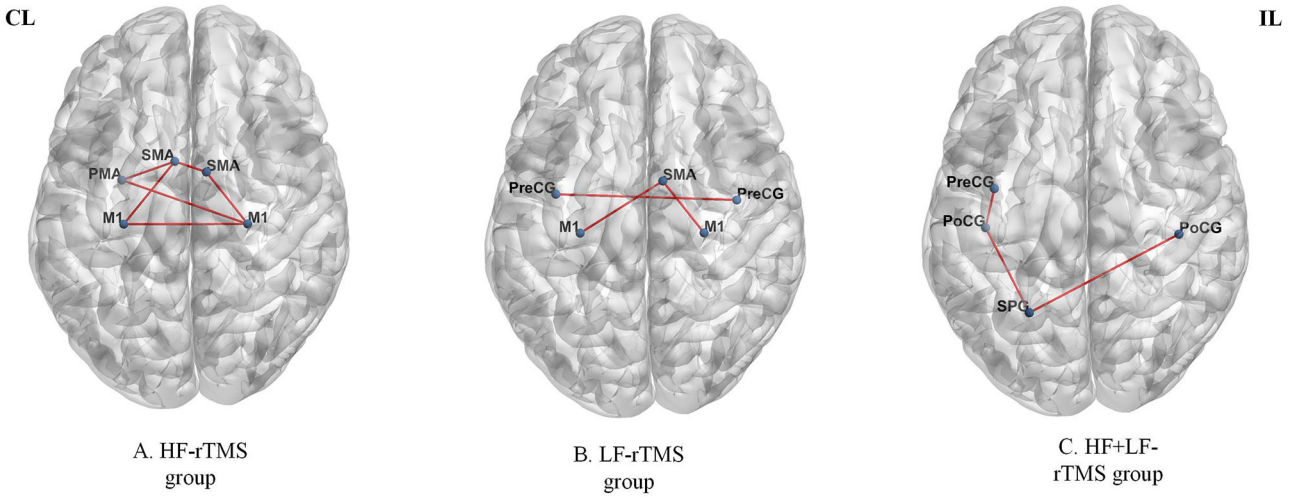

FIGURE 4
Significant functional connectivity changes after rTMS. The red edge represents an increase in the strength of connection. HF, high frequency; LF, low frequency; CL, contralesional side; IL, ipsilesional side; M1, primary motor cortex; SMA, supplementary motor area; PMA, premotor area; PreCG, precentral gyrus; PoCG, postcentral gyrus; SPG, superior parietal gyrus. The figure was drawn using BrainNet Viewer Software (http://nitrc.org/projects/bnv/).

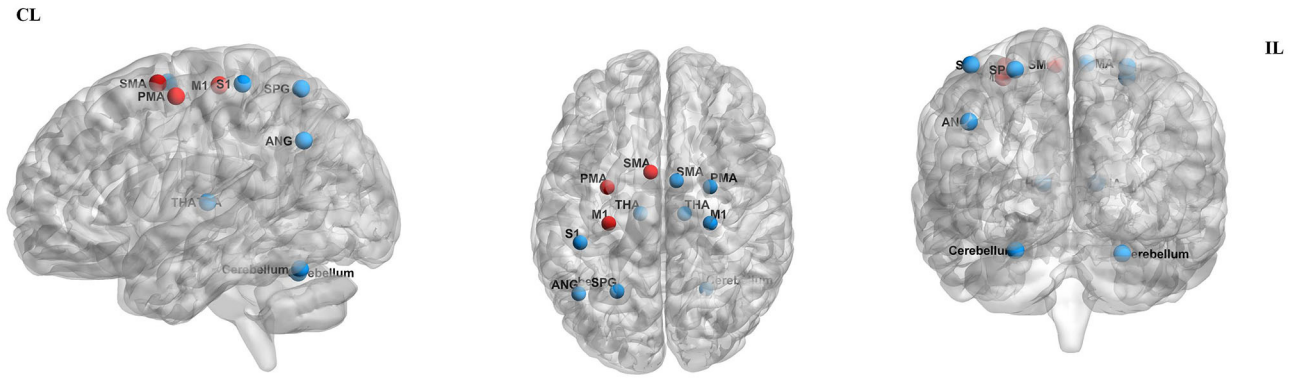

FIGURE 5
Significant activation of the brain areas after rTMS. Areas of significantly decreased activity are shown in red dots, while areas of significantly increased activity are shown in blue dots. CL, contralesional side; IL, ipsilesional side; M1, primary motor cortex; SMA, supplementary motor area; PMA, premotor area SPG, superior parietal gyrus; THA, thalamus; SI, primary somatosensory cortex; ANG, angular gyrus. The figure was drawn using BrainNet Viewer Software (http://nitrc.org/projects/bnv/).

Plasticity changes during recovery

Neural plasticity takes place at a very early stage after stroke, lasts for some time, and involves brain regions remote from the lesioned site. Schulz et al. (56) proved that the corticospinal tract fibers not only originating from the M1 and the ipsilesional PMA and SMA contributed to motor function after stroke. Pathologically, damage to the brain related to motor function, such as M1, PMA, SMA, and S1 (57), contribute to hemiplegia following stroke. Activation in M1 of the affected hemisphere is reduced and the activation is relocated toward the PMA and SMA during movements of the affected hand after stroke (58, 59). By comparing a shift in sensorimotor cortical excitability in both hemispheres, it was found the activation of the contralesional sensorimotor cortex increases accompanying movements of the paretic hand in most post-stroke (60). After a stroke, there are alterations in neural activity in bilateral cerebral hemispheres, which can be beneficial, but can also contribute for maladaptive recovery (61). Conventionally, LF-rTMS or HF-rTMS is effective in improving motor functions by rebalancing hemispheres' the excitability (32).

There have been many studies on local and global functional connections analysis. The most consistent conclusion is that the interhemispheric connection between regions involved in motor function has changed significantly, and the degree of connectivity is related to motor functions. In the early post-stroke period, motor network resting-state connections progressively decrease (62). fMRI studies demonstrated that the patients with reduced the functional connections between bilateral M1 are more severe in motor performance and with increased functional connection between the ipsilesional M1 and the contralesional thalamus, SMA

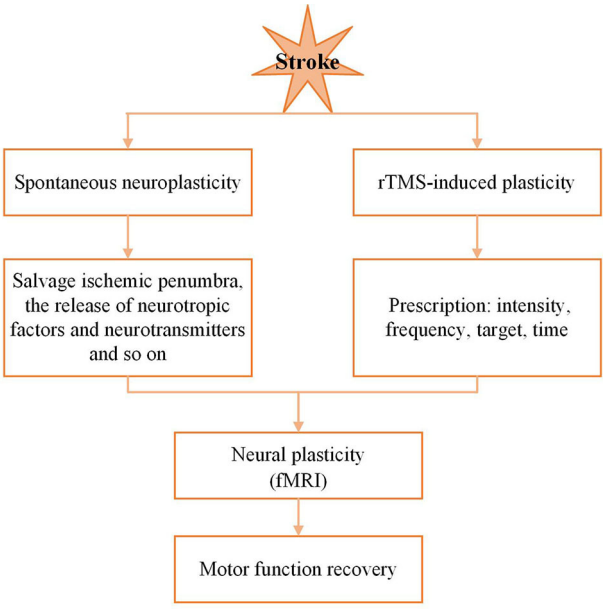

FIGURE 6
Neuroplastic mechanisms of motor recover after stroke.

and middle frontal gyrus at the stage of acute stroke was beneficial to the motor recovery (63). The decreased interhemispheric functional connections between homologous motor areas were associated with the degree of motor function in the acute phase (64), While the enhanced functional connections had a positive correlation with the spontaneous recovery of motor function in the weeks to months after stroke (62). The patients with good motor function recovery showed functional connections between homologous motor regions came back to normal levels in the stable phase after stroke. However, the patients with poor motor function recovery found that functional connections remained low (65, 66). Therefore, it is necessary to seek alternative approaches that strengthen the natural plasticity of the sensorimotor system, which is particularly effective in enhancing motor improvement. In rTMS studies, functional connectivity (FC) evaluation is of value because it enables the evaluation of rTMS effects.

The bimodal balance–recovery model

The interhemispheric competition, assuming the presence of mutual, balanced inhibition between the hemispheres in the healthy people, is found to be altered after stroke (12). Damage to one hemisphere in stroke results not only from neuronal loss within the affected hemisphere but also from the downregulation of remaining neurons within the affected hemisphere resulting in increased inhibition of the affected hemisphere by the unaffected hemisphere (12). That is to say that both the stroke itself and the excessively high interhemispheric inhibition from the contralesional hemisphere result in a double impairment of the ipsilesional cortex. Based on TMS therapy (30), ipsilesional motor areas play an active and vital role in stroke recovery. Therefore, the downregulation of contralesional cortical excitability may be helpful for enhancing motor recovery. Researchers and clinicians have used rTMS to restore the interhemispheric balance to gain motor improvement by either enhancing the activtion of the lesioned hemisphere (38) or inhibiting the healthy hemisphere.

However, it has been found that HF-rTMS given over the M1 of the unaffected side is more effective than LF-rTMS when patients with significant harm to the affected side (67). The significance of the contralesional hemisphere in motor recovery following stroke has been thoroughly investigated in the past few years. According to Ueda et al. (30), the cortical activity of the ipsilesional and the contralesional motor areas changes synchronously during movements of the paralyzed hand after rTMS in stroke survivors with moderate disability. fMRI research found the contralesional PMA was significantly activated during the movement of the paralyzed hand in stroke survivors (68). A meta-analysis (69) shows that consistently activated regions involved the contralesional M1, the bilateral PMA, and SMA in stroke patients compared to healthy controls. The extent of this activation is likely to be influenced by the size and location of the injured region, being greatest in stroke survivors with the greatest impairment. From what has been discussed above, the enhanced activation of the PMA, SMA, and the contralesional hemisphere make up for the lost function in stroke survivors with severe motor impairment. Thus, the vicariation model (12) was presented, which assumes activity in residual networks helps stroke people recover function lost by damaged areas. Similarly, rTMS can support residual motor function following stroke by inducing positive compensatory effects of contralesional mirror motor regions (67).

The vicariation and interhemispheric competition are the two models of functional recovery, which hold opposite views and represent different neuromodulatory treatments. According to interhemispheric competition, stroke recovery would be facilitated by the downregulation of the contralesional hemisphere since it would free the injured hemisphere from aberrant inhibition by the ipsilesional hemisphere. The vicariation model, however, contends that such a tactic would impede compensating activity in the contralesional hemisphere. However, neither the interhemispheric competition model nor the vicariation model could account for all stroke recovery. Therefore, a novel theory called the bimodal balance-recovery model (12) was put out to account for the various contributions made by the contralesional hemisphere to post-stroke motor recovery. The biphasic recovery model of the transcallosal suppression model and the compensatory model may be the neurophysiological basis of functional recovery after stroke. Due to the high level of structural preservation, the interhemispheric competition model is more helpful for stroke survivors with moderate motor impairment. In contrast, patients with little structural reserve may find the vicariation model more helpful in predicting a recovery. Excessive activation in contralesional M1 and nonprimary motor areas can be seen in the early phase after stroke, suggesting recruiting of these brain regions after the cerebral vascular accident (70). This is in accordance with the result that shows overactivity in the ipsilesional and contralesional PMC, SMA, parietal cortex, and contralesional M1 during movements of the hemiplegic hand (71). In a word, bilateral cerebral hemispheres may both participate in the restoration

of motor functions brought about by rTMS intervention. It is necessary to conduct more researches to examine whether rTMS therapy can benefit more stroke patients using individualized stimulation techniques.

RTMS for modulating plasticity following stroke

RTMS improves neural activity

Pathologically, specific brain damage associated with motor functions, such as M1, PMA, and SMA, can lead to motor disorders. The simultaneous activation of bilateral sensorimotor cortices would strengthen coherence of cortical activity, which is a crucial neurophysiological mechanism promoting interaction via transcallosal connections between the related brain regions. rTMS has been considered an effective strategy promoting the recovery of motor functions, which may cause alterations in brain activity and connectivity in local and distant areas after stroke (8). To balance out both sides of cortical excitability, HF-rTMS and LF-rTMS have been used, promoting or hindering the affected and unaffected M1, respectively (32). In both cases, rTMS can correct the maladaptive brain plasticity induced by stroke or enhance adaptive brain plasticity. Based on the fMRI findings, significant clusters in the bilateral cerebellum were observed during the unaffected hand movements after rTMS, suggesting the cerebellum play a role in stroke recovery (35). The cerebellum maintains many neural connections with the motor cortex, which controls motor skills such as motor coordination, fine motor, and motor learning (72). Moreover, the fMRI findings also found activations in bilateral thalamocortical circuits are associated with affected hand motions after rTMS (35). The thalamus served as a relay station for the sensory-motor route, sending relevant sensory and motor information to the cortex (73). Activations of the corpus callosum after rTMS in the included study (35) are in general consistent with previous research that indicated similar change in the affected hand movements after intervention (74). Another study demonstrated that changes in the structure of the corpus callosum are related to transcallosal inhibition and upper limb dysfunction in chronic stroke (75). The regaining of motor function in stroke patients may be influenced by the corpus callosum, which functions as a connector for information between brain hemispheres. Activation of motor cortices triggers brain plasticity, which may lead to enhanced cortico-subcortical connections and cortico-subcortical pathways, which are associated with functional recovery after stroke (53, 76). In these included studies, we found that rTMS reorganizes not only motor-related networks, M1, SMA, and PMA but also the cerebellum, thalamus as well as the corpus callosum.

RTMS improves functional connectivity

Functional connectivity can quantify the functional integration of different brain areas by correlating brain activity in order to detect neural interactions between regions, which are quite convincing (77). Not only are many brain activities related to particular brain regions, but also to connections between different brain regions. Damage to the brain's structural components may result from the localized neurological condition, and this damage may have an impact on how distant brain areas function (78). Stroke may result in neurological impairment by affecting localized, specific areas of the brain, but more evidence proves that the network effects resulting from the loss of connections between distant brain areas are important reasons for neurological impairment (5). Restoration of interhemispheric functional connectivity was only seen in stroke survivors who had recovered well, not in those who had recovered poorly (79), suggesting that interhemispheric functional connectivity in stroke patients is a significant indicator established (80). Therefore, increasing motor network connections after stroke may be particularly useful for promoting motor recovery.

Furthermore, not only does rTMS affect the stimulated functional network, but also physically or functionally related remote brain areas. A large body of studies suggests that increased connections between major motor areas in bilateral cerebral hemispheres may underlie rTMS-mediated functional gains. By altering connections between motor areas in both the stimulated and non-stimulated hemispheres, rTMS may be used to improve motor function by reversing pathological alterations in the functional network architecture. The majority of interhemispheric connections, including M1, S1, and PMA, were involved in motor performance. Interhemispheric functional connections between ipsilesional M1 and contralesional M1 were significantly decreased after stroke (81). The studies (31, 33) indicated that increased functional connections of ipsilesional/contralesional M1 could be served as the main target of motor rehabilitative regimes for stroke patients. Guo et al. (33) demonstrated the increased functional connections between ipsilesional M1 and contralesional PMA were associated with motor recovery after rTMS, suggesting contralesional PMA may be contributed to mediating motor recovery after stroke. Grefkes et al. (36) proved LF-rTMS enhanced coupling of SMA and M1, constituting a significant mechanism for better motor function. Some rodents studies confirmed improving function is mostly dependent on the restoration of neural networks in the ipsilesional hemisphere (82). Motor recovery is the result of a repair of ipsilesional effective connectivity between SMA and M1 as well as a reduction of abnormal transcallosal impacts. The activation of SMA is linked to the attention to intention, which is essential for voluntary motor movement, and it is an important compensatory area of movement (83). Gottlieb et al. (37) found the connectivity between the motor cortex and the angular gyrus increased after the LF-rTMS, and the angular gyrus is responsible for controlling upper limb motions (84). A previous study has shown that the postcentral gyrus is the primary somatosensory cortical center (85). The preservation of connectivity between the ipsilesional M1 and the contralesional postcentral gyrus indicates better motor performance (86). Therefore, the activation of contralesional postcentral gyrus is a significant part in the reorganization of motor function. Upper limb movement is closely related to M1 region located in the precentral gyrus (87). A better prognosis of motor function is associated with activation of precentral gyrus and postcentral gyrus in stroke patients (88). In an earlier study, the superior parietal gyrus was shown to be part of space object positioning and visual-motor coordination (89). Chen et al. (34) confirm increased functional connectivity in the contralesional precentral gyrus, postcentral

gyrus, and the parietal gyrus in the recovery of motor function. Changes in interhemispheric connectivities are associated with an imbalance between the contralesional hemispheres and ipsilesional hemispheres after stroke onset. Interhemispheric connectivities are increased by the rebalancing of bilateral hemispheric networks during the recovery period. These functional connectivity changes were linked to the recovery of motor function restoration and could be targeted for neurorehabilitation interventions following stroke. Although LF-rTMS and HF-rTMS have opposite effects on cortical activity of the directly stimulated region, these two frequencies of rTMS tend to increase functional connectivity. Especially, most studies using LF-rTMS protocol, reported increases in functional connectivity rather than reductions. Interhemispheric functional connection decreased sharply, and increased significantly in parallel with motor recovery after rTMS, suggesting the importance of interhemispheric functional connection in the recovery of motor function after stroke.

In summary, these studies have demonstrated that rTMS can promote interhemispheric connectivity by increasing activation in ipsilesional regions, enhancing excitatory connectivity from the ipsilesional to the contralesional brain regions, and reducing stroke-induced transcallosal inhibition to facilitate facilitates the recovery of motor performance.

RTMS protocols

It has been shown that the long-lasting after-effects of plasticity-inducing rTMS can easily impact human behavior. The combination of rTMS with fMRI provides a unique opportunity to elucidate the mechanistic basis for such behavioral effects. Thus, this combination allows us to gain insight into the local and distant effects of different interventions and provides a means of addressing changes in functional connectivity that underlie potential behavioral effects. The currently accepted strategy to promote the recovery of motor function after stroke is to either apply HF-rTMS (31–33) to the M1 region of the ipsilesional hemisphere or apply LF-rTMS (30–33, 35–38) to the M1 region of the contralesional hemisphere. In clinical practice, the combination of HF-rTMS and LF-rTMS is relatively rare, but some studies have shown that the combination of the two is feasible and safe, and the therapeutic effect is better than the single application (90). In comparison to sham stimulation or single-course rTMS, coupled inhibitory-facilitatory rTMS significantly improved motor function.

rTMS is a noninvasive neuromodulation technique whose variability in the stimulation intensity, frequency, duration, and target location influence modulatory effects (91). The HF-rTMS stimulation and the LF-rTMS stimulation both can improve motor function by rebalancing motor cortex excitability and regulating connectivity in patients after stroke (32). Du et al. (25) found that rTMS could dramatically enhance motor function, and this enhancement was strongly connected with changes in the motor cortex excitability, and LF-rTMS may have more profound effects than HF-rTMS. The HF-rTMS group offers better advantages for the functional connection recombination of the motor network on the ipsilesional brain, bringing greater benefits for the recovery of motor disorders (33). A meta-analysis revealed that HF-rTMS is marginally more efficient than LF-rTMS (92). Another meta-analysis, however, revealed a different outcome (93). Chen et al. (34) also found that the combined application of low-frequency and high-frequency rTMS had a synergistic effect on improving motor function and cortical excitability of patients. At present, the optimal effective frequency of rTMS is still uncertain. The 2014 European Guidelines for the treatment of rTMS indicate that both LF-rTMS or HF-rTMS can be used to restore motor function after stroke (94). The application of LF-rTMS shows level A evidence for motor stroke in the post-acute phase, as well as level C evidence in the chronic phase. While the application of HF-rTMS shows level A evidence in the post-acute phase (15).

Limitations and future direction

The summary of current evidence suggests that rTMS may change neural plasticity, which was associated with movement improvement after stroke. This scoping review revealed some important findings. First, in the process of searching the literature, we discovered most rTMS studies only focused on the functional connectivity changes in motor network, and few studies have involved deep brain areas. However, many movement diseases, including Parkinson's disease and stroke, are associated with the damage of the thalamus, putamen, cerebellum, and other subcortical regions (95, 96). As the included studies in the review seldom focused on whole-brain connectivity, but rather specific regions of interest, more researches should pay attention to the whole-brain connectivity. In the future, the regulation mechanism of rTMS on deep brain regions can be explored by analyzing the changes in functional connectivity in cortical and subcortical regions, which will provide a reference for the treatment of these diseases. Second, it should be highlighted that the number of studies applied fMRI to investigate the aftereffects of rTMS on the functional brain network following stroke is relatively limited, and the effects of rTMS, in particular, have seldom been mapped with task-based fMRI. Future research should concentrate on mapping the effects of rTMS on task-related activity and connectivity (97). Third, the last three decades have seen the progress of neuroimaging technology, which allow people to examine neuroplasticity noninvasively. However, each of them has its merits and demerits. Multimodal neuroimaging technology can merge information and overcome some of the limitations of the stand-alone neuroimaging method. Multimodal fusion technology permits more granular inspection of the underlying mechanisms of plastic after-effects of rTMS protocols. However, studies using multimodal fusion technology to explore neural mechanisms underlying rTMS intervention are relatively rare. Therefore, incorporating multimodal neuroimaging technology into clinical trials will help expand our knowledge of neural mechanisms underlying rTMS intervention and ultimately tailor the therapeutic use of rTMS. Fourth, fMRI studies have confirmed the role of bilateral M1 areas after a stroke, indicating functional connectivity between the areas and functional connectivity between M1 and other brain areas is associated with motor recovery (63). Although M1, as an important brain area responsible for planning

and performing motor functions, is the ideal stimulated brain area, stimulating rather the PMA has many benefits (98). When brain damage is severe, PMA of the contralesional hemispheres exerts an excitatory effect on the M1 affected hemisphere. When brain lesions are small, PMA of the contralesional hemispheres exerts an inhibitory effect (99). SMA is related to complicated motions and the programming of these complicated motions, which is a crucial issue to address in motor skill recovery. In addition, for patients with motor dysfunction accompanied by cognitive impairment or depression, the left dorsolateral frontal lobe can be selected as the stimulation target (100), and the recovery of motor function can be promoted by improving the cognitive and depression symptom. To date, studies have focused mostly on the motor cortex, whereas other parts of the brain are still underrepresented. Future researches may deepen the topic to concomitantly evaluate different targets areas. Lastly, none of the studies perform fMRI during rTMS, and a fMRI scan was usually performed at baseline and after rTMS that lasted several weeks. This approach is limited in its sensitivity to capture post-stimulation effects, and is likely to fail to map the immediate consequences of the stimulation. For solving this problem, simultaneous rTMS-fMRI, in which rTMS is applied during fMRI scan, permits research into the immediate effects of rTMS and the underlying processes of rTMS-mediated neuronal regulation.

Conclusion

The studies reviewed above strongly suggest that rTMS can be used to modulate disturbed cortical networks thereby improving motor function. As a noninvasive imaging method, fMRI is commonly used in brain activation studies. It works based on the changes in blood flow caused by neuronal activity. In response to neuronal activity, blood flow to the region can be accelerated to meet the increased demand for oxygen (101). fMRI studies can show a changing process of recovery of motor function. fMRI studies can start in the first few days poststroke and continue for several months to a year poststroke (102). The integration of fMRI and rTMS represents a powerful tool for manipulating and observing neural activity, which can unravel the mechanisms of TMS-mediated neural modulation. We deeply think that creating innovative techniques for the effective treatment of post-stroke movement disorders requires a thorough knowledge of the neural mechanisms underlying recovery from movement disorders.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SC and RX: conception and design of the work, acquisition, analysis, interpretation of data for the work, and drafting the manuscript. PW, PL, and WF: supervising the manuscript and final approval of the manuscript to be submitted. YZ and PL: revising the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke.* (2021) 52:e364–467. doi: 10.1161/STR.0000000000000375

3. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation.* (2020) 141:e139–596. doi: 10.1161/CIR.0000000000000746

4. Micera S, Caleo M, Chisari C, Hummel FC, Pedrocchi A. Advanced neurotechnologies for the restoration of motor function. *Neuron.* (2020) 105:604–20. doi: 10.1016/j.neuron.2020.01.039

5. Guggisberg AG, Koch PJ, Hummel FC, Buetefisch CM. Brain networks and their relevance for stroke rehabilitation. *Clin Neurophysiol.* (2019) 130:1098–124. doi: 10.1016/j.clinph.2019.04.004

6. Lee J, Park E, Lee A, Chang WH, Kim DS, Kim YH. Alteration and role of interhemispheric and intrahemispheric connectivity in motor network after stroke. *Brain Topogr.* (2018) 31:708–19. doi: 10.1007/s10548-018-0644-9

7. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, Jong A, et al. Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. Part one: rehabilitation and recovery following stroke; 6th edition update 2019. *Int J Stroke.* (2020) 15:763–88. doi: 10.1177/1747493019897843

8. Heng HM, Lu MK, Chou LW, Meng NH, Huang HC, Hamada M, et al. Changes in balance, gait and electroencephalography oscillations after robot-assisted gait training: an exploratory study in people with chronic stroke. *Brain Sci.* (2020) 10:821. doi: 10.3390/brainsci10110821

9. Cirillo C, Brihmat N, Castel-Lacanal E, Le Friec A, Barbieux-Guillot M, Raposo N, et al. Post-stroke remodeling processes in animal models and humans. *J Cereb Blood Flow Metab.* (2020) 40:3–22. doi: 10.1177/0271678X19882788

10. Dorszewska J, Kozubski W, Waleszczyk W, Zabel M, Ong K. Neuroplasticity in the pathology of neurodegenerative diseases. *Neural Plast.* (2020) 2020:4245821. doi: 10.1155/2020/4245821

11. Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. *Front Neural Circuits.* (2016) 10:56. doi: 10.3389/fncir.2016.00056

12. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol.* (2014) 10:597–608. doi: 10.1038/nrneurol.2014.162

13. Jannati A, Oberman LM, Rotenberg A, Pascual-Leone A. Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation. *Neuropsychopharmacology.* (2023) 48:191–208. doi: 10.1038/s41386-022-01453-8

14. Long H, Wang H, Zhao C, Duan Q, Feng F, Hui N, et al. Effects of combining high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. *Restor Neurol Neurosci.* (2018) 36:21–30. doi: 10.3233/RNN-170733

15. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol.* (2020) 131:474–528. doi: 10.1016/j.clinph.2019.11.002

16. Buchbinder BR. Functional magnetic resonance imaging. *Handb Clin Neurol.* (2016) 135:61–92. doi: 10.1016/B978-0-444-53485-9.00004-0

17. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A.* (2004) 101:4637–42. doi: 10.1073/pnas.0308627101

18. Stagg CJ, O'Shea J, Johansen-Berg H. Imaging the effects of rTMS-induced cortical plasticity. *Restor Neurol Neurosci.* (2010) 28:425–36. doi: 10.3233/RNN-2010-0553

19. Wang X, Li L, Wei W, Zhu T, Huang GF Li X, et al. Altered activation in sensorimotor network after applying rTMS over the primary motor cortex at different frequencies. *Brain Behav.* (2020) 10:e1670. doi: 10.1002/brb3.1670

20. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med.* (1995) 34:537–41. doi: 10.1002/mrm.1910340409

21. Beynel L, Powers JP, Appelbaum LG. Effects of repetitive transcranial magnetic stimulation on resting-state connectivity: a systematic review. *Neuroimage.* (2020) 211:116596. doi: 10.1016/j.neuroimage.2020.116596

22. Ge R, Humaira A, Gregory E, Alamian G, MacMillan EL, Barlow L, et al. Predictive value of acute neuroplastic response to rTMS in treatment outcome in depression: a concurrent TMS-fMRI trial. *Am J Psychiatry.* (2022) 179:500–08. doi: 10.1176/appi.ajp.21050541

23. Szelenberger R, Kostka J, Saluk-Bijak J, Miller E. Pharmacological interventions and rehabilitation approach for enhancing brain self-repair and stroke recovery. *Curr Neuropharmacol.* (2020) 18:51–64. doi: 10.2174/1570159X17666190726104139

24. Caglayan AB, Beker MC, Caglayan B, Yalcin E, Caglayan A, Yulug B, et al. Acute and post-acute neuromodulation induces stroke recovery by promoting survival signaling, neurogenesis, and pyramidal tract plasticity. *Front Cell Neurosci.* (2019) 13:144. doi: 10.3389/fncel.2019.00144

25. Du J, Tian L, Liu W, Hu J, Xu G, Ma M, et al. Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. *Eur J Neurol.* (2016) 23:1666–72. doi: 10.1111/ene.13105

26. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol.* (2005) 8:19–32. doi: 10.1080/1364557032000119616

27. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* (2014) 67:1291–94. doi: 10.1016/j.jclinepi.2014.03.013

28. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* (1998) 52:377–84. doi: 10.1136/jech.52.6.377

29. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Can J Ophthalmol.* (2008) 43:180–87. doi: 10.3129/i08-001

30. Ueda R, Yamada N, Abo M, Ruwan PW, Senoo A. MRI evaluation of motor function recovery by rTMS and intensive occupational therapy and changes in the activity of motor cortex. *Int J Neurosci.* (2020) 130:309–17. doi: 10.1080/00207454.2019.1680553

31. Juan D, Yao W, Li J, Yang F, Hu J, Xu Q, et al. Motor network reorganization after repetitive transcranial magnetic stimulation in early stroke patients: a resting state fMRI study. *Neurorehabil Neural Repair.* (2022) 36:61–8. doi: 10.1177/15459683211054184

32. Du J, Yang F, Hu J, Hu J, Xu Q, Cong N, et al. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. *Neuroimage Clin.* (2019) 21:101620. doi: 10.1016/j.nicl.2018.101620

33. Guo Z, Jin Y, Bai X, Jiang B, He L, McClure MA, et al. Distinction of high- and low-frequency repetitive transcranial magnetic stimulation on the functional reorganization of the motor network in stroke patients. *Neural Plast.* (2021) 2021:8873221. doi: 10.1155/2021/8873221

34. Chen Q, Shen W, Sun H, Zhang H, Liu C, Chen Z, et al. The effect of coupled inhibitory-facilitatory repetitive transcranial magnetic stimulation on shaping early reorganization of the motor network after stroke. *Brain Res.* (2022) 1790:147959. doi: 10.1016/j.brainres.2022.147959

35. Wanni AP, Ryo U, Karunarathna S, Senoo A. Evaluation of fMRI activation in hemiparetic stroke patients after rehabilitation with low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy. *Int J Neurosci.* (2021). doi: 10.1080/00207454.2021.1968858. [Epub ahead of print].

36. Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. *Neuroimage.* (2010) 50:233–42. doi: 10.1016/j.neuroimage.2009.12.029

37. Gottlieb A, Boltzmann M, Schmidt SB, Gutenbrunner C, Krauss JK, Stangel M, et al. Treatment of upper limb spasticity with inhibitory repetitive transcranial magnetic stimulation: a randomized placebo-controlled trial. *NeuroRehabilitation.* (2021) 49:425–34. doi: 10.3233/NRE-210088

38. Tosun A, Ture S, Askin A, Yardimci EU, Demirdal SU, Kurt IT, et al. Effects of low-frequency repetitive transcranial magnetic stimulation and neuromuscular electrical stimulation on upper extremity motor recovery in the early period after stroke: a preliminary study. *Top Stroke Rehabil.* (2017) 24:361–67. doi: 10.1080/10749357.2017.1305644

39. James MA. Use of the medical research council muscle strength grading system in the upper extremity. *J Hand Surg Am.* (2007) 32:154–56. doi: 10.1016/j.jhsa.2006.11.008

40. Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing wolf motor function test as outcome measure for research in patients after stroke. *Stroke.* (2001) 32:1635–39. doi: 10.1161/01.STR.32.7.1635

41. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, action research arm test and box and block test: a multicentre study. *Clin Rehabil.* (2005) 19:404–11. doi: 10.1191/0269215505cr832oa

42. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol.* (1980) 19:382–89. doi: 10.1159/000115178

43. Fayazi M, Dehkordi SN, Dadgoo M, Salehi M. Test-retest reliability of motricity index strength assessments for lower extremity in post stroke hemiparesis. *Med J Islam Repub Iran.* (2012) 26:27–30.

44. Haggag H, Hodgson C. Clinimetrics: modified Rankin scale (MRS). *J Physiother.* (2022) 68:281. doi: 10.1016/j.jphys.2022.05.017

45. Ohura T, Hase K, Nakajima Y, Nakayama T. Validity and reliability of a performance evaluation tool based on the modified Barthel index for stroke patients. *BMC Med Res Methodol.* (2017) 17:131. doi: 10.1186/s12874-017-0409-2

46. Dromerick AW, Edwards DF, Diringer MN. Sensitivity to changes in disability after stroke: a comparison of four scales useful in clinical trials. *J Rehabil Res Dev.* (2003) 40:1–08. doi: 10.1682/JRRD.2003.01.0001

47. Motolese F, Capone F, Di Lazzaro V. New tools for shaping plasticity to enhance recovery after stroke. *Handb Clin Neurol.* (2022) 184:299–315. doi: 10.1016/B978-0-12-819410-2.00016-3

48. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. *Brain.* (2011) 134(Pt 6):1591–609. doi: 10.1093/brain/awr039

49. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol.* (2006) 5:708–12. doi: 10.1016/S1474-4422(06)70525-7

50. Kraft AW, Bauer AQ, Culver JP, Lee JM. Sensory deprivation after focal ischemia in mice accelerates brain remapping and improves functional recovery through arc-dependent synaptic plasticity. *Sci Transl Med.* (2018) 10:eaag1328. doi: 10.1126/scitranslmed.aag1328

51. Liu G, Dang C, Chen X, Xing S, Dani K, Xie C, et al. Structural remodeling of white matter in the contralesional hemisphere is correlated with early motor recovery in patients with subcortical infarction. *Restor Neurol Neurosci.* (2015) 33:309–19. doi: 10.3233/RNN-140442

52. Luo HY, Rahman M, Bobrovskaya L, Zhou XF. The level of proBDNF in blood lymphocytes is correlated with that in the brain of rats with photothrombotic ischemic stroke. *Neurotox Res.* (2019) 36:49–57. doi: 10.1007/s12640-019-00022-0

53. Tennant KA, Taylor SL, White ER, Brown CE. Optogenetic rewiring of thalamocortical circuits to restore function in the stroke injured brain. *Nat Commun.* (2017) 8:15879. doi: 10.1038/ncomms15879

54. Rizzi G, Coban M, Tan KR. Excitatory rubral cells encode the acquisition of novel complex motor tasks. *Nat Commun.* (2019) 10:2241. doi: 10.1038/s41467-019-10223-y

55. Hartwigsen G. Adaptive plasticity in the healthy language network: implications for language recovery after stroke. *Neural Plast.* (2016) 2016:9674790. doi: 10.1155/2016/9674790

56. Schulz R, Park CH, Boudrias MH, Gerloff C, Hummel FC, Ward NS. Assessing the integrity of corticospinal pathways from primary and secondary cortical motor areas after stroke. *Stroke.* (2012) 43:2248–51. doi: 10.1161/STROKEAHA.112.662619

57. Zhang J, Lu C, Wu X, Nie D, Yu H. Neuroplasticity of acupuncture for stroke: an evidence-based review of MRI. *Neural Plast.* (2021) 2021:2662585. doi: 10.1155/2021/2662585

58. Seitz RJ, Hoflich P, Binkofski F, Tellmann L, Herzog H, Freund HJ. Role of the premotor cortex in recovery from middle cerebral artery infarction. *Arch Neurol.* (1998) 55:1081–88. doi: 10.1001/archneur.55.8.1081

59. Weiller C, Chollet F, Friston KJ, Wise RJ, Frackowiak RS. Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Ann Neurol.* (1992) 31:463–72. doi: 10.1002/ana.410310502

60. Sun L, Yin D, Zhu Y, Fan M, Zang L, Wu Y, et al. Cortical reorganization after motor imagery training in chronic stroke patients with severe motor impairment: a longitudinal fMRI study. *Neuroradiology.* (2013) 55:913–25. doi: 10.1007/s00234-013-1188-z

61. Altman K, Shavit-Stein E, Maggio N. Post stroke seizures and epilepsy: from proteases to maladaptive plasticity. *Front Cell Neurosci.* (2019) 13:397. doi: 10.3389/fncel.2019.00397

62. Lu Q, Huang G, Chen L, Li W, Liang Z. Structural and functional reorganization following unilateral internal capsule infarction contribute to neurological function recovery. *Neuroradiology.* (2019) 61:1181–90. doi: 10.1007/s00234-019-02278-x

63. Park CH, Chang WH, Ohn SH, Kim ST, Bang OY, Pascual-Leone A, et al. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke.* (2011) 42:1357–62. doi: 10.1161/STROKEAHA.110.596155

64. Golestani AM, Tymchuk S, Demchuk A, Goodyear BG. Longitudinal evaluation of resting-state fMRI after acute stroke with hemiparesis. *Neurorehabil Neural Repair.* (2013) 27:153–63. doi: 10.1177/1545968312457827

65. Urbin MA, Hong X, Lang CE, Carter AR. Resting-state functional connectivity and its association with multiple domains of upper-extremity function in chronic stroke. *Neurorehabil Neural Repair.* (2014) 28:761–69. doi: 10.1177/1545968314522349

66. Xu H, Qin W, Chen H, Jiang L, Li K, Yu C. Contribution of the resting-state functional connectivity of the contralesional primary sensorimotor cortex to motor recovery after subcortical stroke. *PLoS ONE.* (2014) 9:e84729. doi: 10.1371/journal.pone.0084729

67. Wang Q, Zhang D, Zhao YY, Hai H, Ma YW. Effects of high-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex on motor recovery in severe hemiplegic stroke: a randomized clinical trial. *Brain Stimul.* (2020) 13:979–86. doi: 10.1016/j.brs.2020.03.020

68. Plow EB, Sankarasubramanian V, Cunningham DA, Potter-Baker K, Varnerin N, Cohen LG, et al. Models to tailor brain stimulation therapies in stroke. *Neural Plast.* (2016) 2016:4071620. doi: 10.1155/2016/4071620

69. Rehme AK, Eickhoff SB, Rottschy C, Fink GR, Grefkes C. Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *Neuroimage.* (2012) 59:2771–82. doi: 10.1016/j.neuroimage.2011.10.023

70. Marshall RS, Perera GM, Lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke.* (2000) 31:656–61. doi: 10.1161/01.STR.31.3.656

71. Nowak DA, Grefkes C, Dafotakis M, Eickhoff S, Kust J, Karbe H, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch Neurol.* (2008) 65:741–47. doi: 10.1001/archneur.65.6.741

72. Clausi S, Siciliano L, Olivito G, Leggio M. Cerebellum and emotion in social behavior. *Adv Exp Med Biol.* (2022) 1378:235–53. doi: 10.1007/978-3-030-99550-8_15

73. Dickenson JA, Diamond L, King JB, Jenson K, Anderson JS. Understanding heterosexual women's erotic flexibility: the role of attention in sexual evaluations and neural responses to sexual stimuli. *Soc Cogn Affect Neurosci.* (2020) 15:447–65. doi: 10.1093/scan/nsaa058

74. Liu H, Song L, Zhang T. Changes in brain activation in stroke patients after mental practice and physical exercise: a functional MRI study. *Neural Regen Res.* (2014) 9:1474–84. doi: 10.4103/1673-5374.139465

75. Bertolucci F, Chisari C, Fregni F. The potential dual role of transcallosal inhibition in post-stroke motor recovery. *Restor Neurol Neurosci.* (2018) 36:83–97. doi: 10.3233/RNN-170778

76. Baumgartner P, El AM, Bracko O, Luft AR, Wegener S. Sensorimotor stroke alters hippocampo-thalamic network activity. *Sci Rep.* (2018) 8:15770. doi: 10.1038/s41598-018-34002-9

77. Maximo JO, Cadena EJ, Kana RK. The implications of brain connectivity in the neuropsychology of autism. *Neuropsychol Rev.* (2014) 24:16–31. doi: 10.1007/s11065-014-9250-0

78. Chen X, Dang G, Dang C, Liu G, Xing S, Chen Y, et al. An ischemic stroke model of nonhuman primates for remote lesion studies: a behavioral and neuroimaging investigation. *Restor Neurol Neurosci.* (2015) 33:131–42. doi: 10.3233/RNN-140440

79. Hoshino T, Oguchi K, Inoue K, Hoshino A, Hoshiyama M. Relationship between lower limb function and functional connectivity assessed by EEG among motor-related areas after stroke. *Top Stroke Rehabil.* (2021) 28:614–23. doi: 10.1080/10749357.2020.1864986

80. Vecchio F, Tomino C, Miraglia F, Iodice F, Erra C, Di Iorio R, et al. Cortical connectivity from EEG data in acute stroke: a study via graph theory as a potential biomarker for functional recovery. *Int J Psychophysiol.* (2019) 146:133–38. doi: 10.1016/j.ijpsycho.2019.09.012

81. Li Y, Wang Y, Liao C, Huang W, Wu P. Longitudinal brain functional connectivity changes of the cortical motor-related network in subcortical stroke patients with acupuncture treatment. *Neural Plast.* (2017) 2017:5816263. doi: 10.1155/2017/5816263

82. Weber R, Ramos-Cabrer P, Justicia C, Wiedermann D, Strecker C, Sprenger C, et al. Early prediction of functional recovery after experimental stroke: functional magnetic resonance imaging, electrophysiology, and behavioral testing in rats. *J Neurosci.* (2008) 28:1022–29. doi: 10.1523/JNEUROSCI.4147-07.2008

83. Haggard P. Neuroscience. The sources of human volition. *Science.* (2009) 324:731–33. doi: 10.1126/science.1173827

84. Seghier ML. The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist.* (2013) 19:43–61. doi: 10.1177/1073858412440596

85. Li XG, Florence SL, Kaas JH. Areal distributions of cortical neurons projecting to different levels of the caudal brain stem and spinal cord in rats. *Somatosens Mot Res.* (1990) 7:315–35. doi: 10.3109/08990229009144711

86. Yin D, Song F, Xu D, Peterson BS, Sun L, Men W, et al. Patterns in cortical connectivity for determining outcomes in hand function after subcortical stroke. *PLoS ONE.* (2012) 7:e52727. doi: 10.1371/journal.pone.0052727

87. Zhao Z, Wang X, Fan M, Yin D, Sun L, Jia J, et al. Altered effective connectivity of the primary motor cortex in stroke: a resting-state fMRI study with granger causality analysis. *PLoS ONE.* (2016) 11:e166210. doi: 10.1371/journal.pone.0166210

88. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *JAMA.* (2004) 292:1853–61. doi: 10.1001/jama.292.15.1853

89. McGregor HR, Gribble PL. Functional connectivity between somatosensory and motor brain areas predicts individual differences in motor learning by observing. *J Neurophysiol.* (2017) 118:1235–43. doi: 10.1152/jn.00275.2017

90. Chen Q, Shen D, Sun H, Ke J, Wang H, Pan S, et al. Effects of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation on motor recovery in patients following acute cerebral infarction. *NeuroRehabilitation.* (2021) 48:83–96. doi: 10.3233/NRE-201606

91. Grohn H, Gillick BT, Tkac I, Bednarik P, Mascali D, Deelchand DK, et al. Influence of repetitive transcranial magnetic stimulation on human neurochemistry and functional connectivity: a pilot MRI/MRS study at 7T. *Front Neurosci.* (2019) 13:1260. doi: 10.3389/fnins.2019.01260

92. Xiang H, Sun J, Tang X, Zeng K, Wu X. The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil.* (2019) 33:847–64. doi: 10.1177/0269215519829897

93. Lee J, Park E, Lee A, Chang WH, Kim DS, Shin YI, et al. Modulating brain connectivity by simultaneous dual-mode stimulation over bilateral primary motor cortices in subacute stroke patients. *Neural Plast.* (2018) 2018:1458061. doi: 10.1155/2018/1458061

94. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol.* (2014) 125:2150–206. doi: 10.1016/j.clinph.2014.05.021

95. Berardelli A, Suppa A. Noninvasive brain stimulation in Huntington's disease. *Handb Clin Neurol.* (2013) 116:555–60. doi: 10.1016/B978-0-444-53497-2.00044-9

96. Han JY, Kim JH, Park JH, Song MY, Song MK, Kim DJ, et al. Scalp acupuncture and electromagnetic convergence stimulation for patients with cerebral infarction: study protocol for a randomized controlled trial. *Trials.* (2016) 17:490. doi: 10.1186/s13063-016-1611-y

97. Grefkes C, Fink GR. Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials!. *Curr Opin Neurol.* (2016) 29:714–20. doi: 10.1097/WCO.0000000000000395

98. Plow EB, Cunningham DA, Varnerin N, Machado A. Rethinking stimulation of the brain in stroke rehabilitation: why higher motor areas might be better alternatives for patients with greater impairments. *Neuroscientist.* (2015) 21:225–40. doi: 10.1177/1073858414537381

99. Bestmann S, Swayne O, Blankenburg F, Ruff CC, Teo J, Weiskopf N, et al. The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. *J Neurosci.* (2010) 30:11926–37. doi: 10.1523/JNEUROSCI.5642-09.2010

100. Gu SY, Chang MC. The effects of 10-hz repetitive transcranial magnetic stimulation on depression in chronic stroke patients. *Brain Stimul.* (2017) 10:270–74. doi: 10.1016/j.brs.2016.10.010

101. Attwell D, Iadecola C. The neural basis of functional brain imaging signals. *Trends Neurosci.* (2002) 25:621–25. doi: 10.1016/S0166-2236(02)02264-6

102. Nelles G, Spiekermann G, Jueptner M, Leonhardt G, Muller S, Gerhard H, et al. Reorganization of sensory and motor systems in hemiplegic stroke patients. A positron emission tomography study. *Stroke.* (1999) 30:1510–16. doi: 10.1161/01.STR.30.8.1510

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Effects of perioperative cognitive function training on postoperative cognitive dysfunction and postoperative delirium: a systematic review and meta-analysis

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Background: Randomized controlled trials (RCTs) have shown conflicting results regarding the effects of perioperative cognitive training (CT) on the incidence of postoperative cognitive dysfunction (POCD) and postoperative delirium (POD). We, therefore, performed a meta-analysis to assess the overall effects of studies on this topic.

Methods: We searched PubMed, Embase, the Cochrane Library, and Web of Science for all RCTs and cohort studies that investigated the effects of perioperative CT on the incidence of POCD and POD. Data extraction and quality assessment were conducted independently by two researchers.

Results: This study included nine clinical trials with a total of 975 patients. The results showed that perioperative CT significantly reduced the incidence of POCD compared with the control group [risk ratio (RR) = 0.5, 95% CI (confidence interval): 0.28–0.89, $P = 0.02$]. Nevertheless, for the incidence of POD, the difference between the two groups was not statistically significant (RR = 0.64; 95% CI: 0.29–1.43, $P = 0.28$). In addition, the CT group had less postoperative decline in the cognitive function scores compared with the control group [mean differences (MD): 1.58, 95% CI: 0.57–2.59, $P = 0.002$]. In addition, there were no statistically differences in length of hospital stay between the two groups (MD: −0.18, 95% CI: −0.93–0.57, $P = 0.64$). Regarding CT adherence, the proportion of patients in the cognitive training group who completed the planned duration of CT was 10% (95% CI: 0.05–0.14, $P = 0.258$).

Conclusion: Our meta-analysis revealed that perioperative cognitive training is possibly an effective measure to reduce the incidence of POCD, but not for the incidence of POD.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022371306, identifier: CRD42022371306.

KEYWORDS

cognitive function training, cognitive intervention, perioperative cognitive disorders, postoperative cognitive dysfunction, postoperative delirium

1. Introduction

Alongside an aging population, the number of older adults undergoing surgical procedures is also increasing (1). Postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) are common and serious postoperative complications in older people that can prolong hospital stay, reduce the quality of life, increase healthcare costs, and even increase mortality (2, 3). POCD is defined as a significant reduction in the cognitive performance from baseline following surgery (4). The incidence of POCD reportedly varies from 1.5 to 28% (5). POD is a postoperative acute and reversible cerebral dysfunction, mainly manifested as confusion and altered consciousness (6). Studies have reported that the incidence of POD after cardiovascular surgery is as high as 15.3–23.4% (7). The specific mechanisms of POCD and POD are still unclear, but studies have revealed that POCD and POD are the result of the interaction between multiple risk factors, including the patient's cognitive function level, coexisting chronic diseases, nutritional status, use of anesthetic drugs, surgery, and pain (8–12). Because of the difficulty in the prevention and treatment of POCD and POD, it is important to find an effective method to reduce the incidence of POCD and POD.

Cognitive training (CT) refers to training programs that involve structured practice of specific cognitive tasks with the goal of improving performance in one or more cognitive domains, such as memory, attention, or executive function (13). Playing video games, reading books, practicing writing, remembering spatial locations, remembering objects or words, and communicating more with the patient are some common ways of CT (14–17). Many studies have shown that CT can improve cognitive function (18). Ball et al. (19) found that cognitive function training with three different cognitive functions (memory, reasoning, and processing speed) was effective in improving the cognitive performance in older adults over the age of 65 years, which was maintained for 2 years. Walton

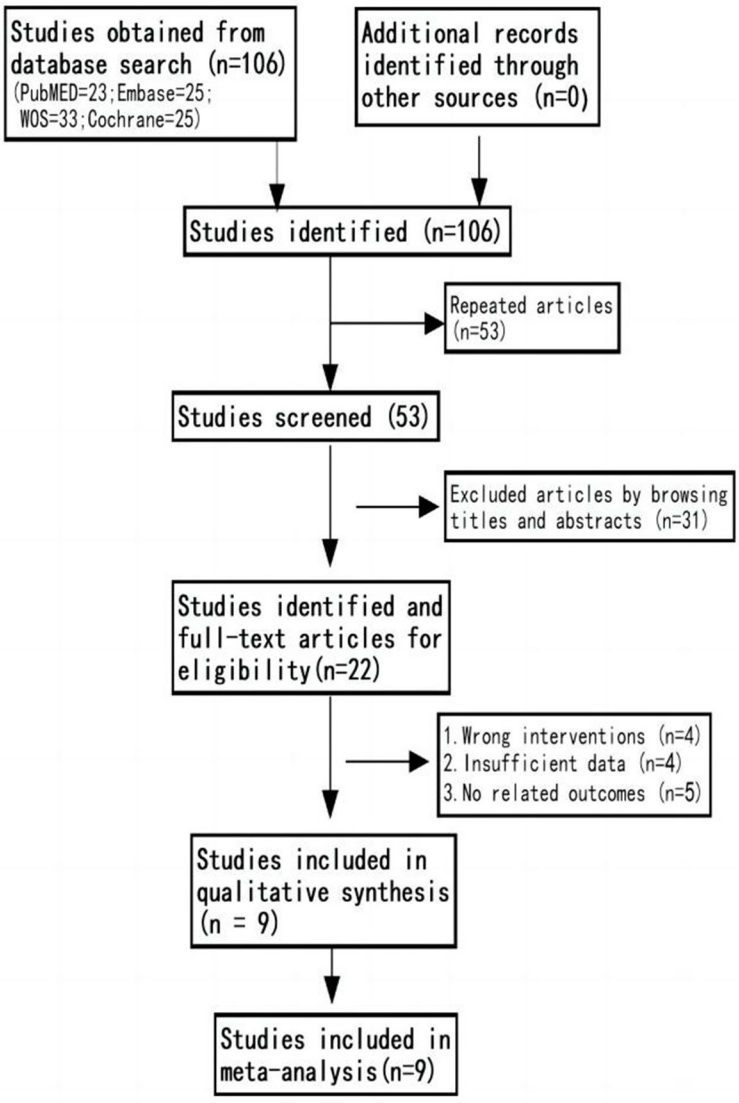

FIGURE 1
Flow diagram of the literature search strategy.

Study	Nation	Type of surgery	Anesthesia methods	outcome	Experimental group				Control group		
					Sample size (m/f)	Age (years)	Interventions	Duration	Sample size	Age (years)	Measures
Vlisides，2019	USA	non-cardiac non-neurosurgical	General Anaesthesia	POD within 3 days postoperatively	23(10/13)	66±4.9	By playing computer games	20mins per day for 7 days preoperatively	29(15/14)	68±5.4	Conventional perioperative treatment
Humeidan,2021	USA	non-cardiac non-neurosurgical	General Anaesthesia	POD within 7 days postoperatively	125(48/77)	67(64-70)	By playing tablet games	>1 hour daily preoperatively	126(40/86)	67.5(63-72)	Conventional perioperative treatment
Saleh, 2015	China	Gastrointestinal tumour	General Anaesthesia	POCD within 7 days postoperatively	69(36/41)	71±6	By memorizing spatial locations	Total 3 hours preoperatively	72(38/34)	70±6	Conventional perioperative
Butz，2022	Germany	Cardiac surgery	General Anaesthesia	POCD at discharge	47(39/8)	71.2±4.6	By reading and writing	36mins daily for three weeks postoperatively	47(34/13)	73.0±4.9	Conventional perioperative treatment
Duan，2022	China	Orthopaedics	Intraspinal anaesthesia	POCD within 7 days postoperatively	50(21/29)	70±6	By reading books	Preoperative lasts until 6 days of surgery，30mins a day	36(18/18)	70±6	Conventional perioperative treatment
O'Gara，2020	Israel	Cardiac surgery	General Anaesthesia	POCD at discharge/POD 1-7 days postoperatively	20(14/6)	70±6	By using mobile phone software	Preoperative lasts until 4 weeks postoperative, 30mins a day	20(15/5)	69±7	Conventional perioperative treatment
Lee, 2013	Korea	Cardiac surgery	General Anaesthesia	POD within 7 days postoperatively	49(33/16)	58.5 ± 10.9	By increasing communication with patients	1 hour preoperatively and 1 hour postoperatively	46(30/16)	61.7± 10.4	Conventional perioperative treatment
Chen，2011	Taiwan, China	Abdominal Surgery	General Anaesthesia	POD at discharge	102(47/55)	73.3±5.4	By communication and word games	Preoperative lasts until about 7 days postoperative, 3 times a	77(34/43)	72.6±6.1	Conventional perioperative treatment
Cheng，2012	Taiwan, China	Orthopaedics	General/Intra spinal Anaesthesia	POCD at discharge	25(21/4)	70.3±6.3	By discussing current events, recalling past events and word games	Postoperative duration until discharge, 20-30 mins a day	25(24/1)	72.6±5.1	Conventional perioperative treatment

FIGURE 2
Characteristics of the included studies. Plus-minus values are mean ± SD. IQR, interquartile range.

et al. (20), Xuefang et al. (21), Hu et al. (22), and Woolf et al. (23) found that CT can improve the cognitive function of patients with Parkinson's disease, stroke, mild cognitive impairment, and major depression, respectively. However, the effects of CT on POCD and POD are controversial. Saleh et al. (14) showed that preoperative CT significantly reduced the incidence of POCD after gastrointestinal surgery. However, other studies have found no significant difference in the incidence of POCD and POD between patients receiving perioperative CT and the control group, and CT had limitations in terms of the feasibility and patient adherence (24, 25). Therefore, in this meta-analysis, we aimed to investigate the effects of CT on POCD and POD.

2. Methods

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist (26). Ethics approval was not necessary because this study was a systematic review and meta-analysis. We registered this study in PROSPERO under number CRD42022371306 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022371306).

2.1. Search strategy

Two reviewers (Li Zhao and Hongyu Zhu) independently searched PubMed, EMBASE, the Cochrane library, and Web of Science from the inception of the databases to 31 August 2022. The search terms used were as follows: "cognitive training or cognitive intervention or memory training" and "perioperative neurocognitive disorders or postoperative cognitive dysfunction or POCD or postoperative delirium or POD". No limitation was imposed. In addition, we searched the reference lists of the identified articles for relevant studies and manually screened the additional eligible studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria of this study were as follows: (1) Patients in the intervention group received either preoperative CT, postoperative CT, or both. (2) Patients in the control group were treated only for the disease itself, without CT. (3) The diagnostic criteria of POCD and POD were clearly stated in the study. (4) Primary or secondary outcomes must include the incidence of POCD or POD. (5) There was no statistical difference in the cognitive function between the CT and control groups at the time of enrollment. (6) The included studies should be randomized controlled studies or cohort studies. We excluded studies where the data could not be extracted and used for analysis.

2.3. Outcomes

The primary outcomes were the incidence of POD and POCD. Secondary outcomes were CT adherence, length of hospital stay, and scores of cognitive function.

2.4. Data extraction and assessment of risk of bias

Data extraction and quality assessment were carried out by two independent authors (Li Zhao and Hongyu Zhu). If disagreements

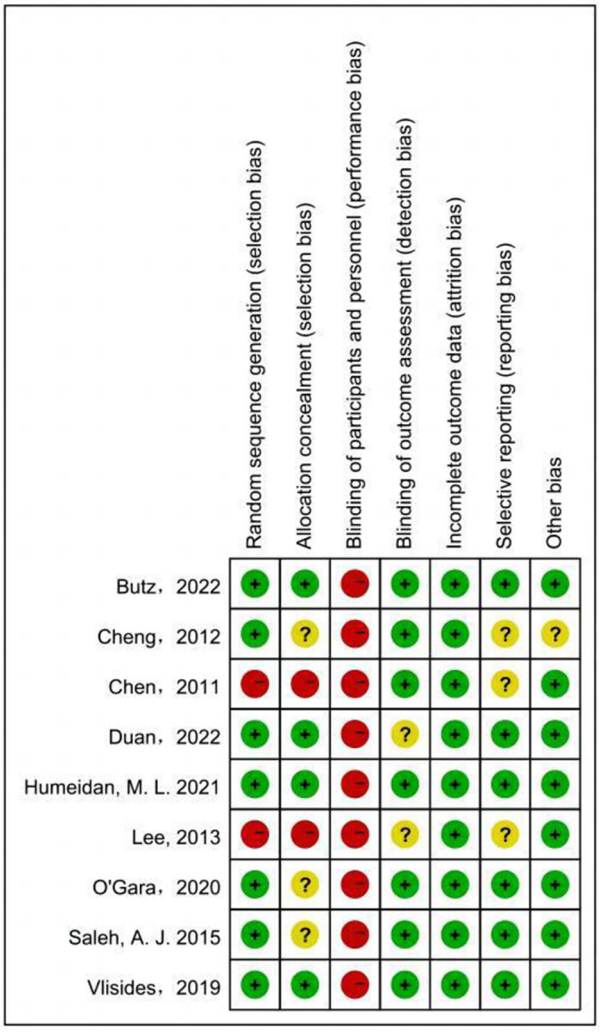

FIGURE 3
Risk-of-bias summary for all the trials.

arose, they were discussed with the corresponding author (Linji Li). The following information was extracted: first author's name, year of publication, country, the average age of the participants, sample size, types of surgery, type of anesthesia, intervention measures, and results of POCD and POD assessment. Study quality was assessed using the Cochrane risk of bias tool. Some data conversion tools were used to convert interquartile ranges to means and standard deviation in some studies (27).

2.5. Statistical analysis

Data analysis was performed by Review Manager (version 5.3) and Stata (version 14) software. Dichotomous and continuous data were analyzed using risk ratio (RR) and mean differences (MD) with 95% confidence interval (CI), with a P-value of <0.05 considered statistically significant. Statistical heterogeneity was used to identify the differences among the included studies. I^2 statistic was used to assess statistical heterogeneity, with $I^2 > 50\%$ considered to be high heterogeneity and $I^2 < 50\%$ considered to be low heterogeneity (28). The random effects model was used if there was high heterogeneity, while the fixed effects model was used if low heterogeneity was detected (29). Sensitivity analyses and subgroup analyses were used for studies with high heterogeneity. Publication bias was measured by Egger's test (30).

3. Results

3.1. Identification and characteristics of the studies

We initially identified a total of 106 studies through database search. Nine studies were eventually included, with a sample size of 975 cases, including 500 cases in the CT group and 475 cases in the control group (14–17, 24, 25, 31–33). The flow chart of study selection is shown in Figure 1.

The characteristics of the studies are shown in Figure 2. A total of five studies assessed the effects of CT on POCD, and five studies assessed the effects of CT on POD.

3.2. Quality of the included studies

The results of assessing the risk of bias for the included studies are shown in the Figure 3. Two studies were considered to have high risk of random sequence generation and allocation concealment (31, 33). Three studies were considered to have unclear risk in allocation concealment (14, 24, 31). None of the included studies were blinded to patients probably because CT requires patient cooperation and takes a long time. Blinding for outcome assessment was unclear in two studies (32, 33). Clinical registrations for three studies were not found, and therefore, the risk was unclear for selective reporting (16, 31, 33). The total sample size of a study was only 50 people, which may have led to partial bias (16).

3.3. Primary outcome

3.3.1. Incidence of POCD

Five studies assessed the incidence of POCD (14, 16, 17, 24, 32). Two studies (14, 32) reported the incidence of POCD at 7 days postoperatively, and three studies (16, 17, 24) reported the incidence of POCD at hospital discharge. Due to the high heterogeneity ($I^2 = 61\%$), the random effects model was chosen and showed that the CT group had a significantly reduced incidence of POCD compared to the control group (RR = 0.5, 95% CI: 0.28–0.89, $P = 0.02$, Figure 4). No significant publication bias was found using Egger's test ($P = 0.718$). The Galbraith plots (Figure 5) show a clear heterogeneity between the study by O'Gara et al. and other studies. Sensitivity analysis revealed a significant decrease in heterogeneity ($I^2 = 0$) when the study by O'Gara et al. was removed, but the result was unchanged (RR = 0.38, 95% CI: 0.14–0.49, $P < 0.00001$). Subgroup analysis (Figure 4) showed significant differences between the CT group and control group for non-cardiac surgery ($I^2 = 0\%$, RR = 0.39, 95%: 0.24–0.62, $P = 0.0001$) but not for cardiac surgery ($I^2 = 82\%$, RR = 0.74, 95% CI: 0.19–2.79, $P = 0.65$). Subgroup analysis of the timing of intervention

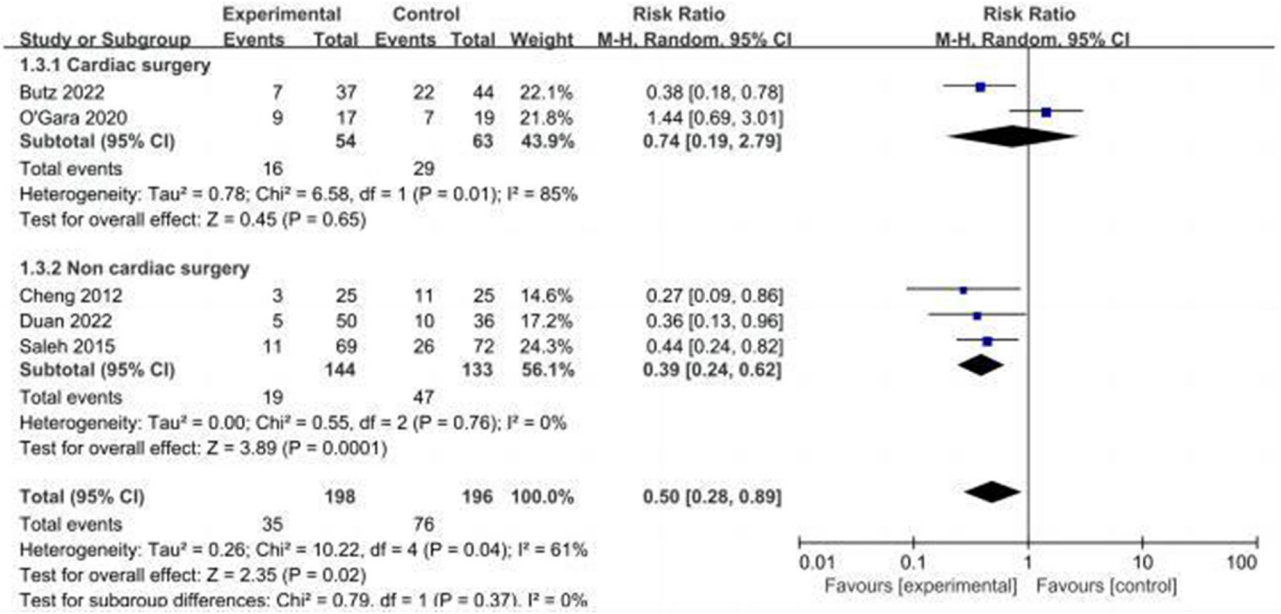

FIGURE 4
Forest plot of primary outcome—incidence of POCD.

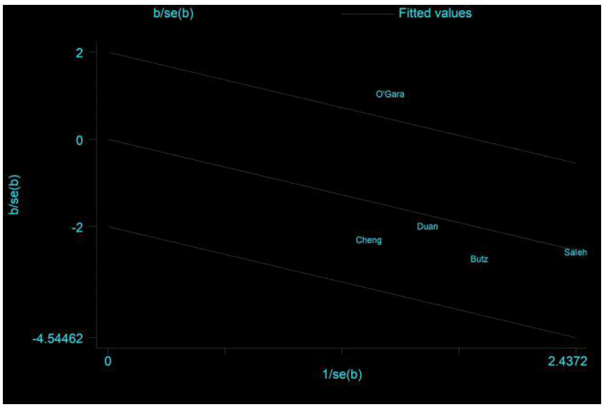

FIGURE 5
Galbraith plots of primary outcome—incidence of POCD.

(Figure 6) revealed that preoperative CT (RR = 0.44, 95% CI: 0.24–0.82, $P = 0.01$) or postoperative CT (RR = 0.41, 95%: 0.26–0.66, $P = 0.0003$) significantly reduced the incidence of POCD, but CT during both preoperative and postoperative periods showed no statistically significant difference compared to the control group (RR = 0.72, 95% CI: 0.17–3.03, $P = 0.65$).

3.3.2. Incidence of POD

Five studies assessed the incidence of POD (15, 24, 25, 31, 33). One study (25) reported POD within 3 days postoperatively, three studies (15, 24, 33) reported POD within 7 days postoperatively, and one study (31) reported POD at discharge. Due to the high heterogeneity ($I^2 = 67\%$), we chose the random effects model and the results showed no statistically significant difference between the two groups (RR = 0.64; 95% CI: 0.29–1.43, $P = 0.28$, Figure 7). No significant publication bias was found according to Egger's test ($P = 0.810$). On sensitivity analysis, the results did not change when any of the studies were removed. The Galbraith plots (Figure 8) show a clear heterogeneity between the study by Chen et al. and other studies. The results of the subgroup analysis (Figure 7) showed that there was no statistically significant difference between the CT group and control group for both cardiac surgery (RR = 0.71, 95% CI: 0.16–3.22, $P = 0.65$) and non-cardiac surgery (RR = 0.54, 95% CI: 0.14–2.11, $P = 0.38$). Subgroup analysis of the timing of intervention revealed (Figure 9) that preoperative CT (RR = 0.86, 95% CI: 0.37–1.98, $P = 0.73$) and CT during both the preoperative and postoperative periods (RR = 0.37, 95% CI: 0.06–2.15, $P = 0.27$) were not statistically different compared to the control group.

3.4. Secondary outcome

3.4.1. Cognitive training adherence

Two studies reported CT adherence in the intervention group (15, 25). We defined CT adherence as the proportion of patients in the studies who completed the planned duration of CT. Due to high heterogeneity ($I^2 = 21.9\%$), the fixed effects model was chosen and the result showed that the proportion of patients in the CT group who completed the planned duration of CT was 10% (95% CI: 0.05–0.14, $P < 0.001$, Figure 10).

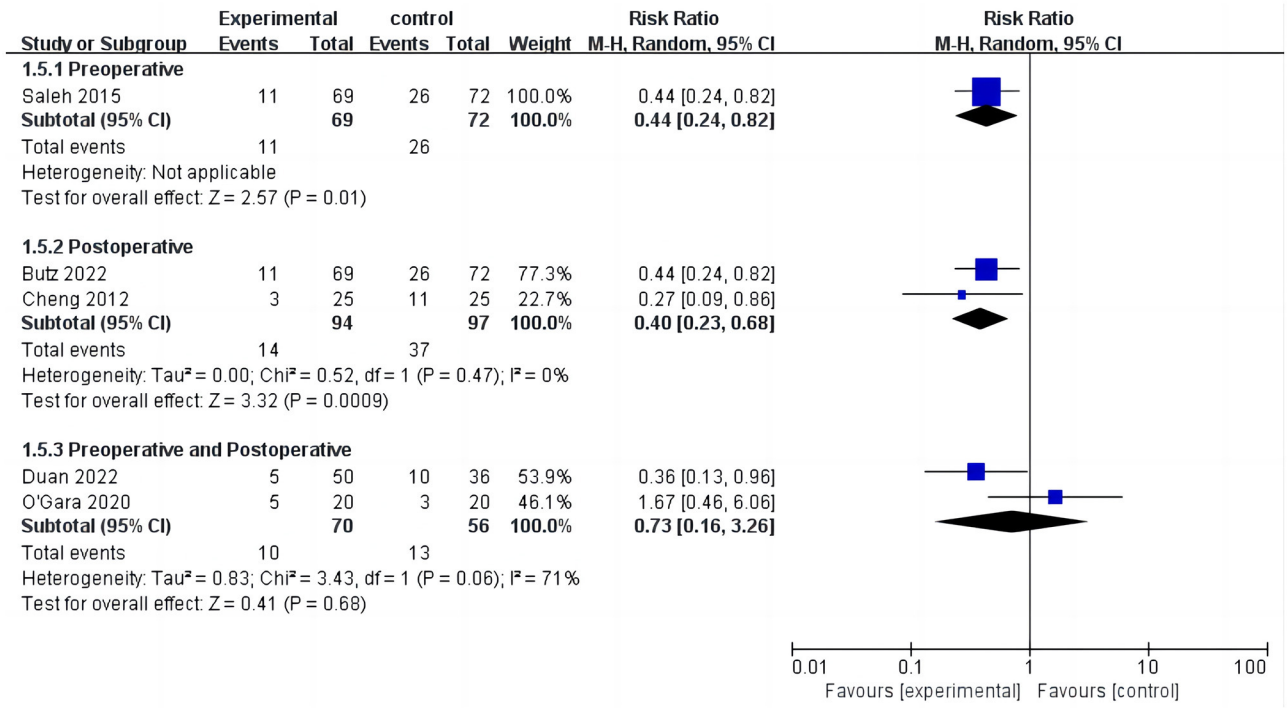

FIGURE 6
Subgroup analysis of cognitive training timing—incidence of POCD.

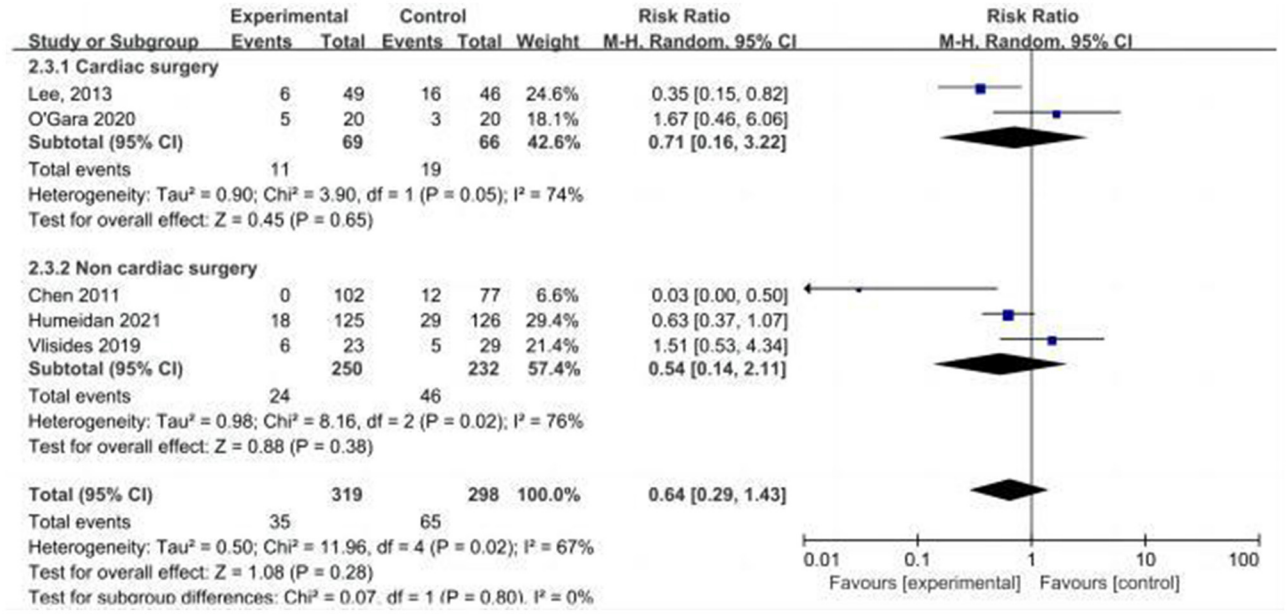

FIGURE 7
Forest plot of primary outcome—incidence of POD.

3.4.2. Scores of cognitive function

Two studies (16, 31) used the Mini-mental State Examination (MMSE) scores to assess cognitive function, and one study (24) used the Montreal Cognitive Assessment (MOCA) scores. We extracted the difference by subtracting the baseline measurement from the post-intervention assessment scores of cognitive function

in the studies. Due to high heterogeneity ($I^2 = 85\%$), we selected the random effects model. The results showed less decline in MMSE scores in the CT group compared to the control group (MD = 1.58, 95% CI: 0.57–2.59, $P = 0.002$, Figure 11). Another study used MOCA scores, and the difference between the two groups was not statistically significant ($P = 0.74$).

3.4.3. Length of hospital stay

A total of five studies evaluated the length of hospital stay in the CT and control groups (14, 16, 24, 31, 32). Due to high heterogeneity ($I^2 = 73\%$), we used the random effects model and the results showed that the difference in the length of hospital stay between the CT and control groups was not statistically significant (MD: −0.18, 95% CI: −0.93–0.57, $P = 0.64$, Figure 12). On sensitivity analysis, there was a significant decrease in heterogeneity ($I^2 = 1\%$) when the study by Saleh et al. was removed, but the result was unchanged (MD: 0.08, 95% CI: −0.30–0.46, $P = 0.68$).

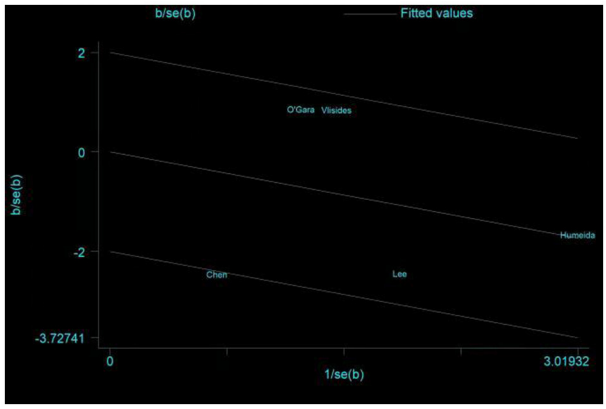

FIGURE 8
Galbraith plots of primary outcome—incidence of POD.

4. Discussion

With the increasing demand for comfortable perioperative care, more studies have begun to focus on postoperative complications (34). We, therefore, carried out this meta-analysis to evaluate the effect of perioperative CT on POCD and POD. In this meta-analysis, we found that perioperative CT is potentially an effective measure to reduce the incidence of POCD but not the incidence of POD. In addition, our study showed less decline in the cognitive function scores in the CT group compared to the control group. In addition, there was no significant difference in the length of hospital stay. Regarding CT adherence, we found that the proportion of patients in the CT group who completed the planned duration of CT was 10%.

The new 2018 guidelines defined neurocognitive disorders occurring in the perioperative period, including preoperative cognitive impairment, POD, cognitive decline diagnosed within 30 days postoperatively (delayed neurocognitive recovery), and cognitive decline diagnosed within 2–12 months postoperatively (35). As most previous studies have used POD and POCD as the outcome indicators of postoperative cognitive function, we

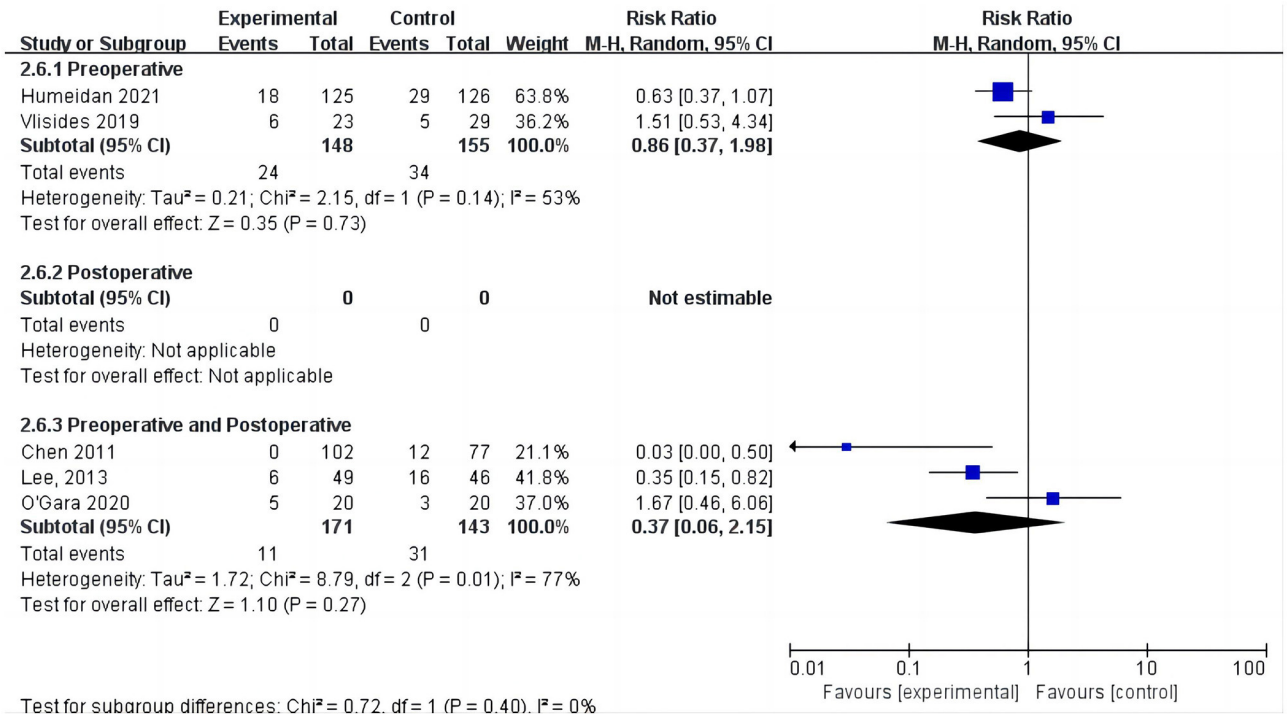

FIGURE 9
Subgroup analysis of cognitive training timing—incidence of POD.

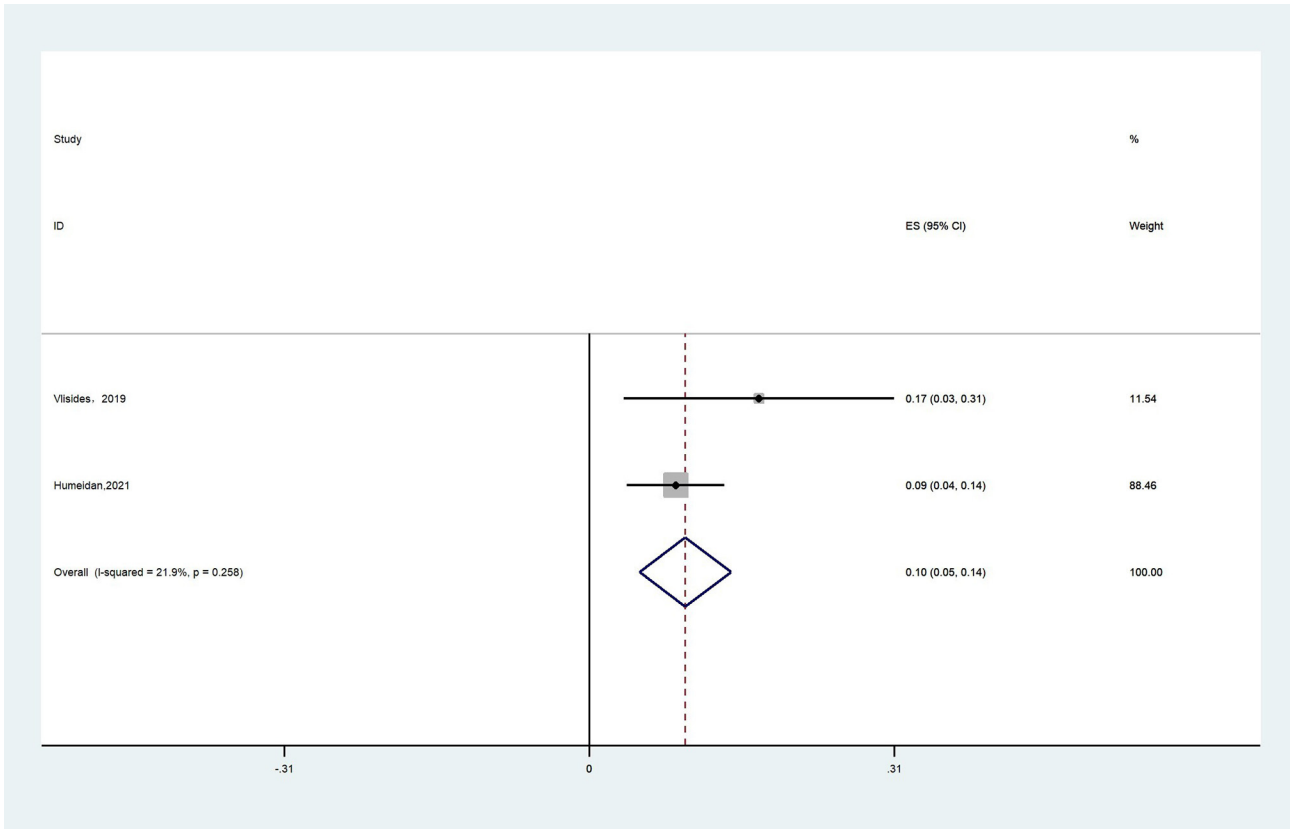

FIGURE 10
Forest plot of secondary outcome—cognitive training adherence.

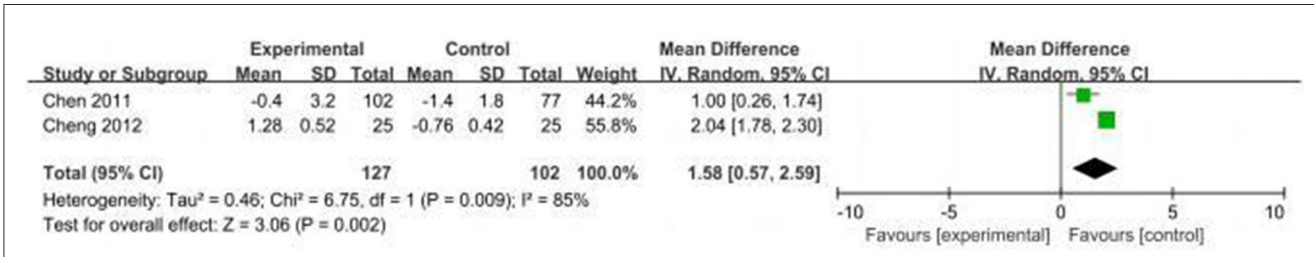

FIGURE 11
Forest plot of secondary outcome—cognitive function scores.

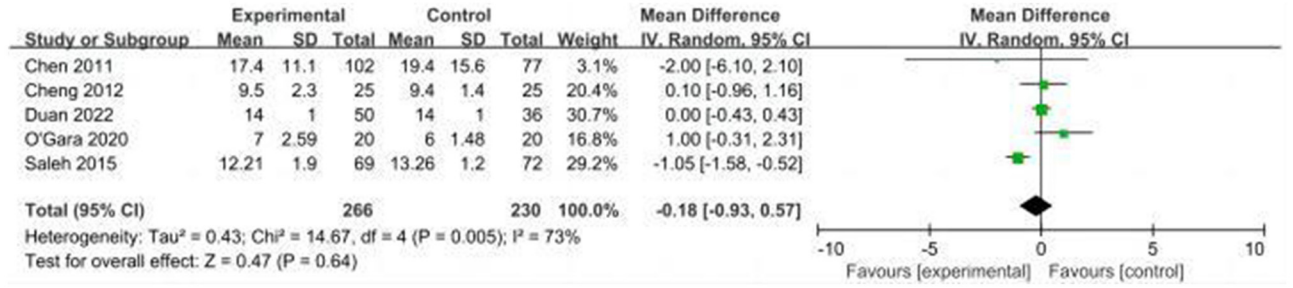

FIGURE 12
Forest plot of secondary outcome—length of hospital stay.

also used POCD and POD to assess the postoperative cognitive function (4).

This meta-analysis showed that perioperative CT significantly reduced the incidence of POCD ($P = 0.02$). Possible mechanisms underlying the effects of CT in improving cognitive function are as follows. First, CT may increase the density of cortical dopamine D1 receptors, which play a key role in human cognition as it is dependent on adequate dopamine neurotransmission (36). Second, Feinkohl et al. found that patients with more cognitive reserve had a lower incidence of POCD (36). In addition, Mondini et al. have found that CT enhances patients' cognitive reserve (37); thus, CT may improve patients' cognitive function by enhancing their cognitive reserve. Third, studies have found that cognitive function, perception, and memory function decline progressively with age, but the brain retains lifelong plasticity and adaptive reorganization; therefore, some cognitive functions of the brain can be improved by using appropriately designed training programs (38–40).

Furthermore, the results of this meta-analysis showed no statistically significant difference in the incidence of POD between the CT and control groups ($P = 0.28$). The reason for this outcome is unclear, and it is speculated that it may be due to significant heterogeneity ($I^2 = 67\%$) and inadequate sample size of the study.

Of note, three studies assessed CT adherence in the CT group (15, 24, 25). The proportion of patients in the CT group who completed the planned duration of CT was 10% (15, 25). One study reported that the main reasons for low CT adherence were lack of computer access, time constraints, and feeling overwhelmed (25). Another study reported that the main reasons were "I did not have enough energy, I forget, the frequency of game was too often (24)." Therefore, simplifying the training methods and providing computer assistance are necessary to avoid low adherence. O'Gara et al. found that a low proportion of people completed the total scheduled training duration (10 h); however, most were able to complete a longer duration of the cognitive training (>4 h).

Statistical heterogeneity was high in our meta-analysis. This heterogeneity may be due to differences in the types of surgery, diagnostic tools for cognitive function, mean age, duration of CT, timing of CT, and methods of CT. However, we performed subgroup analyses for the type of surgery and timing of CT. Only the non-cardiac surgery subgroup for the POCD outcome showed low heterogeneity ($I^2 = 0$). Subgroup analyses for other categories were not performed due to the variety of diagnostic tools for cognitive function and CT methods, lack of detailed intervention duration, and the small difference in mean age.

5. Limitations

There are some limitations of this study. First, the sample size was relatively small. Second, many factors including the methods of CT, duration of CT, and diagnostic methods for POCD and POD differed among the studies, which led to high clinical heterogeneity. Third, as the incidence rates of POCD and POD were our primary outcomes, we excluded studies that did not include data on POCD and POD; therefore, the evidence for secondary outcomes may be insufficient.

6. Conclusion

Our meta-analysis revealed that perioperative cognitive training is possibly an effective measure to reduce the incidence of POCD but not for the incidence of POD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LZ designed the study and wrote the manuscript. LZ, HZ, XZ, and WM participated in the extraction and analysis of the data. LL and YX critically supervised, evaluated, and validated the article. All of the authors worked on the article and agreed with the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1146164/full#supplementary-material

References

1. Safavynia SA, Goldstein PA. The role of neuroinflammation in postoperative cognitive dysfunction: moving from hypothesis to treatment. *Front Psychiatry.* (2018) 9:752. doi: 10.3389/fpsyt.2018.00752

2. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology.* (2009) 110:548–55. doi: 10.1097/ALN.0b013e318195b569

3. Rengel KF, Pandharipande PP, Hughes CG. Special considerations for the aging brain and perioperative neurocognitive dysfunction. *Anesthesiol Clin.* (2019) 37:521–36. doi: 10.1016/j.anclin.2019.04.010

4. Evered LA, Silbert BS. Postoperative cognitive dysfunction and noncardiac surgery. *Anesth Analg.* (2018) 127:496–505. doi: 10.1213/ANE.0000000000003514

5. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ispocd1 study. Ispocd investigators International study of post-operative cognitive dysfunction. *Lancet.* (1998) 351:857–61. doi: 10.1016/S0140-6736(97)07382-0

6. Mattison MLP. Delirium. *Ann Intern Med.* (2020) 173:C49–64. doi: 10.7326/AITC202010060

7. Sockalingam S, Parekh N, Bogoch II, Sun J, Mahtani R, Beach C, et al. Delirium in the postoperative cardiac patient: a review. *J Card Surg.* (2005) 20:560–67. doi: 10.1111/j.1540-8191.2005.00134.x

8. Evered L, Atkins K, Silbert B, Scott DA. Acute peri-operative neurocognitive disorders: a narrative review. *Anaesthesia.* (2022) 77(Suppl. 1):34–42. doi: 10.1111/anae.15613

9. Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: a narrative review focusing on diagnosis, prevention, and treatment. *Cns Neurosci Ther.* (2022) 28:1147–67. doi: 10.1111/cns.13873

10. Xu X, Hu Y, Yan E, Zhan G, Liu C, Yang C. Perioperative neurocognitive dysfunction: thinking from the gut? *Aging.* (2020) 12:15797–817. doi: 10.18632/aging.103738

11. Ding L, Chen DX Li Q. Effects of electroencephalography and regional cerebral oxygen saturation monitoring on perioperative neurocognitive disorders: a systematic review and meta-analysis. *BMC Anesthesiol.* (2020) 20:254. doi: 10.1186/s12871-020-01163-y

12. Feinkohl I, Winterer G, Pischon T. Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis. *Diabetes Metab Res Rev.* (2016) 32:643–51. doi: 10.1002/dmrr.2786

13. Guglietti B, Hobbs D, Collins-Praino LE. Optimizing cognitive training for the treatment of cognitive dysfunction in Parkinson's disease: current limitations and future directions. *Front Aging Neurosci.* (2021) 13:709484. doi: 10.3389/fnagi.2021.709484

14. Saleh AJ, Tang GX, Hadi SM, Yan L, Chen MH, Duan KM, et al. Preoperative cognitive intervention reduces cognitive dysfunction in elderly patients after gastrointestinal surgery: a randomized controlled trial. *Med Sci Monit.* (2015) 21:798–805. doi: 10.12659/MSM.893359

15. Humeidan ML, Reyes JC, Mavarez-Martinez A, Roeth C, Nguyen CM, Sheridan E, et al. Effect of cognitive prehabilitation on the incidence of postoperative delirium among older adults undergoing major noncardiac surgery: the neurobics randomized clinical trial. *JAMA Surg.* (2021) 156:148–56. doi: 10.1001/jamasurg.2020.4371

16. Cheng CM, Chiu MJ, Wang JH, Liu HC, Shyu YI, Huang GH, et al. Cognitive stimulation during hospitalization improves global cognition of older taiwanese undergoing elective total knee and hip replacement surgery. *J Adv Nurs.* (2012) 68:1322–29. doi: 10.1111/j.1365-2648.2011.05842.x

17. Butz M, Gerriets T, Sammer G, El-Shazly J, Tschernatsch M, Huttner HB, et al. Effects of postoperative cognitive training on neurocognitive decline after heart surgery: a randomized clinical trial. *Eur J Cardiothorac Surg.* (2022) 62. doi: 10.1093/ejcts/ezac251

18. Scott JE, Mathias JL, Kneebone AC, Krishnan J. Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients. *J Clin Exp Neuropsychol.* (2017) 39:459–72. doi: 10.1080/13803395.2016.1233940

19. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA.* (2002) 288:2271–81. doi: 10.1001/jama.288.18.2271

20. Walton CC, Naismith SL, Lampit A, Mowszowski L, Lewis SJG. Cognitive training in parkinson's disease. *Neurorehabil Neural Repair.* (2017) 31:207–16. doi: 10.1177/1545968316680489

21. Xuefang L, Guihua W, Fengru M. The effect of early cognitive training and rehabilitation for patients with cognitive dysfunction in stroke. *Int J Methods Psychiatr Res.* (2021) 30:e1882. doi: 10.1002/mpr.1882

22. Hu M, Wu X, Shu X, Hu H, Chen Q, Peng L, et al. Effects of computerised cognitive training on cognitive impairment: a meta-analysis. *J Neurol.* (2021) 268:1680–88. doi: 10.1007/s00415-019-09522-7

23. Woolf C, Lampit A, Shahnawaz Z, Sabates J, Norrie LM, Burke D, et al. A systematic review and meta-analysis of cognitive training in adults with major depressive disorder. *Neuropsychol Rev.* (2022) 32:419–37. doi: 10.1007/s11065-021-09487-3

24. O'Gara BP, Mueller A, Gasangwa D, Patxot M, Shaefi S, Khabbaz K, et al. Prevention of early postoperative decline: a randomized, controlled feasibility trial of perioperative cognitive training. *Anesth Analg.* (2020) 130:586–95. doi: 10.1213/ANE.0000000000004469

25. Vlisides PE, Das AR, Thompson AM, Kunkler B, Zierau M, Cantley MJ, et al. Home-based cognitive prehabilitation in older surgical patients: a feasibility study. *J Neurosurg Anesthesiol.* (2019) 31:212–17. doi: 10.1097/ANA.0000000000000569

26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535

27. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* (2014) 14:135. doi: 10.1186/1471-2288-14-135

28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

29. Fletcher J. What is heterogeneity and is it important? *BMJ.* (2007) 334:94–96. doi: 10.1136/bmj.39057.406644.68

30. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

31. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: effects on abdominal surgery patients. *J Am Coll Surg.* (2011) 213:245–42. doi: 10.1016/j.jamcollsurg.2011.05.004

32. Duan S, Liao Y, Tang Y, Zhang B, Peng M, Tong J, et al. Short-term perioperative cognitive therapy combined with rehabilitation exercise reduces the incidence of neurocognitive disorder in elderly patients: a randomized controlled trial. *Minerva Anestesiol.* (2022) 88:145–55. doi: 10.23736/S0375-9393.21.15877-8

33. Lee J, Jung J, Noh JS, Yoo S, Hong YS. Perioperative psycho-educational intervention can reduce postoperative delirium in patients after cardiac surgery: a pilot study. *Int J Psychiatry Med.* (2013) 45:143–58. doi: 10.2190/PM.45.2.d

34. Kehlet H. Enhanced postoperative recovery: good from afar, but far from good? *Anaesthesia.* (2020) 75(Suppl. 1):e54–61. doi: 10.1111/anae.14860

35. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth.* (2018) 121:1005–12. doi: 10.1097/ALN.0000000000002334

36. Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive reserve and the risk of postoperative cognitive dysfunction. *Dtsch Arztebl Int.* (2017) 114:110–17. doi: 10.3238/arztebl.2017.0110

37. Mondini S, Madella I, Zangrossi A, Bigolin A, Tomasi C, Michieletto M, et al. Cognitive reserve in dementia: implications for cognitive training. *Front Aging Neurosci.* (2016) 8:84. doi: 10.3389/fnagi.2016.00084

38. Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A.* (2006) 103:12523–28. doi: 10.1073/pnas.0605194103

39. Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, et al. A cognitive training program based on principles of brain plasticity: results from the improvement in memory with plasticity-based adaptive cognitive training (impact) study. *J Am Geriatr Soc.* (2009) 57:594–603. doi: 10.1111/j.1532-5415.2008.02167.x

40. Calero MD, Navarro E. Cognitive plasticity as a modulating variable on the effects of memory training in elderly persons. *Arch Clin Neuropsychol.* (2007) 22:63–72. doi: 10.1016/j.acn.2006.06.020

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Effect of web-implemented exercise interventions on depression and anxiety in patients with neurological disorders: a systematic review and meta-analysis

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Introduction: Web-implemented exercise intervention is the latest and innovative method to improve people's mental health. Currently, many studies have proven that web-implemented interventions are effective to improve depression and anxiety in adults. However, the influence of different web-implemented exercise interventions on depression and anxiety in patients with neurological disorders is still unclear.

Objective: The study aims to systematically summarize the type and content of web-implemented exercise interventions and quantify the effect of different web-implemented exercise interventions on depression and anxiety in patients with neurological disorders.

Methods: Four literature databases (PubMed, Web of Science, China National Knowledge Infrastructure, and WanFang data) were searched. The literature search considered studies published in English or Chinese before October 13, 2022. Randomized controlled trials (RCTs) that participants accepted web-implemented interventions were included. Two authors independently extracted data and assessed the risk of bias for included studies. Standardized mean differences (SMD) with 95% CI were used to integrate the effect size.

Results: 16 RCTs (a total of 963 participants) were included. The results showed that web-implemented exercise intervention had a significant effect on depression (SMD = −0.80; 95% CI, −1.09 to −0.52; I^2 = 75%; $P < 0.00001$) and anxiety (SMD = −0.80; 95% CI, −1.23 to −0.36; I^2 = 75%; $P = 0.0003$) in patients with a neurological disorder. The subgroup analysis showed that the effectiveness of the web-implemented exercise intervention was influenced by several factors, such as web-implemented exercise intervention type, component, and intervention duration.

Conclusion: Web-implemented exercise intervention has a relieving effect on depression and anxiety symptoms in patients with neurological disorders. Additionally, the intervention type, intervention duration, and component can influence the effect size.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/#recordDetails, identifier: CRD42023409538.

KEYWORDS

web-implemented exercise, neurological disorder, depression, anxiety, mental health

Introduction

The Global Burden of Disease (GBD) shows that the impact of neurological disease on global health is grossly underestimated and the prevalence of neurological and is also on the rise (1). Over the past 30 years, neurological disorders have become the leading cause of disability and the second leading cause of death in the world, with a 39% increase in the number of deaths and a 15% increase in the disability-adjusted life years (2). Many studies have shown that these neurological disorders have an evident negative impact on the physical function and quality of life (QOL) of patients with the onset of the disease. For example, multiple sclerosis (MS), as a non-traumatic disabling neurological disorder, can result in a variety of adverse symptoms (e.g., mobility problems, impaired balance, and loss of sensation), which pose an obstacle to people's normal life (e.g., the ability to work and social activities) and ultimately reduce the QOL of patients (3, 4). Other neurological diseases, such as stroke and Parkinson's disease (PD) which have different etiologies, can also lead to alternations in movement and sensation that impair balance and finally reduce the QOL of individuals (5–7). This decrease in QOL may indirectly lead patients to mood swings (8, 9). Except that, the symptoms such as disability and pain caused by neurological disorders can also directly induce several mental-related emotional disorders (e.g., depression and anxiety) (10).

Mental disorders are likely to be the leading cause of disease burden worldwide by 2030 (11). To some extent, compared with the healthy population, psychological disorders like depression and anxiety are more likely to occur in the patients, especially patients who suffer from dysfunction in the neurological system. One study has compared patients with Alzheimer, a degenerative disease of the central nervous system, to healthy people and found that the incidence rate of depression in Alzheimer's patients (67%) is twice as much as that in ordinary people (31%) (12). Another study has also indicated that people with MS have a risk of depression high to 50%, compared to 10–15% in general people (13). In addition, for patients with serious physical illnesses like neurological disorders, mental problems (e.g., depression and anxiety) can also decrease compliance with the treatment plan by increasing the burden of symptoms, thus affecting the treatment effect (14, 15). Hence, an effective intervention that can alleviate the depression and anxiety of patients with neurological disorders is expected.

As a non-medicine and non-invasive intervention, exercise has been proven effective in relieving depression and anxiety (16–18). Compared to pharmacology, exercise interventions are low-cost and can treat depression and anxiety without side effects. For example, one study has compared the effects of a 20-week resistance training exercise intervention and a 20-week pharmacological treatment on the depressive symptoms in PD patients and found that resistance training had a significant effect on reducing depression and improving the QOL, and functionality of PD (19). Besides, Gracizli et al. (20) have conducted a 12-week exercise prescription of a combination of aerobic and resistance training on MS patients and ordinary individuals and found that the combined exercise has a significant benefit in improving balance, QOL, and relieving depressive symptoms. Hence, exercise therapy can be suggested as an effective method to improve both the physical and mental health of patients with nervous system diseases.

In recent years, with the development of electronic technology and the lockdowns caused by COVID-19, more and more people prefer "online exercise." The web-implemented exercise interventions which support people who do not seek help from health services because of social stigma or transport problems could prescribe a structured exercise program to be carried out at home with varying degrees of supervision, differing from interventions that focus solely on motivating people to exercise (21, 22). Using web-implemented (e.g., online and digital) communication and technology to implement exercise interventions has become a new fashion (23). In China, more than 780 million people exercise through a variety of online platforms. In the COVID-19 pandemic, online exercise interventions have become a focus for doctors and researchers to treat various patients with different symptoms. Because web-implemented tele-exercise intervention can overcome the inconveniences induced by space and time. Doctors can easily use electronic devices (e.g., mobile phones and computers) as a medium to provide patients with exercise-related knowledge and training programs automatically or artificially (24, 25).

Web-implemented exercise can also play an essential role in the improvement of mental health in patients. Turner et al. have evaluated the effect of the web-implemented exercise intervention on the mental health of MS patients. They have provided the 6-month personalized exercise guidance using a remote health system to monitor exercise plans and progress for MS patients in the experimental group and a 6-month self-directed education method for MS patients in the control group. Eventually, they found that 53.3% of MS patients in the experimental group experienced a clinical improvement in depression symptoms, whereas only 9.1% of MS patients in the control group experienced a clinical improvement in depression symptoms (26). Obviously, this web-implemented exercise intervention can reduce the cost of time and space and facilitate behavioral change through monitoring, ultimately bringing benefits for patients in improving physical activity and depression. Besides, another digital intervention, Virtual Reality (VR) exergames, has also been proven effective for neurological patients' activities of daily living and mental health. For example, Lee et al. (27) have demonstrated that VR dance exergames can enhance balance and alleviate depression symptoms of PD patients effectively. Although there is some evidence indicating the effectiveness of certain specific web-implemented exercise interventions on depression and anxiety in patients with different neurological disorders, few studies have intergraded the effects of different web-implemented exercise interventions on mental health in patients with different neurological diseases.

Therefore, the purpose of this study was to summarize various types of web-implemented exercise and integrate the effects of different web-implemented exercise interventions on depression and anxiety in patients with different neurological disorders. It has important value for the development of exercise interventions on mental health, especially for the future expansion of VR exergames and intelligent exercise intervention modes.

TABLE 1 Search strategy.

Step	Search strategy
#1	"Neurological disorder" OR "stroke" OR "Parkinson's disease" OR "multiple sclerosis" OR "cognitive impairment" [Title/Abstract]
#2	"Virtual Reality" OR "mobile health" OR "exercise" OR "exergame" OR "online training" OR "sports" OR "video game") [Title/Abstract]
#3	"Anxiety" OR "depression" OR "mental health" [Title/Abstract]
#4	#1 AND #2 AND #3

Methods

Search strategy

This search followed the Preferred Reported Items for Systematic Review and Meta-analysis (PRISMA) guidelines. The protocol was registered on the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number: CRD42023409538. We searched two English databases, including PubMed and Web of Science (WOS), and two Chinese databases, including CNKI and WANFANG Data. All articles were published before October 13, 2022. Table 1 shows the specific search strategy.

Inclusion and exclusion criteria

The PICOS principle determined eligibility criteria, including participants, intervention, comparison, outcome, and study design. Studies were included if they met the following criteria: (1) participants were diagnosed with neurological diseases; (2) the experimental group used tele-exercise intervention or game-based exercise intervention, all exercise interventions should be based on the Internet; (3) the interventions in control group include empty, usual care, general physical therapy or exercise without web-implemented methods (offline); (4) the outcomes were the common indicators reflecting depression and anxiety, such as the scores of HADS, BDI, BAI, etc. (5) only randomized controlled trials (RCTs) were selected.

Studies were excluded if they met any of the following exclusion criteria: (1) the articles were not published in English or Chinese; (2) no full-text or data was available; (3) gray literature such as conference abstracts, literature review, thesis or dissertation; (4) no web-implemented exercise intervention involved in the experimental group; (5) using web-implemented exercise interventions in the control group; (6) the intervention in the experimental group was cognitive behavior therapy or mindfulness-based intervention only.

Study selection and data extraction

After searching the articles based on the search strategy, all studies were exported into the reference management software EndNote 20 by one researcher (HY.Z). Two researchers (R.W and M.C) independently screened the articles. After removing the duplicates and reviewing the title and abstract, the articles those are completely incompatible with the topic were deleted. Finally, two researchers (R.W and M.C) confirmed the final included studies according to the inclusion and exclusion criteria. If these two authors had an agreement and the argument was not achieved, a third arbitrator (HY.Z) would make the final determination.

Two researchers (R.W and M.C) independently extracted data from the included studies. The following information was extracted into standardized data tables: (1) study details (author, year, and country); (2) participants (sex, age, sample size, and type of patient); (3) components of interventions (types, frequency, and duration); (4) outcomes (the measurements of depression and anxiety).

Risk of bias assessment (study quality)

Two researchers (M.C and R.W) used the Cochrane risk of bias collaboration tool to examine the study quality independently. The bias includes: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias. Three levels were used to evaluate the quality of included articles (i.e., low risk, high risk, and unclear risk). If the results did not match, a third researcher would make the final decision (HY.Z).

Statistical analysis

We used Review Manager software (Review Manager 5.4) to conduct the meta-analysis. In this study, depression and anxiety were assessed using different scales. To be specific, the depression was assessed by the Hamilton depression scale (HAMD), Geriatric depression scale (GDS), Beck depression inventory (BDI), Self-rating depression scale (SDS), Depressive symptoms-9 subscale (PHQ-9), Hospital anxiety and depression (HADS) and EuroQoL (EQ-5D). The anxiety was assessed by the Hamilton anxiety scale (HAMA), beck anxiety inventory (BAI), and Self-rating anxiety scale (SAS).

Considering that the outcomes of this study were evaluated by different scales, we used standardized mean difference (SMD) to integrate the total effect size. According to the Cochrane Handbook, both the post-intervention values ($Mean_{post-intervention} \pm SD_{post-intervention}$) of the outcome and changes from baseline ($Mean_{changes} \pm SD_{changes}$) could be applied to synthesize the effect size (28). When the statistical variable was presented as the standard error (SE), the formula for calculating the standard deviation (SD) is "SE $\times\sqrt{}$N." Specifically, N is the number of subjects (29). If the statistical variable was presented as the median and quartile, the Mean and SD were calculated by the following formula:

$$SD \approx \frac{q_3 - q_1}{2\Phi^{-1}\left(\frac{0.75n-0.125}{n+0.25}\right)} \quad (30)$$

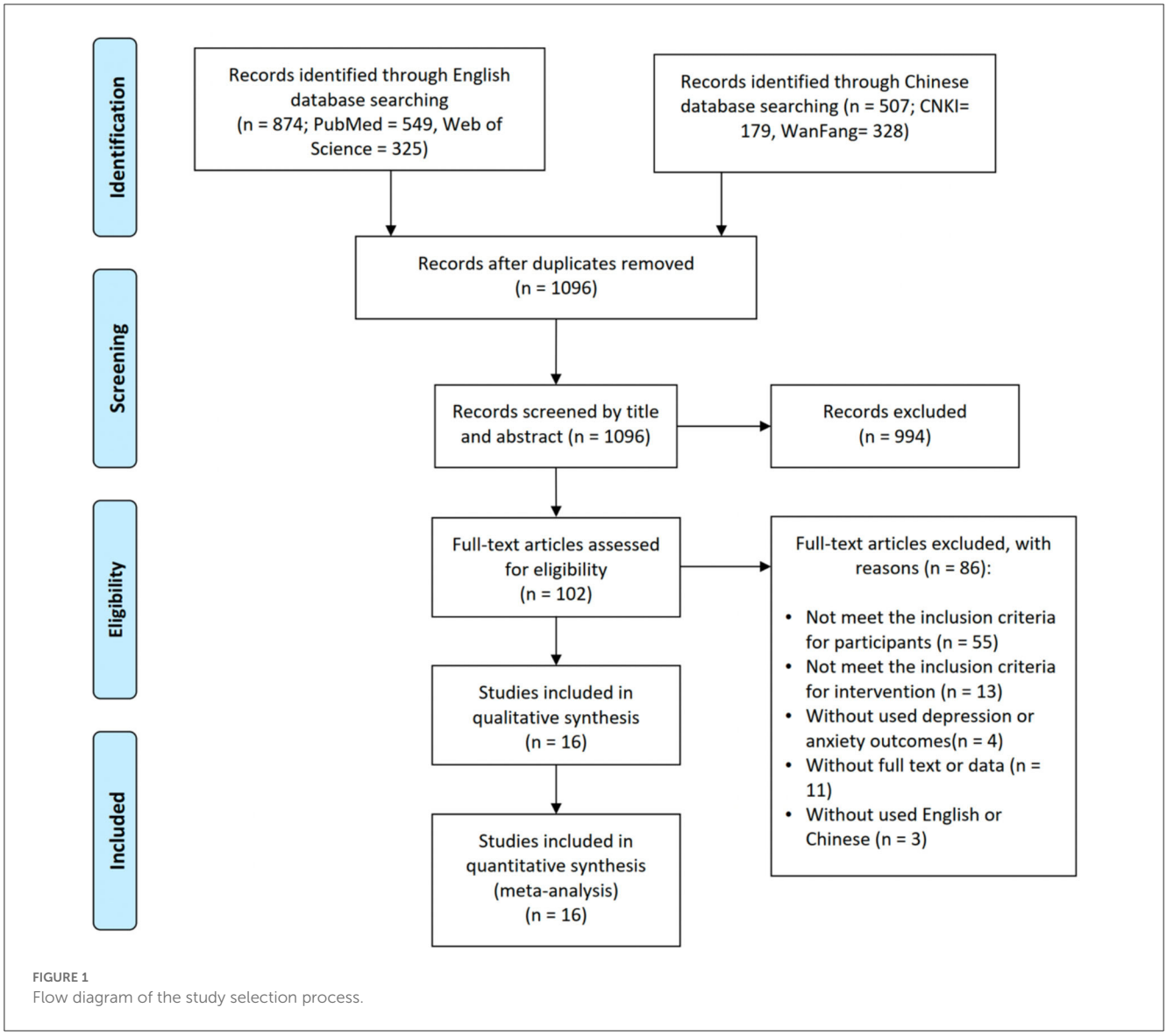

FIGURE 1
Flow diagram of the study selection process.

$$\bar{X} \approx \left(0.7 + \frac{0.39}{n}\right)\frac{q_1 + q_3}{2} + \left(0.3 - \frac{0.39}{n}\right)m \quad (31)$$

In two formulas above:

q_1 = the first quartile
m = the median
q_3 = the third quartile
n = the sample size

A compiled and published online calculator based on the formula above was provided: https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html.

If the study did not provide any of the statistical variables above, we would contact the authors via email. If we have not got a response, the study would be excluded.

In the Meta-Analysis, the effect of heterogeneity was evaluated using I^2. When $I^2 = 0$, it indicates no heterogeneity. The low, medium, and high levels of heterogeneity were represented by $I^2 \leq 25\%$, $25\% < I^2 \leq 50\%$, and $I^2 > 75\%$, respectively (32). The funnel plot was used to analyze publication bias. The forest plots was uesed to display the results of meta-analysis. And the sensitivity analysis was conducted to analyze the individual influence of each study on the overall result. The level of significance was set at $p < 0.05$.

Results

Search results

We identified a total of 1,381 articles, including 874 articles from the English databases and 507 articles from the Chinese databases, and 1,096 duplicates were removed. After screening the titles and abstracts, 102 articles were selected for the following full-text assessment. According to the eligibility criteria, a total of 86 articles

were excluded. Among them, 55 articles did not meet the participant-related inclusion criteria, 13 articles did not meet the intervention-related inclusion criteria, four articles did not meet the outcome-related inclusion criteria, 11 articles did not provide full text or data, and three articles were not written in English or Chinese. Ultimately, a total of 16 articles were included in the meta-analysis (Figure 1).

Study quality and bias

The quality assessment results of included studies were as follows (Figure 2). The majority of the studies have a low risk of bias. But the relatively high bias was performance bias and detection bias.

The sensitivity analysis was conducted using the one-by-one elimination method and the results were not affected. And the funnel plots tests did not identify any publication bias. Thus, we suggested that the pooled results were relatively stable.

General characteristics of studies

Table 2 shows the characteristics of the selected studies, including the authors, country, participants (age, sample size, and type), interventions (type, group, frequency, and duration), and outcomes. A total of 16 studies included 963 participants from eight countries. Among these 16 studies, all patients suffered from neurological symptoms, including multiple sclerosis (MS, n = 6, 37.5%), cognitive impairment (n = 2, 12.5%), stroke (n = 5, 31.25%), and Parkinson's disease (PD, n = 3,18.75%).

Web-implemented exercise interventions were separated into two main categories (i.e., tele-exercise intervention and VR exergame), respectively (Wii, Xbox and Kinect). There are six studies (37.5%) involving tele-exercise intervention and 10 studies (62.5%) involving VR exergame (Wii, Xbox, and Kinect). In addition, according to the concrete contents of interventions in the experimental group, 10 studies (62.5%) conducted single-component interventions (only web-implemented exercise) and six studies (37.5%) conducted multi-component interventions (e.g., the exercise intervention combined with psychological, physical therapy, and some other interventions). In terms of outcomes, 15 studies (93.8%) involved depression and seven studies (43.8%) involved anxiety.

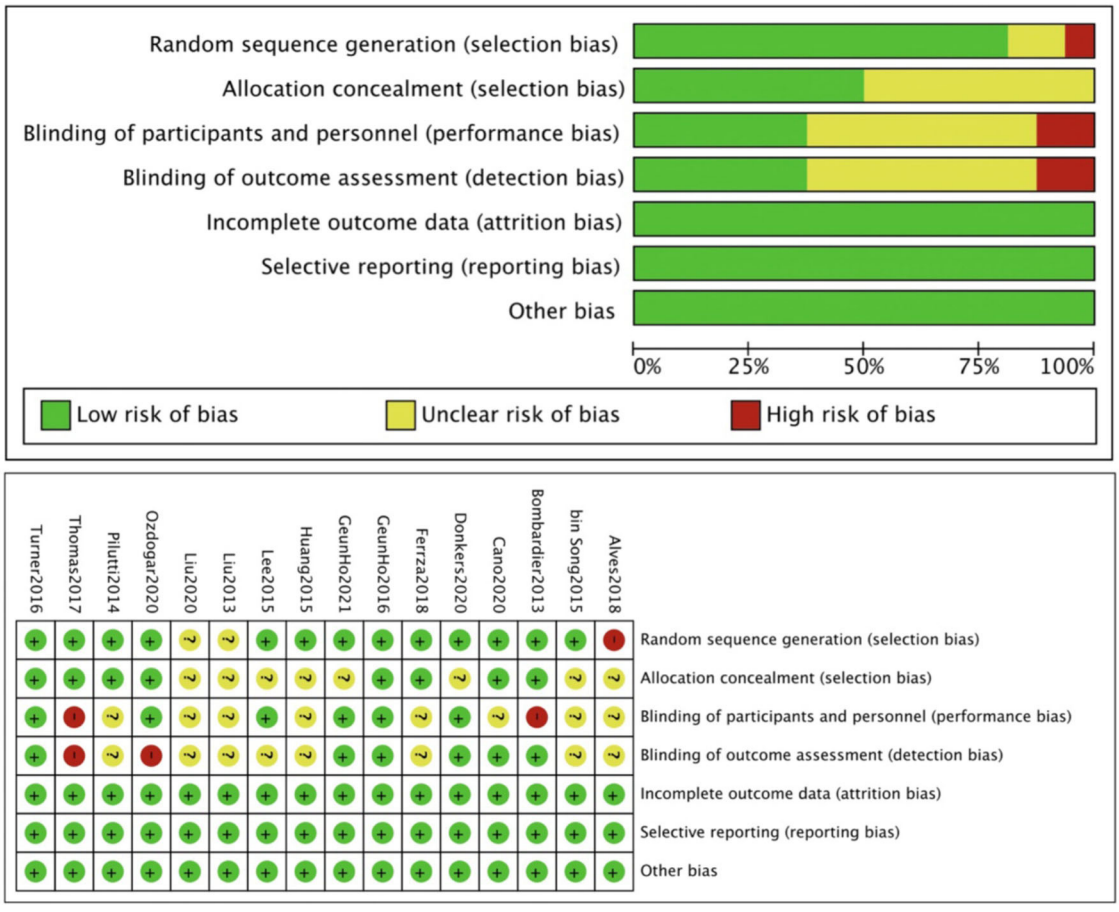

FIGURE 2
Quality assessment of included studies.

TABLE 2 Characteristics of the included studies.

References	Country	Participants			Different exercise interventions based on the internet			Outcomes (measurement)
		Age Mean (SD)	Sample size (male/female)	Diseases	Type	Group	Frequency and duration	
Alves et al. (33)	Brazil	**EG1:** 58.89 (11.16) **EG2:** 62.67 (13.81) **CG:** 61.67 (10.74)	27 (25/2) **EG1:** 9 (9/0) **EG2:** 9 (8/1) **CG:** 9 (8/1)	Parkinson	VR exergame (Xbox and Kinect, Wii)	**EG1:** VR exergame (Will) **EG2:** VR exergame (Xbox) **CG:** without any intervention	5 weeks 45–60 min;	Anxiety: BAI
Bin Song and Cho Park (34)	South Korea	**EG:** 51.37 (4.6) **CG:** 50.1 (7.83)	40 (22/18) **EG:** 20 (10/10) **CG:** 20 (12/8)	Stroke	VR exergame (Xbox and Kinect)	**EG:** VR exergame (bowling, skiing, and golf) **CG:** bicycle training	8 weeks 30-min; 5 times/wk.	Depression: BDI
Bombardier et al. (35)	America	**EG:** 47.1 (8.9) **CG:** 49.7 (7.9)	92 (13/79) **EG:** 44 (5/39) **CG:** 48 (8/40)	Multiple sclerosis	Tele-exercise intervention	**EG:** Telephone-counseling-based physical activity **CG:** wait-list	12 weeks 30-min; telephone counseling calls in weeks 1, 2, 3, 4, 6, 8, and 10.	Depression: HAMD
Cano-Mañas et al. (36)	Spain	**EG:** 60.35 (9.84) **CG:** 65.68 (10.68)	48 (23/25) **EG:** 23 (12/11) **CG:** 25 (11/14)	Stroke	VR exergame (Xbox and Kinect)	**EG:** VR exergame (20-min) (tennis, baseball, etc.) + conventional rehabilitation (35 min physical + 35 min occupational therapy) **CG:** conventional rehabilitation (single leg support, standing with assistance and autonomy, etc.)	8 weeks **EG:** 3 times/wk. **CG:** conventional rehabilitation (45 min physical + 45 min occupational therapy)	Depression and anxiety: EQ-5D
Geun-Ho (37)	South Korea	**EG:** 63.8 (10.2) **CG:** 65.5 (8.1)	30 (18/12) **EG:** 15 (10/5) **CG:** 15 (8/7)	Cognitive impairment (early dementia)	VR exergame (Wii-fit and Wii)	**EG:** VR exercise program [30-min Will Fit balance game + 10-min Wii sports game (golf or bowling)] + cognitive rehabilitation **CG:** Cognitive rehabilitation program	12 weeks 36 sessions **EG:** 40-min; 3 times/wk. **CG:** 20-min/sessions	Depression: GDS-K
Geun-Ho (12)	South Korea	**EG:** 71.45 (6.33) **CG:** 72.12 (6.48)	40 (30/10) **EG:** 20 (13/7) **CG:** 20 (12/8)	Cognitive impairment (early dementia)	VR exergame (Wii)	**EG:** VR exergame (fencing, bowling, table tennis, and frisbee) **CG:** Usual care	12 weeks 15 min; 3 times/wk.	Depression: GDS-K
Huang and Xiaotong (38)	China	**EG:** 65.8 (8.01) **CG:** 66.4 (8.16)	60 (35/25) **EG:** 30 (17/13) **CG:** 30 (18/12)	Stroke	Tele-exercise intervention	**EG:** Video conference (live face-to-face): Brunnstrom training (walking, sit and stand balance, the upper and lower limbs lift and fall) + Medical and psychological guidance **CG:** Usual care	6 months 45-min; In the 1st month, 1 time/week; in the 2–6-month, 1 time/2 week.	Anxiety: HAMA; Depression: HAMD.
Lee et al. (27)	South Korea	**EG:** 68.4 (2.9) **CG:** 70.1 (3.3)	20 (10/10) **EG:** 10 (5/5) **CG:** 10 (5/5)	Parkinson	VR exergame (Wii)	**EG:** VR dance exergame (K-pop dance festival) + neurodevelopment treatment (NDT) + functional electrical stimulation (FES) **CG:** NDT + FES	6 weeks 5 times/wk. **EG:** 30-min exergame + 30-min NDT + 15-min FES **CG:** 30-min NDT + 15-min FES	Depression: BDI

(Continued)

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TABLE 2 (Continued)

References	Country	Participants			Different exercise interventions based on the internet			Outcomes (measurement)
		Age Mean (SD)	Sample size (male/female)	Diseases	Type	Group	Frequency and duration	
Liu (39)	China	**EG:** 52.93 (6.2) **CG:** 51.67 (7.18)	60 (46/14) **EG:** 30 (24/6) **CG:** 30 (22/8)	Stroke	VR exergame (Kinect)	**EG:** VR exergame (skiing) + physiotherapy **CG:** Regular exercise + physiotherapy	4 weeks 30-min; 3 times 4 week	Depression: SDS
Liu (40)	China	**EG:** 61.36 (7.81) **CG:** 63.15 (8.46)	200 (117/83) **EG:** 100 (61/39) **CG:** 100 (56/44)	Stroke	Tele-exercise intervention	**EG:** Functional training (live face-to-face video conferencing, App) + Medical and psychological guidance **CG:** Usual care	3 months 60-min; 5 times/wk.	Anxiety: SAS Depression: SDS
Ozdogar et al. (41)	Turkey	**EG:** 39.2 (8.6) **CG1:** 43.6 (10.5) **CG2:** 37.9 (12.4)	60 (16/44) **EG:** 21 (5/16) **CG1:** 19 (6/12) **CG2:** 20 (5/15)	Multiple sclerosis	VR exergame (Xbox and Kinect)	**EG:** Kinect sports rivals' game (bowling, Jet Ski racing, rock climbing, football, tennis, and target shooting) **CG1:** Conventional rehabilitation in the center (balance, arm, and core stability exercise) **CG2:** wait-list	8 weeks 45-min, 1 time/wk.	Depression: BDI
Pilutti et al. (42)	America	**EG:** 48.4 (9.1) **CG:** 49.5 (9.2)	82 (20/62) **EG:** 41 (11/30) **CG:** 41 (9/32)	Multiple sclerosis	Tele-exercise intervention	**EG:** Telehealth monitoring, web-implemented video scheduled **CG:** wait-list	6 months Total 15 web-implemented video coaching sessions	Depression and anxiety: HADS
Thomas et al. (43)	Britain	**EG:** 50.9 (8.08) **CG:** 47.6 (9.26)	30 (3/27) **EG:** 15 (1/14) **CG:** 15 (2/13)	Multiple sclerosis	VR exergame (Wii)	**EG:** VR exergame **CG:** wait-list	6 months	Depression and anxiety: HADS
Turner et al. (26)	America	**EG:** 52.7 (11.6) **CG:** 53.6 (13.1)	64 (41/23) **EG:** 31 (22/9) **CG:** 33 (19/14)	Multiple sclerosis	Tele-exercise intervention	**EG:** Telephone counseling (TC + DVD) + home telehealth monitoring **CG:** Self-directed education (DVD)	6 months **EG:** TC in 6 times/wk.; suggestion: moderate-intensity activity; 45-min; 1–2 times/wk.	Depression: PHQ-9
Ferraz et al. (44)	Brazil	**G1:** 68.57 (9.92) **G2:** 64.66 (13.1) **G3 (EG):** 67.76 (14.45)	62 (37/25) **G1:** 22 (16/6) **G2:** 20 (11/9) **G3 (EG):** 20 (10/10)	Parkinson	VR exergame (Xbox and Kinect)	**G1:** Functional group **G2:** Bike training group **G3 (EG):** Exergaming group	8 weeks 50-min; 3 times/wk.	Depression: GDS-15
Donkers et al. (45)	Canada	**EG:** 54.6 (11.9) **CG:** 53.8 (12.2)	48 (17/31) **EG:** 32 (12/20) **CG:** 16 (5/11)	Multiple sclerosis	Tele-exercise intervention	**EG:** Website contains exercise (video, text, and audio descriptions) **CG:** Usual care	6 months 2 times/wk.;	Depression and anxiety: HADS

EG, experimental group; CG, control group; VR, virtual reality; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; PHQ-9, Depressive symptoms-9 subscale; SAS, Self-rating anxiety scale; SDS, Self-rating depression scale; GDS-K, Geriatric depression scale-Korean; BDI, Beck depression inventory; wait-list, participant were told that baseline testes need to be repeated after a certain amount of time, and will have opportunity to receive intervention; HADS, Hospital anxiety and depression. EQ-5D, Self-administered questionnaire, evaluated the QOL in five dimensions (including depression and anxiety); BAI, Beck anxiety inventory; GDS-15, 15-item geriatric depression scale.

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Effect of web-implemented exercise interventions on depression and anxiety

Seventeen data points from 15 studies reported the influence of web-implemented exercise interventions on depression in patients with neurological symptoms. Figure 3 showed that the web-implemented exercise intervention has a significant effect on depression in patients with neurological symptoms. Based on a random-effect model, the pooled effect size was SMD = −0.80 (95% CI, −1.09 to −0.52). The heterogeneity was high and significant (I^2 = 75%, $p < 0.00001$).

Eight data points from seven studies reported the influence of web-implemented exercise interventions on anxiety in patients with neurological symptoms. Figure 4 showed that the web-implemented exercise intervention has a significant effect on anxiety in patients with neurological symptoms. Based on a random-effect model, the pooled effect size was SMD = −0.80 (95% CI, −1.23 to −0.36). The heterogeneity was high and significant (I^2 = 75%, $p = 0.0003$).

Subgroup analysis

We performed subgroup analysis based on the type of interventions, type of patients, duration of interventions, and intervention components. Table 3 showed the subgroup analysis of the effect of web-implemented exercise interventions on depression. For intervention types, based on a random-effect model, both tele-exercise (SMD = −0.83, 95% CI, −1.23 to −0.43, I^2 = 77%, $P < 0.0001$) and VR exergame (SMD = −0.79, 95% CI, −1.21 to −0.37, I^2 = 76%, $P = 0.0002$) had a significant relieving effect on depression. According to the effect size, the tele-exercise interventions appeared to have a better-alleviating effect on depression than VR exergame interventions. For contents of tele-exercise intervention, both face-to-face intervention (SMD = −1.30, 95% CI, −1.57 to −1.03, $I^2 = 0\%$, $P < 0.00001$) and offline delayed interventions (SMD = −0.56, 95% CI, −0.96 to −0.16, I^2 = 59%, $P = 0.006$) had a significant effect on reducing depression. For the components of interventions in the experimental group, both single-component (only web-implemented exercise) intervention (SMD = −0.54, 95% CI, −0.89 to −0.19, I^2 = 73%, $P = 0.003$) and multi-component (the web-implemented exercise intervention combined with other interventions) interventions (SMD = −1.28, 95% CI, −1.49 to −1.07, $I^2 = 0\%$, $P < 0.00001$) had a significant effect on reducing depression. According to the effect size, the multi-component interventions had a better effect than the single-component intervention. Based on the difference in interventions in the control group, we divided the control group into the empty control group (e.g., usual care and wait-list) and the offline-exercise control group. Compared with the empty control group (SMD = −0.89, 95% CI, −1.22 to −0.56, $I^2 = 71\%$, $P < 0.00001$) and offline-exercise control group (SMD = −0.68, 95% CI, −1.22 to −0.13, I^2 = 80%, $P = 0.01$) separately, the web-implemented exercise interventions in the experimental group had a significant relieving effect on decreasing depression. However, when compared with the empty control group, the web-implemented exercise interventions in the experimental group had a better effect. When it comes to the intervention duration, the results of the sub-group analysis showed that the effect of the short-term (i.e., <6 weeks) web-implemented exercise intervention (SMD = −1.30, 95% CI, −1.78 to −0.81, $I^2 = 0\%$, $P < 0.00001$) was better than that of the medium-term (i.e., 6–12 weeks) web-implemented exercise intervention (SMD = −0.80, 95% CI, −1.21 to −0.40, I^2 = 80%, $P < 0.0001$) and the long-term (i.e., more than 12 weeks) web-implemented exercise intervention (SMD = −0.63, 95% CI, −1.13 to −0.13, I^2 = 73%, $P = 0.01$). For patients with different neurological diseases, the results showed that web-implemented exercise interventions had a significant effect on depression among patients with stroke (SMD = −1.29, 95% CI, −1.50 to −1.07, $I^2 = 0\%$, $P < 0.00001$), MS (SMD = −0.54, 95% CI, −0.79 to −0.29, I^2 = 27%, $P < 0.0001$) and Cognitive impairment (SMD = −1.54, 95% CI, −2.24 to −0.85, I^2 = 38%, $P < 0.0001$). No significant effect was observed in patients with PD (SMD = −0.19, 95% CI, −1.03 to 0.65, I^2 = 76%, $P = 0.66$).

Table 4 showed the subgroup analysis of the effect of web-implemented exercise interventions on anxiety. For intervention types, based on a random-effect model, both tele-exercise (SMD = −0.69, 95% CI, −1.15 to −0.23, I^2 = 73%, $P = 0.003$) and VR exergame (SMD = −1.05, 95% CI, −2.08 to −0.01, I^2 = 83%, $P = 0.05$) had a significant relieving effect on anxiety. According to the effect size, the VR exergame interventions appeared to have a better-alleviating effect on anxiety than tele-exercise interventions. For contents of tele-exercise intervention, both face-to-face intervention (SMD = −0.98, 95% CI, −1.46 to −0.51, I^2 = 62%, $P < 0.0001$) and offline delayed interventions (SMD = −0.39, 95% CI, −0.92 to 0.14, I^2 = 40%, $P = 0.15$) had a significant effect on reducing anxiety. For the components of interventions in the experimental group, both single-component (only web-implemented exercise) intervention (SMD = −0.62, 95% CI, −1.29 to 0.06, I^2 = 78%, $P = 0.08$) and multi-component (the web-implemented exercise intervention combined with other interventions) interventions (SMD = −1.05, 95% CI, −1.36 to −0.73, I^2 = 31%, $P < 0.00001$) had a significant effect on reducing anxiety. According to the effect size, the multi-component interventions had a better effect than the single-component intervention. In terms of the intervention duration, the results of the sub-group analysis showed that the effect of the short-term (i.e., <6 weeks) web-implemented exercise intervention (SMD = −1.80, 95% CI, −2.60 to −0.99, $I^2 = 0\%$, $P < 0.00001$) was better than that of the medium-term (i.e., 6–12 weeks) web-implemented exercise intervention (SMD = −1.18, 95%CI, −1.45 to −0.91, $I^2 = 0\%$, $P < 0.00001$) and the long-term (i.e., more than 12 weeks) web-implemented exercise intervention (SMD = −0.30, 95% CI, −0.76 to 0.15, I^2 = 57%, $P = 0.19$). For patients with different neurological diseases, the results showed that web-implemented exercise interventions had a significant effect on anxiety among patients with PD (SMD = −1.80, 95% CI, −2.60 to −0.99, $I^2 = 0\%$, $P < 0.0001$) and strokes (SMD = −1.05, 95% CI, −1.36 to −0.73, I^2 = 31%, $P < 0.00001$). No significant effect was observed in patients with MS (SMD = −0.15, 95% CI, −0.74 to 0.44, I^2 = 62%, $P = 0.62$). Considering that only one study conducted the offline-exercise intervention in the control group, other studies were all blank controls, so we did not perform subgroup analyses based on the difference of interventions in the control group.

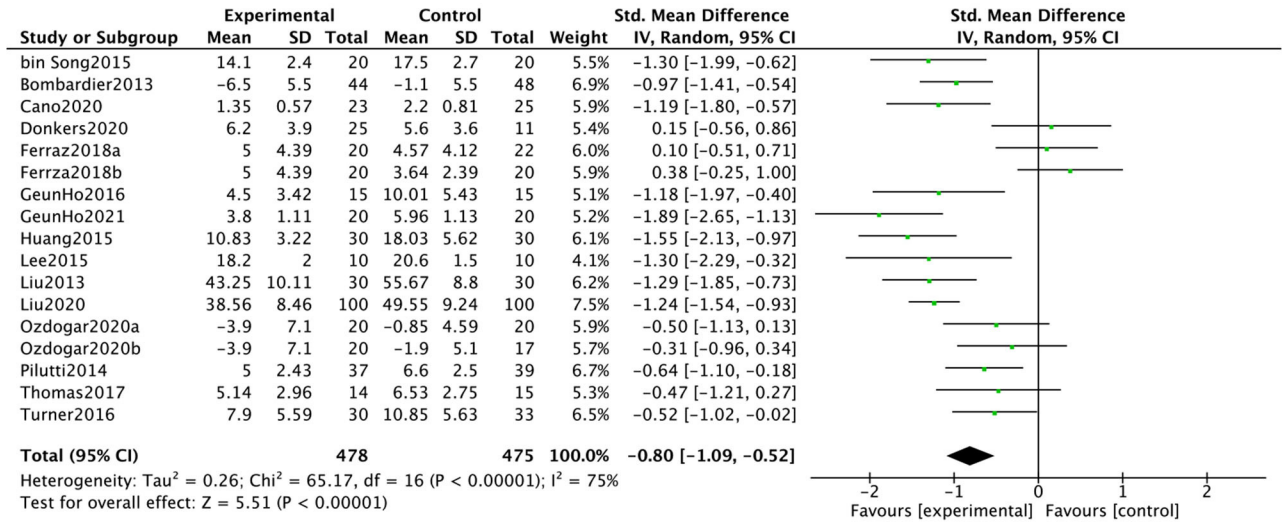

FIGURE 3
Effect of web-implemented exercise interventions on depression.

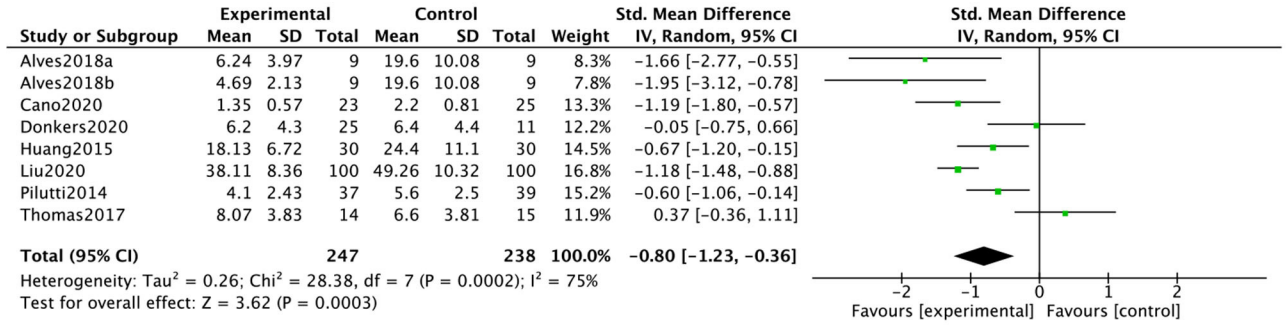

FIGURE 4
Effect of web-implemented exercise interventions on anxiety.

Discussion

This systematic review and meta-analysis has evaluated the effects of web-implemented exercise interventions on depression and anxiety in patients with neurological disorders by integrating 16 scientific studies involving a total of 963 participants. The review has shown that web-implemented exercise intervention significantly improves depression and anxiety in patients with neurological disorders. In addition, the effectiveness of the web-implemented exercise intervention is influenced by several factors, including web-implemented exercise intervention type, component, intervention duration, and patients with different neurological diseases. In terms of the type of web-implemented exercise interventions, the effect of tele-exercise is better than that of VR exergame on depression. While in relieving anxiety, the effect of VR exergame is better than that of tele-exercise. For the components of web-implemented exercise intervention, the effect of the multi-component intervention is better than that of the single-component on depression and anxiety. Additionally, based on the duration-related subgroup analysis, the effects of the web-implemented exercise intervention on both depression and anxiety were worse when the duration of interventions extends.

Our result has demonstrated that web-implemented exercise interventions have a significant effect on the reduction of depression and anxiety in patients with neurological disorders. Exercise, as a non-medicine and non-invasive intervention, has been proven to reduce depression and anxiety in several RCTs (46, 47). It has been proved that a loss of dopamine and norepinephrine innervation in the limbic system can lead to increased depression and anxiety disorder in patients with certain neurological diseases (48). Exercise has been demonstrated to alter the monoamine levels (e.g., serotonin, dopamine, and norepinephrine) and stress hormone cortisol to maintain mood (49, 50). On the other hand, there is some evidence showing that exercise can promote neuroprotection through molecular adaptations (e.g., the activation of the PGC-1α/FNDC5/Irisin pathway), leading to maintaining good mental health (51, 52). In consequence, neurological disorders patients may obtain huge benefits from exercise interventions for depression and

TABLE 3 Subgroup analysis of the effect of web-implemented exercise interventions on depression.

Subgroups	N	n	SMD	95% CI	Z	I^2
Type of intervention	17	953	−0.80	−1.09 to −0.52	5.51**	75%**
Tele-exercise	6	527	−0.83	−1.23 to −0.43	4.10**	77%**
VR exergame	11	426	−0.79	−1.21 to −0.37	3.70**	76%**
Contents of tele-exercise	6	527	−0.83	−1.23 to −0.43	4.10**	77%**
Face-to face	2	260	−1.30	−1.57 to −1.03	9.51**	0%
Offline delayed	4	267	−0.56	−0.96 to −0.16	2.74**	59%
Component	17	953	−0.80	−1.09 to −0.52	5.51**	75%**
Single-component	11	535	−0.54	−0.89 to −0.19	3.01**	73%**
Multi-component	6	418	−1.28	−1.49 to −1.07	11.84**	0%
Control group	17	953	−0.80	−1.09 to −0.52	5.51**	75%**
Therapy or exercise	7	656	−0.68	−1.22 to −0.13	2.43*	80%**
Empty	10	297	−0.89	−1.22 to −0.56	5.31**	71%**
Type of patients	17	953	−0.80	−1.09 to −0.52	5.51**	75%**
PD	3	102	−0.19	−1.03 to 0.65	0.44	76%*
Stroke	5	408	−1.29	−1.50 to −1.07	11.77**	0%
MS	6	373	−0.54	−0.79 to −0.29	4.22**	27%
CI	2	70	−1.54	−2.24 to −0.85	4.36**	38%
Duration (wks.)	17	953	−0.80	−1.09 to −0.52	5.51**	75%**
≤6	2	80	−1.30	−1.78 to −0.81	5.22**	0%
6–12	10	609	−0.80	−1.21 to −0.40	3.91**	80%**
>12	5	264	−0.63	−1.13 to −0.13	2.47*	73%**

N, the number of included studies; n, sample size; SMD, Standardized Mean Difference; CI, confidence interval; MS, multiple sclerosis; CI, Cognitive impairment; PD, Parkinson's disease.
*$p < 0.05$.
**$p < 0.01$.

anxiety. However, it is well-known that pain, fatigue, and the lack of energy induced by the neurological disease may make patients with neurological disorders tend to perform few interests in daily physical activities, even exercise. Hence, traditional exercise interventions may be inapplicable to patients to alleviate depression and anxiety. The exercise interventions with interactive communication and exergame based on virtual reality (VR) technology, video, and some other web-implemented media may help patients be more interested in exercise by allowing participants to immerse themselves in the "digital and interactive world" (53–56). In addition, the web-implemented methods can make patients exercise at home with supervision and develop targeted and personalized training. The web-implemented exercise intervention, as a complementary and alternative exercise intervention, can be used to replace or replenish traditional exercise and rehabilitation medicine, which are relatively inexpensive, time-saving, and spatial flexible. For patients with neurological disorders who have neurological dysfunction and motor system problems, web-implemented exercise interventions are more convenient and efficient than traditional exercise (57, 58). Therefore, web-implemented exercise intervention has a remarkable potential to decrease depression and anxiety in patients with neurological disorders.

The subgroup analysis in our meta-analysis has also indicated that different types of web-implemented exercise interventions have different anesis degrees on depression and anxiety in patients with neurological disorders. The tele-exercise guidance seems to have a better effect on depression than VR exergames. While the VR exergame seems to have a better effect on anxiety than tele-exercise intervention. Although the difference between VR exergame and tele-exercise in our meta-analysis was not significant (depression: $P = 0.89$; anxiety: $P = 0.54$) and the fact that depression and anxiety may occur together make it difficult to distinguish the effect of web-implemented exercise interventions on depression and anxiety separately (59, 60). The trend of difference between the effect of these two web-implemented exercise interventions on depression and anxiety can be discriminated by the effect size (i.e., SMD) of depression (tele-exercise: −0.69 vs. VR exergame: −1.05) and anxiety (tele-exercise: −0.83 vs. VR exergame: −0.79). According to the clinical characteristics of depression and anxiety, the difference may be explained. The symptoms of depressive disorders are mainly reflected in the sense of hopelessness, sadness, repression, and fear of embarrassment (59). Tele-exercise, an online exercise intervention based on the actual communication between individuals, can help patients alleviate depression-related complications through the face-to-face phone- and web-meetings.

TABLE 4 Subgroup analysis on anxiety.

Subgroups	N	n	SMD	95% CI	Z	I^2
Type of intervention	8	485	−0.80	−1.23 to −0.36	3.62**	75%**
Tele-exercise	4	372	−0.69	−1.15 to −0.23	2.97**	73%
VR exergame	4	113	−1.05	−2.08 to −0.01	1.98	83%**
Contents of tele-exercise	4	372	−0.69	−1.15 to −0.24	2.99**	73%*
Face-to face	2	260	−0.98	−1.46 to −0.51	4.03**	62%
Offline delayed	2	112	−0.39	−0.92 to 0.14	1.45**	40%
Component	8	485	−0.80	−1.23 to −0.36	3.62**	75%**
Single–component	5	177	−0.62	−1.29 to 0.06	1.78	74%**
Multi–component	3	308	−1.05	−1.36 to −0.73	6.54**	31%
Type of patients	8	485	−0.80	−1.23 to −0.36	3.62**	75%**
PD	2	36	−1.80	−2.60 to −0.99	4.37**	0%
Stroke	3	308	−1.05	−1.36 to −0.73	6.54**	31%
MS	3	141	−0.15	−0.74 to 0.44	0.49	74%
Duration (wks.)	8	485	−0.80	−1.23 to −0.36	3.62**	75%**
≤6	2	36	−1.80	−2.60 to −0.99	4.37**	0%
6–12	2	248	−1.18	−1.45 to −0.91	8.57**	0%**
>12	4	201	−0.30	−0.76 to 0.15	1.32	57%

N, the number of included studies; n, sample size; SMD, Standardized Mean Difference; CI, confidence interval; MS, multiple sclerosis; PD, Parkinson's disease.
*$p < 0.05$.
**$p < 0.01$.

A targeted and personalized training plan will be conveyed to patients through a real conversation, which makes patients and exercise professionals communicate timely. The professional can give positive information and promote patients with depressive symptoms to produce an optimistic mood (61, 62). Hence, specific online communication may be an advantage in tele-exercise intervention, while VR exergame interventions cannot provide effective interpersonal communication. On the contrary, the characteristics of anxiety disorders were being tense, extreme panic, phobia, and misery (63). Compared to tele-exercise interventions, VR exergames can stabilize and ease patients' anxious emotions by immersing them in exercise games and increasing their autonomy and interest (64). The unique online competition and recreation features of VR exergame and immersive experience may alleviate restlessness and fretfulness caused by anxiety (37). Except that, various sports exercise modes (e.g., golf, bowling, skiing, fencing, rock climbing, shooting, soccer, dancing, tennis, and Frisbee) of VR exergames can bring more choices for patients with different exercise interests to relieve anxiety and maintain a positive mood (39, 65).

We further compared tele-exercise and VR exergame two intervention methods. First, according to the contents of tele-exercise intervention, we found that both web- implemented face-to-face intervention and offline delayed intervention had positive effect on anxiety and depression. Second, we summarized the frequency and intensity of all the studies and found that almost all studies recommend using moderate to high intensity exercise, about 20–60 min/time, 2–5 times/week, and an average of about 100–180 min/week. One meta-analysis of stroke found that high-intensity exercise had a significant effect on depression, while low intensity had no effect (66). Another study also suggests that moderate-intensity exercise may be an optimal intensity when using exercise as a treatment for mental health (67). VR exergame can adjust the intensity of the exercise by adjusting the difficulty and mode of tasks and have high-level repeatability (27, 36). Tele-exercise interventions used personalized to tailor the intensity of exercise to the patient's situation. Even if some patients were not achieving the target intensity, it is recommended that the intensity of exercise can be gradually increased from low to high, and that they will be encouraged to actively participate in exercise and increase their daily physical activity (26, 35).

For the components of web-implemented exercise interventions, our results have demonstrated that the multi-component web-implemented exercise intervention (e.g., the random combination of psychological therapy, physical therapy, neurological therapy, functional electrical therapy, and cognitive rehabilitation therapy) has a better effect than the single-component web-implemented exercise intervention (e.g., tele-exercise or VR exergame only) on reducing both depression and anxiety symptoms in neurological patients. We have found that three studies involving single-exercise component intervention show no significant relieving effect on depression and anxiety symptoms in the experimental group, or even a lower effect in the experimental group than that in the control group (43–45). In contrast, all studies using multi-component interventions appear that the effect of alleviating depression

and anxiety is better in the experimental group than that in the control group. For patients with neurological disorders, the primary purpose of web-implemented exercise intervention is to restore physical function and improve QOL, which can indirectly relieve depression and anxiety by restoring physical function and reducing disease symptoms. However, other medical and psychological interventions like physical therapy, neurological therapy, functional electrical therapy, psychological therapy, and cognitive rehabilitation therapy are also beneficial for the decrease of depression and anxiety as well (36, 38, 41, 44). Thus, the multi-component intervention may have double and multiple effects to alleviate depression and anxiety.

Based on the duration-related subgroup analysis, the result has indicated that the effect of the web-implemented exercise intervention on reducing depression and anxiety became less effective with the extension of intervention duration. This result is contrary to the results of a previous relevant meta-analysis. Huang et al. (68) have found that long-term interventions were more effective in relieving depression. These opposite results may be due to the difference of web-implemented exercise intervention types and sample types. Huang et al. have integrated the effect of isolated VR exergame on depression of a mixed sample including healthy adults and various patients (e.g., MS, stroke, PD, and hemodialysis). Otherwise, our study has merged the effect of the web-implemented exercise interventions consisting of VR exergame and tele-exercise on depression and anxiety in patients with neurological disorders. We have speculated that the population with neurological disorders has better compliance and adherence to the interventions than the healthy population. Thus, compared to a mixed sample, the presence of the effect of web-implemented exercise intervention in patients with neurological diseases does not need to take a too long time.

The meta-analysis still has some limitations. First, most studies used depression and anxiety as the secondary outcomes, which might weaken the causal relationship between the web-implemented exercise intervention and depression and anxiety. Thus, further research is needed to directly prove the relationship between web-implemented exercise intervention and mental health outcomes (e.g., depression and anxiety). Second, this meta-analysis has included a variety of characteristics of web-implemented exercise interventions (e.g., intervention type and intervention dosages). The included studies involved different participant races and study designs, which may lead to moderate to high heterogeneity and lower quality. Finally, the limited number of included studies and the language restrictions may also cause bias on the integrated effect.

Conclusion

This meta-analysis indicates that web-implemented exercise intervention can significantly relieve depression and anxiety symptoms in patients with neurological disorders. The current results suggest that short-term (≤6 weeks) and multi-component web-implemented exercise interventions have the better effect. In addition, tele-exercise has a better-relieving effect on depression, while VR exergame has a better-relieving effect on anxiety. It should be noted that the web-implemented exercise intervention is only a form of clinical therapy support. Except that, due to limitations and scarcity of studies involving the impact of web-implemented exercise interventions on mental health in neurological patients, more relevant studies are needed in the future. It is suggested to increase long-term follow-up and study biological mechanisms to further evaluate the effect of the web-implemented exercise intervention on mental health in neurological patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SZ and XH: conceptualization and supervision. HZ and RW: methodology. HZ: formal analysis and writing—original draft preparation. HZ, RW, and ZK: investigation. ZK and JY: resources. HZ, RW, and XH: writing—review and editing. HZ and SZ: visualization. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. WHO. *Neurological Disorders: Public Health Challenges*. Geneva: World Health Organization (2006).

2. Feigin VL, Vos T, Nichols E, Owolabi MO, Carroll WM, Dichgans M, et al. The global burden of neurological disorders: translating evidence into policy. *Lancet Neurol.* (2020) 19:255–65. doi: 10.1016/S1474-4422(19)30411-9

3. Zou L, Wang H, Xiao Z, Fang Q, Zhang M, Li T, et al. Tai chi for health benefits in patients with multiple sclerosis: a systematic review. *PLoS ONE.* (2017) 12:e0170212. doi: 10.1371/journal.pone.0170212

4. Baird JF, Sandroff BM, Motl RW. Therapies for mobility disability in persons with multiple sclerosis. *Expert Rev Neurother.* (2018) 18:493–502. doi: 10.1080/14737175.2018.1478289

5. Schmid AA, Van Puymbroeck M, Altenburger PA, Miller KK, Combs SA, Page SJ. Balance is associated with quality of life in chronic stroke. *Top Stroke Rehabil.* (2013) 20:340–6. doi: 10.1310/tsr2004-340

6. Bello UM, Chutiyami M, Salihu D, Abdu SI, Tafida BA, Jabbo AA, et al. Quality of life of stroke survivors in Africa: a systematic review and meta-analysis. *Qual Life Res.* (2021) 30:1–19. doi: 10.1007/s11136-020-02591-6

7. Yu X, Wu X, Hou G, Han P, Jiang L, Guo Q. The impact of Tai Chi on motor function, balance, and quality of life in Parkinson's disease: a systematic review and meta-analysis. *Evid Based Complement Alternat Med.* (2021) 2021:6637612. doi: 10.1155/2021/6637612

8. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med.* (2000) 62:463–71. doi: 10.1097/00006842-200007000-00001

9. Martinez-Martin P, Rodriguez-Blazquez C, Paz S, Forjaz MJ, Frades-Payo B, Cubo E, et al. Parkinson symptoms and health related quality of life as predictors of costs: a longitudinal observational study with linear mixed model analysis. *PLoS ONE.* (2015) 10:e0145310. doi: 10.1371/journal.pone.0145310

10. Carson AJ, Ringbauer B, MacKenzie L, Warlow C, Sharpe M. Neurological disease, emotional disorder, and disability: they are related: a study of 300 consecutive new referrals to a neurology outpatient department. *J Neurol Neurosurg Psychiatry.* (2000) 68:202–6. doi: 10.1136/jnnp.68.2.202

11. WHO. *Depression*. (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/depression (accessed September 13, 2021).

12. Geun-Ho. Effect of virtual reality-based training program on patients with mild cognitive impairment. *Asia-pacific J Converg Res Interchange.* (2021) 7:71–80. doi: 10.47116/apjcri.2020.01.07

13. Jones KH, Ford DV, Jones PA, John A, Middleton RM, Lockhart-Jones H, et al. A large-scale study of anxiety and depression in people with Multiple Sclerosis: a survey via the web portal of the UK MS Register. *PLoS ONE.* (2012) 7:e41910. doi: 10.1371/journal.pone.0041910

14. Boeschoten RE, Braamse AM, Beekman AT, Cuijpers P, van Oppen P, Dekker J, et al. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci.* (2017) 372:331–41. doi: 10.1016/j.jns.2016.11.067

15. Tsaras K, Papathanasiou IV, Mitsi D, Veneti A, Kelesi M, Zyga S, et al. Assessment of depression and anxiety in breast cancer patients: prevalence and associated factors. *Asian Pacific J Cancer Prev.* (2018) 19:1661–9. doi: 10.22034/apjcp.2018.19.6.1661

16. Peluso MA, Guerra de Andrade LH. Physical activity and mental health: the association between exercise and mood. *Clinics.* (2005) 60:61–70. doi: 10.1590/S1807-59322005000100012

17. North TC, McCullagh P, Tran ZV, Lavallee D, Williams JM, Jones MV, et al. Effect of exercise on depression. In: Lavallee D, Williams JM, Jones MV, Allen M. Spray C, Peters H, Eys M, Morgan G, Krane V, Douglas C, Jones MI, Papathomas A, Scherzer C, Goodger K, editors. *Key Studies in Sport and Exercise Psychology.* Open University Press (2008). p. 258–84.

18. Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. *Maturitas.* (2017) 106:48–56. doi: 10.1016/j.maturitas.2017.09.003

19. de Lima TA, Ferreira-Moraes R, Alves WMGC, Alves TGG, Pimentel CP, Sousa EC, et al. Resistance training reduces depressive symptoms in elderly people with Parkinson disease: a controlled randomized study. *Scand J Med Sci Sports.* (2019) 29:1957–67. doi: 10.1111/sms.13528

20. Grazioli E, Tranchita E, Borriello G, Cerulli C, Minganti C, Parisi A. The effects of concurrent resistance and aerobic exercise training on functional status in patients with multiple sclerosis. *Curr Sports Med Rep.* (2019) 18:452–7. doi: 10.1249/JSR.0000000000000661

21. Lambert JD, Greaves CJ, Farrand P, Price L, Haase AM, Taylor AH. Web-based intervention using behavioral activation and physical activity for adults with depression (the eMotion Study): pilot randomized controlled trial. *J Med Internet Res.* (2018) 20:e10112. doi: 10.2196/10112

22. Teychenne M, Abbott G, Stephens LD, Opie RS, Olander EK, Brennan L, et al. Mums on the Move: a pilot randomised controlled trial of a home-based physical activity intervention for mothers at risk of postnatal depression. *Midwifery.* (2021) 93:102898. doi: 10.1016/j.midw.2020.102898

23. Jahangiry L, Farhangi MA, Shab-Bidar S, Rezaei F, Pashaei T. Web-based physical activity interventions: a systematic review and meta-analysis of randomized controlled trials. *Public Health.* (2017) 152:36–46. doi: 10.1016/j.puhe.2017.06.005

24. Hong J, Kong H-J, Yoon H-J. Web-based telepresence exercise program for community-dwelling elderly women with a high risk of falling: randomized controlled trial. *JMIR Mhealth Uhealth.* (2018) 6:e132. doi: 10.2196/mhealth.9563

25. Busse M, Latchem-Hastings J, Button K, Poile V, Davies F, O'Halloran R, et al. Web-based physical activity intervention for people with progressive multiple sclerosis: application of consensus-based intervention development guidance. *Br Med J Open.* (2021) 11:e045378. doi: 10.1136/bmjopen-2020-045378

26. Turner AP, Hartoonian N, Sloan AP, Benich M, Kivlahan DR, Hughes C, et al. Improving fatigue and depression in individuals with multiple sclerosis using telephone-administered physical activity counseling. *J Consult Clin Psychol.* (2016) 84:297. doi: 10.1037/ccp0000086

27. Lee N-Y, Lee D-K, Song H-S. Effect of virtual reality dance exercise on the balance, activities of daily living, and depressive disorder status of Parkinson's disease patients. *J Phys Ther Sci.* (2015) 27:145–7. doi: 10.1589/jpts.27.145

28. Higgins JP, Green S. *The Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. Chichester: The Cochrane Collaboration (2008). doi: 10.1002/9780470712184

29. Altman DG, Bland JM. Standard deviations and standard errors. *Br Med J.* (2005) 331:903. doi: 10.1136/bmj.331.7521.903

30. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* (2014) 14:135. doi: 10.1186/1471-2288-14-135

31. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res.* (2018) 27:1785–805. doi: 10.1177/0962280216669183

32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

33. Alves ML, Mesquita BS, Morais WS, Leal JC, Satler CE, dos Santos Mendes FA. Nintendo Wii™ versus Xbox Kinect™ for assisting people with Parkinson's disease. *Percept Mot Skills.* (2018) 125:546–65. doi: 10.1177/0031512518769204

34. Bin Song G, Cho Park E. Effect of virtual reality games on stroke patients' balance, gait, depression, and interpersonal relationships. *J Phys Ther Sci.* (2015) 27:2057–60. doi: 10.1589/jpts.27.2057

35. Bombardier CH, Ehde DM, Gibbons LE, Wadhwani R, Sullivan MD, Rosenberg DE, et al. Telephone-based physical activity counseling for major depression in people with multiple sclerosis. *J Consult Clin Psychol.* (2013) 81:89. doi: 10.1037/a0031242

36. Cano-Mañas MJ, Collado-Vázquez S, Rodríguez Hernández J, Muñoz Villena AJ, Cano-de-la-Cuerda R. Effects of video-game based therapy on balance, postural control, functionality, and quality of life of patients with subacute stroke: a randomized controlled trial. *J Healthc Eng.* (2020) 2020:5480315. doi: 10.1155/2020/5480315

37. Geun-Ho. Effects of virtual reality exercise program on balance, emotion and quality of life in patients with cognitive decline. *J Kor Phys Ther.* (2016) 28:355–63. doi: 10.18857/jkpt.2016.28.6.355

38. Huang HZ, Xiaotong W. The rehabilitative effects on stroke patients of hospital at home under remote guidance. *J Wenzhou Med Univ.* (2015) 45:383–7. doi: 10.3969/j.issn.2095-9400.2015.05.016

39. Liu XZ. Effect of intervention of somatosensory interaction (kinect) on post-stroke depression. *Chin J Rehabil Theory Pract.* (2013) 19:1049–51. doi: 10.3969/j.issn.1006-9771.2013.11.014

40. Liu ZY. Effects of telenursing mode based on internet on the motor function and mental state of patients with cerebral stroke. *Hebei Med J.* (2020) 42:2066–70. doi: 10.3969/j.issn.1002-7386.2020.13.036

41. Ozdogar AT, Ertekin O, Kahraman T, Yigit P, Ozakbas S. Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: a randomized controlled trial. *Mult Scler Relat Disord.* (2020) 40:101966. doi: 10.1016/j.msard.2020.101966

42. Pilutti L, Dlugonski D, Sandroff B, Klaren R, Motl R. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. *Multi Scler J.* (2014) 20:594–601. doi: 10.1177/1352458513503391

43. Thomas S, Fazakarley L, Thomas PW, Collyer S, Brenton S, Perring S, et al. MiiVitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis. *Br Med J Open.* (2017) 7:e016966. doi: 10.1136/bmjopen-2017-016966

44. Ferraz DD, Trippo KV, Duarte GP, Neto MG, Santos KOB, Oliveira Filho J. The effects of functional training, bicycle exercise, and exergaming on walking capacity of

elderly patients with Parkinson disease: a pilot randomized controlled single-blinded trial. *Arch Phys Med Rehabil.* (2018) 99:826–33. doi: 10.1016/j.apmr.2017.12.014

45. Donkers SJ, Nickel D, Paul L, Wiegers SR, Knox KB. Adherence to physiotherapy-guided web-based exercise for persons with moderate-to-severe multiple sclerosis: a randomized controlled pilot study. *Int J MS Care.* (2020) 22:208–14. doi: 10.7224/1537-2073.2019-048

46. Herring MP, Jacob ML, Suveg C, Dishman RK, O'Connor PJ. Feasibility of exercise training for the short-term treatment of generalized anxiety disorder: a randomized controlled trial. *Psychother Psychosom.* (2012) 81:21–8. doi: 10.1159/000327898

47. Henriksson M, Wall A, Nyberg J, Adiels M, Lundin K, Bergh Y, et al. Effects of exercise on symptoms of anxiety in primary care patients: a randomized controlled trial. *J Affect Disord.* (2022) 297:26–34. doi: 10.1016/j.jad.2021.10.006

48. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain.* (2005) 128:1314–22. doi: 10.1093/brain/awh445

49. Greenwood BN, Strong PV, Loughridge AB, Day HE, Clark PJ, Mika A, et al. 5-Ht2c Receptors in the Basolateral Amygdala and Dorsal Striatum are a novel target for the anxiolytic and antidepressant effects of exercise. *PLoS One.* (2012) 7:e46118. doi: 10.1371/journal.pone.0046118

50. Wegner M, Helmich I, Machado SE, Nardi A, Arias-Carrion O, Budde H. Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms. *CNS Neurol Disord.* (2014) 13:1002–14. doi: 10.2174/1871527313666140612102841

51. Hu S, Tucker L, Wu C, Yang L. Beneficial effects of exercise on depression and anxiety during the covid-19 pandemic: a narrative review. *Front Psychiatry.* (2020) 11:587557. doi: 10.3389/fpsyt.2020.587557

52. De Sousa RAL, Improta-Caria AC, Aras-Júnior R, de Oliveira EM, Soci ÚPR, Cassilhas RC. Physical exercise effects on the brain during COVID-19 pandemic: links between mental and cardiovascular health. *Neurol Sci.* (2021) 42:1325–34. doi: 10.1007/s10072-021-05082-9

53. Yang D, Hur J-W, Kwak YB, Choi S-W. A systematic review and meta-analysis of applicability of web-based interventions for individuals with depression and quality of life impairment. *Psychiatry Investig.* (2018) 15:759–66. doi: 10.30773/pi.2018.03.15

54. Baghaei N, Chitale V, Hlasnik A, Stemmet L, Liang H-N, Porter R. Virtual reality for supporting the treatment of depression and anxiety: scoping review. *JMIR Ment Health.* (2021) 8:e29681. doi: 10.2196/29681

55. Emmelkamp PMG, Meyerbröker K. Virtual reality therapy in mental health. *Annu Rev Clin Psychol.* (2021) 17:495–519. doi: 10.1146/annurev-clinpsy-081219-115923

56. Piech J, Czernicki K. Virtual reality rehabilitation and exergames—Physical and psychological impact on fall prevention among the elderly—A literature review. *Appl Sci.* (2021) 11:4098. doi: 10.3390/app11094098

57. Haller N, Lorenz S, Pfirrmann D, Koch C, Lieb K, Dettweiler U, et al. Individualized web-based exercise for the treatment of depression: randomized controlled trial. *JMIR Ment Health.* (2018) 5:e10698. doi: 10.2196/10698

58. Carneiro L, Rosenbaum S, Ward PB, Clemente FM, Ramirez-Campillo R, Monteiro-Júnior RS, et al. Web-based exercise interventions for patients with depressive and anxiety disorders: a systematic review of randomized controlled trials. *Brazil J Psychiatry.* (2021) 2021:2026. doi: 10.1590/1516-4446-2021-2026

59. Tiller JW. Depression and anxiety. *Med J Aust.* (2013) 199:S28–31. doi: 10.5694/mja12.10628

60. Beard C, Millner AJ, Forgeard MJ, Fried EI, Hsu KJ, Treadway M, et al. Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychol Med.* (2016) 46:3359–69. doi: 10.1017/S0033291716002300

61. Castonguay J, Filer CR, Pitts MJ. Seeking help for depression: applying the health belief model to illness narratives. *South Commun J.* (2016) 81:289–303. doi: 10.1080/1041794X.2016.1165729

62. Yang L, Wu D, Hou Y, Wang X, Dai N, Wang G, et al. Analysis of psychological state and clinical psychological intervention model of patients with COVID-19. *MedRxiv.* (2020) 22:20040899. doi: 10.1101/2020.03.22.20040899

63. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? *Focus.* (2011) 9:369–88. doi: 10.1176/foc.9.3.foc369

64. Bonnechere B, Jansen B, Omelina L, Sholukha V, Van Sint Jan S. Validation of the balance board for clinical evaluation of balance during serious gaming rehabilitation exercises. *Telemed e-Health.* (2016) 22:709–17. doi: 10.1089/tmj.2015.0230

65. De Bock R. *The Advantages of Exergaming*. Amsterdam: Vrije Universiteit Amsterdam (2016). Available online at: https://www.cs.vu.nl/~eliens/project/local/student/study-exergames.pdf (accessed April 02, 2023).

66. Eng JJ, Reime B. Exercise for depressive symptoms in stroke patients: a systematic review and meta-analysis. *Clin Rehabil.* (2014) 28:731–9. doi: 10.1177/0269215514523631

67. Paolucci EM, Loukov D, Bowdish DME, Heisz JJ. Exercise reduces depression and inflammation but intensity matters. *Biol Psychol.* (2018) 133:79–84. doi: 10.1016/j.biopsycho.2018.01.015

68. Huang K, Zhao Y, He R, Zhong T, Yang H, Chen Y, et al. Exergame-based exercise training for depressive symptoms in adults: a systematic review and meta-analysis. *Psychol Sport Exerc.* (2022) 63:102266. doi: 10.1016/j.psychsport.2022.102266

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Variation in the rate of recovery in motor function between the upper and lower limbs in patients with stroke: some proposed hypotheses and their implications for research and practice

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Background: Stroke results in impairment of motor function of both the upper and lower limbs. However, although it is debatable, motor function of the lower limb is believed to recover faster than that of the upper limb. The aim of this paper is to propose some hypotheses to explain the reasons for that, and discuss their implications for research and practice.

Method: We searched PubMED, Web of Science, Scopus, Embase and CENTRAL using the key words, stroke, cerebrovascular accident, upper extremity, lower extremity, and motor recovery for relevant literature.

Result: The search generated a total of 2,551 hits. However, out of this number, 51 duplicates were removed. Following review of the relevant literature, we proposed four hypotheses: natural instinct for walking hypothesis, bipedal locomotion hypothesis, central pattern generators (CPGs) hypothesis and role of spasticity hypothesis on the subject matter.

Conclusion: We opine that, what may eventually account for the difference, is the frequency of use of the affected limb or intensity of the rehabilitation intervention. This is because, from the above hypotheses, the lower limb seems to be used more frequently. When limbs are used frequently, this will result in use-dependent plasticity and eventual recovery. Thus, rehabilitation techniques that involve high repetitive tasks practice such as robotic rehabilitation, Wii gaming and constraint induced movement therapy should be used during upper limb rehabilitation.

KEYWORDS

stroke, upper extremity, lower extremity, motor recovery, natural instinct for walking hypothesis, bipedal locomotion hypothesis, central pattern generators hypothesis, role of spasticity hypothesis

Highlights

- There is reported difference in the rate of recovery of motor function between upper and lower limbs following stroke. The latter is believed to recover faster than the former.
- One of the reasons attributed to this is that, the cortical homunculus of the upper limb is larger in size due to its higher tactile sensitivity.
- We also proposed natural instinct for walking, bipedal locomotion, central pattern generators hypotheses to further help explain the reasons for the difference.
- However, most importantly, the difference could a factor of intensity or frequency of use of the lower limb compared to the upper limb, and spasticity.
- Therefore, interventions for upper limb motor function should consider increasing the intensity and effective management of spasticity.

1. Introduction

Stroke causes impairment in motor, sensory and cognitive functions. For the motor function, its impairment results in disability in carrying out activities of daily living (ADL), which can negatively affect the patient's quality of life (1–4). Thus, for stroke survivours to regain the ability to carry out ADL such as feeding, bathing, wearing clothes, grooming and picking up the telephone to answer calls, recovery of upper limb motor function is needed (5). Similarly, recovery of lower limb motor function is essential for walking which is required for ADLs such as transfer from one place to another, going for shopping and participating in social and other activities (6). In addition, recovery of motor function, independence in carrying out ADL, and the ability to participate in social and other activities are important in achieving good quality of life (7, 8). Therefore, the importance of upper and lower limb motor function recovery cannot be overemphasized.

However, to date, the rate of recovery of upper and lower limb motor function following stroke is a subject of debate that requires the attention of clinician scientists and researchers. For instance, for a very long time, it has been suggested that, the difference is due mainly to the size of the areas representing the limbs in the cortical homunculus. The area representing the upper limb is larger than that of the lower limb (9, 10); and as such, it was suggested that, its recovery may take a longer time following stroke. Although this could be a possible explanation for the difference, a more recent evidence has however not shown any significant correlation between lesion volume or size and motor function (11); suggesting that, other factors may be responsible for the difference in the rate of recovery between the two.

In addition, although, some researchers opined that, there is essentially no difference in the rate of recovery between the two (12, 13); yet, some studies reported lower limb to recover faster than the upper limb (14–22). However, the fast recovery of the lower limb compared to the upper limb, has been observed to be in a subpopulation of patients with anterior circulation infarct (14). Anterior circulation supplies brain areas that are mainly responsible for the motor and sensory functions of the lower limb, and speech production (23). Moreover, it is noteworthy in the study by Paci and colleagues that, all the participants included in the study received rehabilitation (14). During rehabilitation, it was observed that more attention is usually given to the lower limb compared to the upper limb (24). Thus, allocating attention to the limb may result in intensive practice during rehabilitation, which is important for use-dependent plasticity and recovery (25). Therefore, this could be another reason for the difference.

Another reason for the variation could be the type of stroke. This is because, ischemic type of stroke generally shows better functional outcomes compared to the hemorrhagic type (26). This is because, hemorrhagic type of stroke is associated with complications such as expansion of hematoma, increased blood pressure, venous thrombotic events and perihematomal oedema with increased intracranial pressure that can cause further damage to brain cells (27). In addition, other factors such as severity of the impairment and age may be the possible explanation for the difference in rate of recovery (28–30). Furthermore, pattern or rate of recovery that is observed following stroke largely depends on the type of outcome measures used to determine the recovery. The neurophysiological measures of recovery such as the transmagnetic stimulation (TMS), are generally more sensitive than the behavioral measures such as the Fugl-Meyer motor assessment (31). Unfortunately, most studies used the behavioral measures to assess recovery following stroke (15–22).

However, considering that all the above arguments may not be exhaustive on the subject matter, there seems to be many other factors which require further investigation that have not yet been considered in the debate on the variation in the rate of recovery of motor function between the upper and lower limbs following stroke (30). The aim of this paper is to propose several hypotheses for the possible difference in the rate of recovery of motor function between upper and lower limbs following stroke, and their implications for research and practice.

2. Literature search

For this purpose, five databases, PubMED, Web of Science, Scopus, Embase and CENTRAL were searched from their inceptions to February, 2023 using the key words, stroke, cerebrovascular accident, upper extremity, lower extremity and motor recovery for relevant literature. The search generated a total of 2,551 hits. However, out of this number, 51 duplicates were removed using Endnote software. Thereafter, relevant articles on recovery of motor function were read, and based on our understanding of the reviewed literature,

experience and knowledge of the subject matter, we proposed 4 hypotheses: natural instinct for walking hypothesis, bipedal locomotion hypothesis, central pattern generators (CPGs) hypothesis, and role of spasticity hypothesis on the subject matter to help explain why the difference exists. See Table 1 for the summary of the articles guiding the proposed hypotheses.

3. The hypotheses

3.1. Natural instinct for walking hypothesis

Humans seem to have a natural instinct for wanting to walk no matter what. This can be seen even early in life, where stepping/walking reflex, which is the placement of one foot in front of the other when the soles of feet touch ground, is present at birth (32). Although this reflex disappears at age 6 weeks, it voluntarily reappears at age 8–12 months (32). In addition, humans consider walking as a means to an end; and as such they walk to carry out their ADL such as going for shopping, and participating in social and leisure activities (40).

Moreover, historically, it is believed that, "humans made multiple journeys on foot out of Africa to the Eurasian landmass, and dispersing eventually to the Americas and Asia-Pacific region" (41–43). This seems to suggest that, importance of the lower limbs for all human endeavors is as old as the humans themselves. Consequently, in the event of an injury to the nervous system such as after stroke, the natural instinct of the patient is to want to recover walking ability as soon as possible, to help achieve independence in carrying out ADL as much as possible (44, 45). This is probably because, recovery of lower limb motor function significantly influences health-related quality of life (46). Interestingly, early mobilization following stroke results in early recovery (33). In addition, repetitive steps that are taken during walking can help induce recovery of lower limb motor function through use-dependent plasticity (47, 48).

See Figure 1 for the mechanism of the natural instinct for walking hypothesis.

3.2. Bipedal locomotion hypothesis

Human locomotion is bipedal, which involves three subtasks, propulsion, limb advancement and body weight support (34). As such, following stroke, the less affected or sound lower limb can be used during propulsion to help force the use of the affected limb (35, 49–51). Forced use of limb following stroke helps with reversing learned non-use, and promoting recovery (49, 52). In addition, bearing weight on the affected limb that generate proprioceptive information in the foot, can serve as important sources of sensory outputs for recovery (53). Consequently, bearing weight on the affected limb helps with the recovery of walking speed and functional mobility (52, 53).

See Figure 2 for the mechanism of the bipedal locomotion hypothesis.

3.3. Central pattern generators hypothesis

Walking in humans is mainly produced by the combined roles of the reflex circuit, which produces motor patterns triggered by sensory feedback, and the central pattern generators (CPGs), which is a network of neurons capable of generating rhythmic pattern movements even in the absence of command from the higher motor centers (36, 37, 54–57). The CPGs innervate mainly the muscles of the lower limb (54); and they may not be affected following stroke. In addition, the neurons that orchestrates walking reside predominantly in the lumbar spine (58, 59). Consequently, rythmic pattern movement such as stepping during walking can be generated even in the absence of control of the higher centers. Evidence of rhythmic-locomotor

TABLE 1 Summary of some of the important articles guiding the proposed hypotheses.

Authors	Type of article	Main points from the article	Hypothesis
O'Mara (32)	Narrative review	The article opines that walking is a natural phenomenon adapted by human being for their social participation	Natural instinct for walking hypothesis
Yen et al. (33)	RCT	Early mobilization involving standing and stepping practices resulted in improved ability to carry out ADL and functional ambulation; and reduced length of hospital stay	Natural instinct for walking hypothesis
Awad et al. (34)	Expert review	The authors argue that, human locomotion involves 3 subtasks, propulsion, limb advancement, and body weight support	Bipedal locomotion hypothesis
Abdullahi et al. (35)	Systematic review and meta-analysis	Performing tasks practice with the affected lower limb, while constraining the unaffected limb helps in improving its function including functional mobility	Bipedal locomotion hypothesis
Ryu and Kuo (36)	Modeling study	Walking which is one of the important functions of the lower limb can be produced by central pattern generators (CPGs) located in the spinal cord even in the absence of control of the higher centers	Central pattern generators hypothesis
Minassian et al. (37)	Narrative review	Walking which is one of the important functions of the lower limb can be produced by central pattern generators (CPGs) located in the spinal cord even in the absence of control of the higher centers	Central pattern generators hypothesis
Katoozian et al. (38)	Observational study	Prevalence of spasticity is usually higher in the upper limb compared to the lower limb following stroke	Role of spasticity hypothesis
Kong et al. (39)	Cross-sectional study	Upper limb dexterity is severely affected by the presence of severe spasticity	Role of spasticity hypothesis

RCT, randomized controlled trial; ADL, activities of daily living.

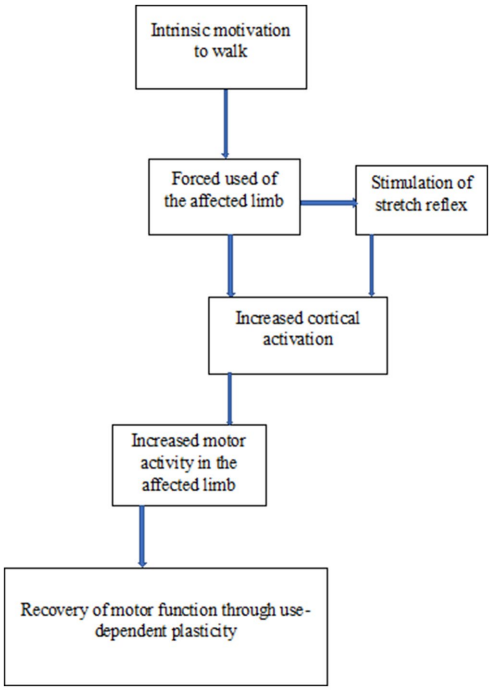

FIGURE 1
Schematic representation of the mechanism of natural instinct for walking hypothesis.

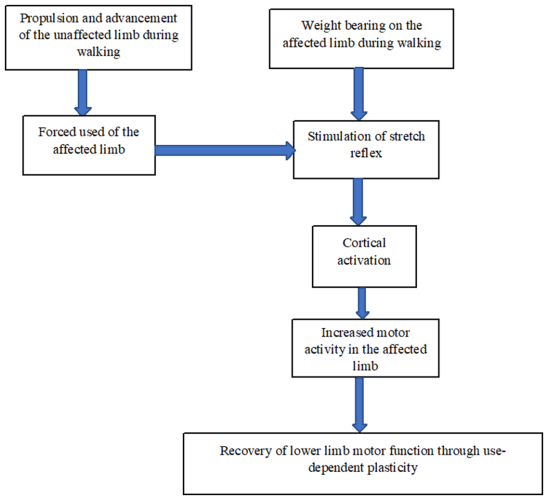

FIGURE 2
Schematic representation of the mechanism of bipedal locomotion hypothesis.

activity in the lower limb was seen following epidural stimulation of the spinal cord (60).

See Figure 3 for the mechanism of the central pattern generators hypothesis.

3.4. Role of spasticity hypothesis

About 25% of patients with stroke develops spasticity, although it depends on the severity of the paresis (61). However, prevalence of the spasticity and its severity, are higher in the upper limb than in the lower limb (38). Presence of severe spasticity in the upper limb, correlates with poor hand dexterity (39). In addition, unlike the lower limb, spasticity in the upper limb is associated with 60, 100, and 33% cases of shoulder pain, elbow pain and wrist pain, respectively, (62). Presence of pain is a significant predictor of poor recovery of function, ability to carry out ADL and quality of life following stroke (63, 64). In contrast, presence of spasticity may not substantially affect functional recovery of the lower limb (65).

In addition, functional specialization of the upper and lower limbs differs. The upper limb is involved in the performance of complex fine motor movement (66). However, as noted earlier, spasticity in the upper limb is significantly associated with poor dexterity, a requirement for fine motor movement ability (39, 65). Moreover, spasticity is associated with decreased joint proprioception (67). Acuity of proprioception in the wrist joint is linked to the control of fine movement (66). Thus, this may be the reason why even in the presence of motor and functional recovery, use of the upper limb in daily activities, which is also an indicator of recovery, may not be easily achieved (68).

4. Discussion, and implications for research and practice

Recovery of motor function following stroke has been considered to depend on so many factors such as the size and location of the lesion, and time since stroke (28–30). Similarly, although it is still debatable, the recovery is considered faster in the lower than the upper limb (14–22). However, following review of the literature, we hereby proposed some hypotheses to help explain other possible reasons why the lower limb may recover faster than the upper limb, and discussed the implications of the hypotheses for research and practice. The hypotheses are natural instinct for walking, bipedal locomotion, central pattern generators and role of spasticity hypotheses.

Following stroke, natural instinct for walking, which will result in motor activity with the affected limb; bipedal locomotion, in which weight is borne on the affected limb, while the unaffected limb is used to propel the affected one; role of CPGs in producing rhythmic movement patterns such as the steps needed during walking; and the role of spasticity in impairing movement, suggest that, the lower limb may recover faster than the upper limb because it is used more than the latter in activities. This is because inadequate amount of activity as may often be the case with upper limb compared to the lower limb, may not be able to drive neural reorganization that is required for recovery (69). Interestingly, walking is an ADL, and use of the limb for daily activities in the real world, is a significant predictor of recovery of motor function following stroke (70).

The above argument seems to suggest that, use-dependent plasticity may be the reason for faster recovery of motor function in the lower limb compared to the upper limb. Thus, increasing activity or intensity of practice during upper limb rehabilitation is important to help optimize recovery, by inducing biochemical, physiological and anatomical changes in the brain (71–74). Increasing the intensity of practice of the affected upper limb can be achieved through the use of technology driven rehabilitation interventions such as the Wii gaming and robotic rehabilitation (75, 76). In addition, techniques such as the constraint induced movement therapy, which comprises of massed

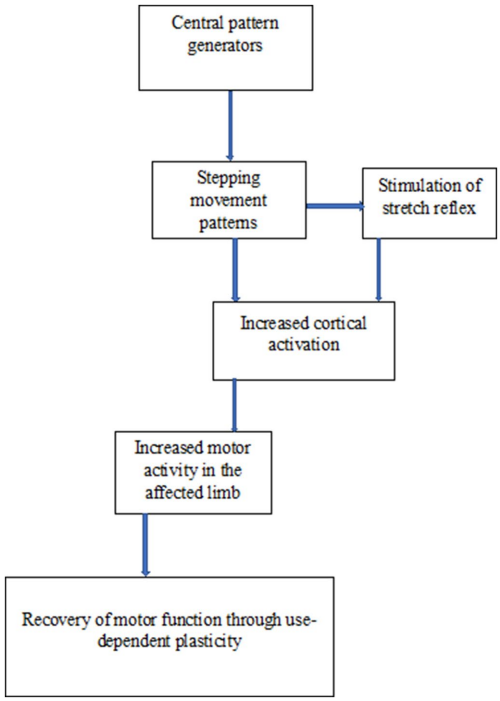

FIGURE 3
Schematic representation of the mechanism of central pattern generators hypothesis.

tasks practice with the affected limb, constraint of the unaffected limb, and transfer package (a contract to ensure continuous use of the affected at home) should be considered (77–79). Already, it is known that, repetitive tasks practice of the upper limb results in greater recovery (80–82); and this will in turn result in increased use of the limb in the real world (83).

In addition, the larger muscles of the lower limb are very important in maintaining standing posture (84). Thus, because of patients' natural instinct for wanting to regain walking, they would have to be able to stand first before they can walk. In doing so, bearing weight on the two limbs will automatically stimulate the stretch reflex, which will in turn activate the motor cortex (85, 86). When the motor cortex is repeatedly activated, recovery of motor function ensues (87). In addition, even during walking, weight is continuously borne on the lower limbs which helps with the restoration of motor function through the mechanisms already mentioned above. This is because, control of gait and posture are intricately related (86). Moreover, due to the bipedal nature of human locomotion, the unaffected limb forces the affected one into activity during propulsion and limb advancement. Thus, this can result in use-dependent plasticity, and eventual recovery of the lower limb (49).

Similarly, the role the CPGs play in the generation of rhythmic movement pattern such as the steps required for walking, may aid with the faster recovery of the lower limb (37, 54). Thus, considering the roles play by bipedal locomotion in humans, where the unaffected limb forces the affected limb into activity during propulsion and limb advancement; and the potential role of the CPGs in lower limb recovery, use of rhythmic bilateral movement training and bilateral upper limb exercise may help promote recovery of upper limb motor function through use-dependent plasticity (88, 89). Furthermore, as noted earlier, presence of spasticity in the upper limb is associated with poor recovery outcomes (39). Thus, this seems to suggest that, presence of spasticity may account for the difference in the rate of recovery between the upper limb and the lower limb. As such, managing spasticity in the upper limb during early post stroke may help hasten its recovery. Consequently, effective interventions for spasticity in patients with stroke such as active exercises, joint positioning and joint stretching should be used (90).

Although, the 4 theories proposed in this paper tried to explain some of the reasons why the lower limb motor function recovers faster than that of the upper limb, they are not in any way exhaustive, and as such other factors should also be considered. One of these factors is the argument that, upper limb occupies a larger area in the motor homunculus due its high tactile sensitivity, compared to the lower limb (9). Thus, to help recruit more areas of the brain to aid with the recovery of upper limb motor function, sensorimotor stimulation techniques such as the brain and peripheral electrical stimulation and tactile stimulation can be used in combination with other interventions (91–93). Stimulation of the nervous system can result in recovery of the upper limb (91, 94).

Secondly, the timing of rehabilitation is also important. This is because early post stroke is the period when the potential for recovery is higher (8, 95, 96). In addition, it is important also to note that, ability to determine or predict recovery depends on the outcome measure used (97). Furthermore, the difference sometimes may also depend on the psychometric properties of the outcome measures used (20). For instance, most studies use measures of daily function or disability rather than measures of impairment (20). Thus, in determining and predicting recovery of motor function after stroke, a combination of clinical, neurophysiological and imaging outcome measures should be used (20, 98, 99). Moreover, research is needed to be carried out, where practice/ activity will be controlled between upper and lower limbs, to determine if one will recover faster than the other. Similarly, studies should compare patients with the same degree of spasticity in the upper and the lower limbs to determine which one recovers faster.

5. Conclusion

The lower limb may regain motor function following stroke at a rate faster than the upper limb. Although many factors can help explain the reason why, most importantly the reason majorly has to do with the intensity or frequency or dose of use of the lower limb compared to the upper limb, and presence of spasticity and its significant impact on the upper limb. Therefore, rehabilitation strategies for upper limb motor function following stroke should consider increasing the intensity of practice especially in the real world, and management of spasticity, especially during early post stroke.

6. Expert opinion

In our opinion, the hypotheses we presented are some of the factors that make the lower limb to recover its motor function faster than the upper limb; and that all of them seem to suggest that, the main factor for the difference is intensity of use of the lower limb

compared to the upper limb. However, these factors we hypothesized seem not to be yet thoroughly investigated, and as such, future studies should focus on investigating them. For instance, views or opinions of stroke survivours using qualitative research methodology should be collected to explore what they prefer to recover immediately after having a stroke. In addition, ethnography method of qualitative research, whereby a group's behavior is observed by the researcher without interfering with their behavior, can be used to observe stroke survivours through their recovery journey. That way, the researchers can document the journeys of recovery of upper and lower limbs motor function with the goal of observing which one of them recovers faster.

Similarly, observational studies using objective outcome measures of motor function (physical function) such as the Fugl Meyer motor assessment and Wolf motor function test (WMFT) can also be used to objectively determine the difference over a long period of at least 1 year. In addition, electrophysiological measures of motor function such as the electromyography (EMG) to measure muscle electrical activity, and functional magnetic resonance imaging (fMRI) to measure cortical activity should also be used to determine the difference. Furthermore, biomechanical measurements of aspects of motor function such as movement speed, smoothness, quality and directness should also be considered. Thus, in determining the difference in recovery of motor function between the upper and lower limbs, a combination of outcomes measures of physical function, electrophysiological function, biomechanics, perspectives or views of patients and the caregivers and participants observation should be used to help with more reliable comparison. Moreover, many variables such the participants' age, sex, time since stroke, side affected, lesion volume, type of stroke, presence of neglect, and handedness before stroke need to be controlled in the studies.

In addition, in practice, clinicians should consider methods and techniques that will help increase the intensity of practice with the upper limb. For instance, transfer package whereby a contract is designed between the clinicians, the patients and their caregivers to make patients practice with the affected limb more in the real world, particularly at home; and home programs to increase the intensity of practice can be used. Furthermore, self-management techniques such as the use of motivational interviewing that will help increase patients' self-efficacy to enable them practice more with the affected limb should be incorporated in upper limb rehabilitation. Similarly, use of mechanical and computer devices such as the AUTOCITE (automated constraint induced movement extension), Wii games and other robotic devices that can help guarantee increased intensity of practice should also be considered during upper limb rehabilitation. However, the challenges that researchers and clinicians may face in determining whether upper limb or lower limb will recover faster in patients include the role of spontaneous recovery, patients own personal motivation and effort, caregiver support and probably the clinical setting.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AA, TW, and SN: conception and design, revising it critically for intellectual content, and the final approval of the version to be published. AA: drafting of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* (2009) 8:741–54. doi: 10.1016/S1474-4422(09)70150-4

2. Morris JH, Van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* (2013) 35:291–9. doi: 10.3109/09638288.2012.691942

3. Ekstrand E, Rylander L, Lexell J, Brogårdh C. Perceived ability to perform daily hand activities after stroke and associated factors: a cross-sectional study. *BMC Neurol.* (2016) 16:208–9. doi: 10.1186/s12883-016-0733-x

4. Waddell KJ, Birkenmeier RL, Bland MD, Lang CE. An exploratory analysis of the self-reported goals of individuals with chronic upper-extremity paresis following stroke. *Disabil Rehabil.* (2016) 38:853–7. doi: 10.3109/09638288.2015.1062926

5. Silva ESM, Pereira ND, Gianlorenço ACL, Camargo PR. The evaluation of non-use of the upper limb in chronic hemiparesis is influenced by the level of motor impairment and difficulty of the activities-proposal of a new version of the motor activity log. *Physiother Theory Pract.* (2019) 35:964–74. doi: 10.1080/09593985.2018.1460430

6. Rakesh N, Boiarsky D, Athar A, Hinds S, Stein J. Post-stroke rehabilitation: factors predicting discharge to acute versus subacute rehabilitation facilities. *Med.* (2019) 98:e15934. doi: 10.1097/MD.0000000000015934

7. Wirz M, Dietz V. European multicenter study of spinal cord injury (EMSCI) network. Recovery of sensorimotor function and activities of daily living after cervical spinal cord injury: the influence of age. *J Neurotrauma.* (2015) 32:194–9. doi: 10.1089/neu.2014.3335

8. Chanubol R, Wongphaet P, Ot NC, Chira-Adisai W, Kuptniratsaikul P, Jitpraphai C. Correlation between the action research arm test and the box and block test of upper extremity function in stroke patients. *J Med Assoc Thail*. (2012) 95:590–7.

9. Saadon-Grosman N, Loewenstein Y, Arzy S. The 'creatures' of the human cortical somatosensory system. *Brain Commun*. (2020) 2:fcaa003. doi: 10.1093/braincomms/fcaa003

10. Reed CL, Ziat M. Haptic perception: from the skin to the brain. In: *Reference module in neuroscience and biobehavioral psychology*: Neuroscience and Biobehavioral Psychology (2017). doi: 10.1016/B978-0-12-809324-5.21972-X

11. Peters DM, Fridriksson J, Richardson JD, Stewart JC, Rorden C, Bonilha L, et al. Upper and lower limb motor function correlates with Ipsilesional corticospinal tract and red nucleus structural integrity in chronic stroke: a cross-sectional. *ROI-Based MRI Study Behav Neurol*. (2021) 2021:1–10. doi: 10.1155/2021/3010555

12. Paci M, Nannetti L, Moretti S, Boccaletti E, Lombardi B. Are there differences in motor recovery between upper and lower limbs in hemiplegic patients with hemorrhagic stroke? *Ital J Physiother*. (2012) 2:59–64. doi: 10.1097/MRR.0000000000000172

13. Verheyden G, Nieuwboer A, De Wit L, Thijs V, Dobbelaere J, Devos H. Time course of trunk, arm, leg, and functional recovery after ischemic stroke. *Neurorehabil Neural Repair*. (2018) 22:173–9. doi: 10.1177/1545968307305456

14. Paci M, Nannetti L, Casavola D, Lombardi B. Differences in motor recovery between upper and lower limbs: does stroke subtype make the difference? *Int J Rehabil Res*. (2016) 39:185–7. doi: 10.1097/MRR.0000000000000172

15. Vincent-Onabajo G, Hamzat T, Owolabi M. Trajectory of motor performance over twelve months in Nigerian stroke survivors. *Brain Impairment*. (2014) 15:43–50. doi: 10.1017/BrImp.2014.3

16. Skurvydas A, Juodzbaliene V, Darbutas T, Brazaitis M. One year after ischemic stroke: changes in leg movement path stability in a speed-accuracy task but no major effects on the hands. *Hum Mov Sci*. (2018) 57:50–8. doi: 10.1016/j.humov.2017.11.005

17. Lee KB, Lim SH, Kim KH, Kim KJ, Kim YR, Chang WN, et al. Six-month functional recovery of stroke patients. *Int J Rehabil Res*. (2015) 38:173–80. doi: 10.1097/MRR.0000000000000108

18. Kong KH, Lee J. Temporal recovery and predictors of upper limb dexterity in the first year of stroke: a prospective study of patients admitted to a rehabilitation Centre. *NeuroRehabil*. (2013) 32:345–50. doi: 10.3233/NRE-130854

19. Rand D, Eng JJ. Disparity between functional recovery and daily use of the upper and lower extremities during subacute stroke rehabilitation. *Neurorehabil Neural Repair*. (2016) 26:76–84. doi: 10.1177/1545968311408918

20. Desrosiers J, Malouin F, Richards C, Bourbonnais D, Rochette A, Bravo G. Comparison of changes in upper and lower extremity impairments and disabilities after stroke. *Int J Rehabil Res*. (2013) 26:109–16. doi: 10.1097/00004356-200306000-00005

21. Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. *Arch Phys Med Rehabil*. (2003) 83:1629–37. doi: 10.1053/apmr.2002.35473

22. Dombovy ML. Rehabilitation and the course of recovery after stroke. In: JP Whisnant, editor. *Stroke: Populations, cohorts, and clinical trials*, Oxford: Butterworth-Heinemann Ltd (1993). 218–37.

23. Tan A, Roberts D. Cerebral circulation 1: anatomy. *BJA Educ*. (2021) 21:390–5. doi: 10.1016/j.bjae.2021.05.004

24. Bernhardt J, Chan J, Nicola I, Collier JM. Little therapy, little physical activity: rehabilitation within the first 14 days of organized stroke unit care. *J Rehabil Med*. (2007) 39:43–8. doi: 10.2340/16501977-0013

25. Abdullahi A, Umar NA, Ushotanefe U, Aliyu AM, Oyeniran AM, Steven T, et al. Effects of two different modes of tasks practice during lower limbs constraint-induced movement therapy in people with stroke: a randomized clinical trial. *Neural Plast*. (2021) 2021:1–9. doi: 10.1155/2021/6664058

26. Salvadori E, Papi G, Insalata G, Rinnoci V, Donnini I, Martini M, et al. Comparison between ischemic and hemorrhagic strokes in functional outcome at discharge from an intensive rehabilitation hospital. *Diagnostics*. (2020) 11:38. doi: 10.3390/diagnostics11010038

27. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol*. (2012) 11:101–18. doi: 10.1016/S1474-4422(11)70264-2

28. Persson HC, Opheim A, Lundgren-Nilsson A, Alt Murphy M, Danielsson A, Sunnerhagen KS. Upper extremity recovery after ischaemic and haemorrhagic stroke: part of the SALGOT study. *Eur Stroke J*. (2016) 1:310–9. doi: 10.1177/2396987316672809

29. Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehabil Neural Repair*. (2015) 29:614–22. doi: 10.1177/1545968314562115

30. Ingwersen T, Wolf S, Birke G, Schlemm E, Bartling C, Bender G, et al. Long-term recovery of upper limb motor function and self-reported health: results from a multicenter observational study 1 year after discharge from rehabilitation. *Neurol Res Pract*. (2021) 3:66. doi: 10.1186/s42466-021-00164-7

31. Hendricks HT, Pasman JW, Merx JL, van Limbeek J, Zwarts MJ. Analysis of recovery processes after stroke by means of transcranial magnetic stimulation. *J Clin Neurophysiol*. (2003) 20:188–95. doi: 10.1097/00004691-200305000-00004

32. Volpe JJ. Neurological examination: normal and abnormal features. In: *Neurology of the newborn*. *5th* ed. Philadelphia, PA: Saunders Elsevier (2008).

33. Yen HC, Jeng JS, Chen WS, Pan GS, Chuang, PT, BS WY, Lee YY, et al. Early mobilization of mild-moderate intracerebral hemorrhage patients in a stroke center: a randomized controlled trial. *Neurorehabil Neural Repair*. (2020) 34:72–81. doi: 10.1177/1545968319893294

34. Awad LN, Lewek MD, Kesar TM, Franz JR, Bowden MG. These legs were made for propulsion: advancing the diagnosis and treatment of post-stroke propulsion deficits. *J Neuroeng Rehabil*. (2020) 17:139. doi: 10.1186/s12984-020-00747-6

35. Abdullahi A, Truijen S, Umar NA, Useh U, Egwuonwu VA, van Criekinge T, et al. Effects of lower limb constraint induced movement therapy in people with stroke: a systematic review and Meta-analysis. *Front Neurol*. (2021) 12:638904. doi: 10.3389/fneur.2021.638904

36. Ryu HX, Kuo AD. An optimality principle for locomotor central pattern generators. *Sci Rep*. (2021) 11:13140. doi: 10.1038/s41598-021-91714-1

37. Minassian K, Hofstoetter US, Dzeladini F, Guertin PA, Ijspeert A. The human central pattern generator for locomotion: does it exist and contribute to walking? *Neuroscientist*. (2017) 23:649–63. doi: 10.1177/1073858417699790

38. Katoozian L, Tahan N, Zoghi M, Bakhshayesh B. The onset and frequency of spasticity after first ever stroke. *J Natl Med Assoc*. (2018) 110:547–52. doi: 10.1016/j.jnma.2018.01.008

39. Kong KH, Chua KS, Lee J. Recovery of upper limb dexterity in patients more than 1 year after stroke: frequency, clinical correlates and predictors. *NeuroRehabilitation*. (2011) 28:105–11. doi: 10.3233/NRE-2011-0639

40. O'Mara S. Biopsychosocial functions of human walking and adherence to Behaviourally demanding belief systems: a narrative review. *Front Psychol*. (2021) 12:654122. doi: 10.3389/fpsyg.2021.654122

41. Hershkovitz I, Weber GW, Quam R, Duval M, Grün R, Kinsley L, et al. The earliest modern humans outside Africa. *Science*. (2018) 359:456–9. doi: 10.1126/science.aap8369

42. Bae CJ, Douka K, Petraglia MD. On the origin of modern humans: Asian perspectives. *Science*. (2017) 358:eaai9067. doi: 10.1126/science.aai9067

43. López S, van Dorp L, Hellenthal G. Human dispersal out of Africa: a lasting debate. *Evol Bioinformatics Online*. (2016) 11:57–68. doi: 10.4137/EBO.S33489

44. Törnbom K, Sunnerhagen KS, Danielsson A. Perceptions of physical activity and walking in an early stage after stroke or acquired brain injury. *PLoS One*. (2017) 12:e0173463. doi: 10.1371/journal.pone.0173463

45. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. *Int J Rehabil Res*. (1988) 11:181–4. doi: 10.1097/00004356-198806000-00012

46. Martino Cinnera A, Bonnì S, Pellicciari MC, Giorgi F, Caltagirone C, Koch G. Health-related quality of life (HRQoL) after stroke: positive relationship between lower extremity and balance recovery. *Top Stroke Rehabil*. (2020) 27:534–40. doi: 10.1080/10749357.2020.1726070

47. Enzinger C, Johansen-Berg H, Dawes H, Bogdanovic M, Collett J, Guy C, et al. Functional MRI correlates of lower limb function in stroke victims with gait impairment. *Stroke*. (2008) 39:1507–13. doi: 10.1161/STROKEAHA.107.501999

48. Yang YR, Chen I, Liao KK, Huang CC, Wang RY. Cortical reorganization induced by body weight-supported treadmill training in patients with hemiparesis of different stroke durations. *Arch Phys Med Rehabil*. (2010) 91:513–8. doi: 10.1016/j.apmr.2009.11.021

49. Mahtani GB, Kinnaird CR, Connolly M, Holleran CL, Hennessy PW, Woodward J, et al. Altered sagittal- and frontal-plane kinematics following high-intensity stepping training versus conventional interventions in subacute stroke. *Phys Ther*. (2016) 97:320–9. doi: 10.2522/ptj.20160281

50. Roelker S, Bowden M, Kautz S, Neptune RR. Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: a review. *Gait Posture*. (2018) 68:6–14. doi: 10.1016/j.gaitpost.2018.10.027

51. Yu WH, Liu WY, Wong AM, Wang TC, Li YC, Lien HY. Effect of forced use of the lower extremity on gait performance and mobility of post-acute stroke patients. *J Phys Ther Sci*. (2015) 27:421–5. doi: 10.1589/jpts.27.421

52. Macleod CA, Meng L, Conway BA, Porr B. Reflex control of robotic gait using human walking data. *PLoS One*. (2014) 9:e109959. doi: 10.1371/journal.pone.0109959

53. Ravichandran H, Shetty KS, Janakiraman B. Effect of gait-specific weight-bearing interventions on physical performance among subjects with stroke: a systematic review and Meta-analysis. *J Stroke Med*. (2022) 5:107–18. doi: 10.1177/25166085221115605

54. Klarner T, Zehr EP. Sherlock Holmes and the curious case of the human locomotor central pattern generator. *J Neurophysiol*. (2018) 120:53–77. doi: 10.1152/jn.00554.2017

55. Grillner S. Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron*. (2006) 52:751–66. doi: 10.1016/j.neuron.2006.11.008

56. Yang JF, Gorassini M. Spinal and brain control of human walking: implications for retraining of walking. *Neuroscientist*. (2006) 12:379–89. doi: 10.1177/1073858406292151

57. Kiehn O. Locomotor circuits in the mammalian spinal cord. *Annu Rev Neurosci*. (2006) 29:279–306. doi: 10.1146/annurev.neuro.29.051605.112910

58. Kathe C, Skinnider MA, Hutson TH, Regazzi N, Gautier M, Demesmaeker R, et al. The neurons that restore walking after paralysis. *Nature*. (2022) 611:540–7. doi: 10.1038/s41586-022-05385-7

59. Sherrington CS. *The integrative action of the nervous system*, New Heaven: Yale University Press (1906).

60. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci*. (1998) 860:360–76. doi: 10.1111/j.1749-6632.1998.tb09062.x

61. Zeng H, Chen J, Guo Y, Tan S. Prevalence and risk factors for spasticity after stroke: a systematic review and Meta-analysis. *Front Neurol*. (2021) 11:616097. doi: 10.3389/fneur.2020.616097

62. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol*. (2010) 257:1067–72. doi: 10.1007/s00415-010-5463-1

63. Payton H, Soundy A. The experience of post-stroke pain and the impact on quality of life: an integrative review. *Behav Sci (Basel)*. (2020) 10:128. doi: 10.3390/bs10080128

64. Westerlind E, Singh R, Persson HC, Sunnerhagen KS. Experienced pain after stroke: a cross-sectional 5-year follow-up study. *BMC Neurol*. (2020) 20:4. doi: 10.1186/s12883-019-1584-z

65. Singer JC, Nishihara K, Mochizuki G. Does Poststroke lower-limb spasticity influence the recovery of standing balance control? A 2-year multilevel growth model. *Neurorehabil Neural Repair*. (2016) 30:626–34. doi: 10.1177/1545968315613862

66. Tseng YT, Chen FC, Tsai CL, Konczak J. Upper limb proprioception and fine motor function in young pianists. *Hum Mov Sci*. (2021) 75:102748. doi: 10.1016/j.humov.2020.102748

67. Mahmoudzadeh A, Nakhostin Ansari N, Naghdi S, Ghasemi E, Motamedzadeh O, Shaw BS, et al. Role of spasticity severity in the balance of post-stroke patients. *Front Hum Neurosci*. (2021) 15:783093. doi: 10.3389/fnhum.2021.783093

68. Rand D, Eng JJ. Predicting daily use of the affected upper extremity 1 year after stroke. *J Stroke Cerebrovasc Dis*. (2015) 24:274–83. doi: 10.1016/j.jstrokecerebrovasdis.2014.07.039

69. Lang CE, Macdonald JR, Reisman DS, Boyd L, Jacobson Kimberley T, Schindler-Ivens SM, et al. Observation of amounts of movement practice provided during stroke rehabilitation. *Arch Phys Med Rehabil*. (2009) 90:1692–8. doi: 10.1016/j.apmr.2009.04.005

70. Abdullahi A, Sabo B, Badaru UM, Saeys W, Truijen S. Factors influencing recovery of upper limb motor function during constraint-induced movement therapy for people with stroke. *Transl Neurosci*. (2022) 13:453–9. doi: 10.1515/tnsci-2022-0260

71. Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the queen square programme. *J Neurol Neurosurg Psychiatry*. (2019) 90:498–506. doi: 10.1136/jnnp-2018-319954

72. Sehatzadeh S. Effect of increased intensity of physiotherapy on patient outcomes after stroke: an evidence-based analysis. *Ont Health Technol Assess Ser*. (2015) 15:1–42.

73. Pang MY, Harris JE, Eng JJ. A community-based upper-extremity group exercise program improves motor function and performance of functional activities in chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. (2006) 87:1–9. doi: 10.1016/j.apmr.2005.08.113

74. Abdullahi A, Truijen S, Saeys W. Neurobiology of recovery of motor function after stroke: the central nervous system biomarker effects of constraint-induced movement therapy. *Neural Plast*. (2020) 2020:1–12. doi: 10.1155/2020/9484298

75. Aprile I, Germanotta M, Cruciani A, Loreti S, Pecchioli C, Cecchi F, et al. Upper limb robotic rehabilitation after stroke: a multicenter, randomized clinical trial. *J Neurol Phys Ther*. (2020) 44:3–14. doi: 10.1097/NPT.0000000000000295

76. McNulty PA, Thompson-Butel AG, Faux SG, Lin G, Katrak PH, Harris LR. The efficacy of Wii-based movement therapy for upper limb rehabilitation in the chronic poststroke period: a randomized controlled trial. *Int J Stroke*. (2015) 10:1253–60. doi: 10.1111/ijs.12594

77. Abdullahi A, Van Criekinge T, Umar NA, Zakari UU, Truijen S, Saeys W. Effect of constraint-induced movement therapy on persons-reported outcomes of health status after stroke: a systematic review and meta-analysis. *Int J Rehabil Res*. (2021) 44:15–23. doi: 10.1097/MRR.0000000000000446

78. Etoom M, Hawamdeh M, Hawamdeh Z, Alwardat M, Giordani L, Bacciu S, et al. Constraint-induced movement therapy as a rehabilitation intervention for upper extremity in stroke patients: systematic review and meta-analysis. *Int J Rehabil Res*. (2016) 39:197–210. doi: 10.1097/MRR.0000000000000169

79. Kwakkel G, Veerbeek JM, van Wegen EE, Wolf SL. Constraint-induced movement therapy after stroke. *Lancet Neurol*. (2015) 14:224–34. doi: 10.1016/S1474-4422(14)70160-7

80. Rocha LSO, Gama GCB, Rocha RSB, Rocha LB, Dias CP, Santos LLS, et al. Constraint induced movement therapy increases functionality and quality of life after stroke. *J Stroke Cerebrovasc Dis*. (2021) 30:105774. doi: 10.1016/j.jstrokecerebrovasdis.2021.105774

81. Abdullahi A. Effects of number of repetitions and number of hours of shaping practice during constraint-induced movement therapy: a randomized controlled trial. *Neurol Res Int*. (2018) 2018:1–9. doi: 10.1155/2018/5496408

82. Birkenmeier RL, Prager EM, Lang CE. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair*. (2010) 24:620–35. doi: 10.1177/1545968310361957

83. Otaki R, Oouchida Y, Aizu N, Sudo T, Sasahara H, Saito Y, et al. Relationship between body-specific attention to a paretic limb and real-world arm use in stroke patients: a longitudinal study. *Front Syst Neurosci*. (2022) 15:806257. doi: 10.3389/fnsys.2021.806257

84. Lee Y-J, Liang JN, Wen Y-T. Characteristics of postural muscle activity in response to a motor-motor task in elderly. *Appl Sci*. (2019) 9:4319. doi: 10.3390/app9204319

85. Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. *J Physiol*. (2012) 590:2443–52. doi: 10.1113/jphysiol.2012.227397

86. Pulverenti TS, Zaaya M, Grabowski M, Grabowski E, Islam MA, Li J, et al. Neurophysiological changes after paired brain and spinal cord stimulation coupled with locomotor training in human spinal cord injury. *Front Neurol*. (2021) 12:627975. doi: 10.3389/fneur.2021.627975

87. Bergfeldt U, Jonsson T, Bergfeldt L, Julin P. Cortical activation changes and improved motor function in stroke patients after focal spasticity therapy--an interventional study applying repeated fMRI. *BMC Neurol*. (2015) 15:52. doi: 10.1186/s12883-015-0306-4

88. Han KJ, Kim JY. The effects of bilateral movement training on upper limb function in chronic stroke patients. *J Phys Ther Sci*. (2016) 28:2299–302. doi: 10.1589/jpts.28.2299

89. Stinear JW, Byblow WD. Rhythmic bilateral movement training modulates corticomotor excitability and enhances upper limb motricity poststroke: a pilot study. *J Clin Neurophysiol*. (2004) 21:124–31. doi: 10.1097/00004691-200403000-00008

90. Monaghan K, Horgan F, Blake C, Cornall C, Hickey PPM, Lyons BE, et al. Physical treatment interventions for managing spasticity after stroke. *Cochrane Database Syst Rev*. (2017) 2017:CD009188. doi: 10.1002/14651858.CD009188.pub2

91. Abdullahi A, Wong TW, Van Criekinge T, Ng SS. Combination of non-invasive brain stimulation and constraint induced movement therapy in patients with stroke: a systematic review and Meta-analysis. *Expert Rev Neurother*. (2023) 23:187–203. doi: 10.1080/14737175.2023.2177154

92. Abdullahi A, Wong TWL, Ng SSM. Rehabilitation of severe impairment in motor function after stroke: suggestions for harnessing the potentials of Mirror neurons and the Mentalizing systems to stimulate recovery. *Brain Sci*. (2022) 12:1311. doi: 10.3390/brainsci12101311

93. Rosenfeldt AB, Linder SM, Davidson S, Clark C, Zimmerman NM, Lee JJ, et al. Combined aerobic exercise and task practice improve health-related quality of life Poststroke: a preliminary analysis. *Arch Phys Med Rehabil*. (2019) 100:923–30. doi: 10.1016/j.apmr.2018.11.011

94. Wu CW, Seo HJ, Cohen LG. Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. *Arch Phys Med Rehabil*. (2006) 87:351–7. doi: 10.1016/j.apmr.2005.11.019

95. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke*. (2008) 37:2348–53. doi: 10.1161/01.STR.0000238594.91938.1e

96. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT. *Neurol*. (2009) 73:195–201. doi: 10.1212/WNL.0b013e3181ab2b27

97. Woldag H, Gerhold LL, de Groot M, Wohlfart K, Wagner A, Hummelsheim H. Early prediction of functional outcome after stroke. *Brain Inj*. (2006) 20:1047–52. doi: 10.1080/02699050600915422

98. Stinear CM, Byblow WD, Ward SH. An update on predicting motor recovery after stroke. *Ann Phys Rehabil Med*. (2014) 57:489–98. doi: 10.1016/j.rehab.2014.08.006

99. Hope TM, Seghier ML, Leff AP, Price CJ. Predicting outcome and recovery after stroke with lesions extracted from MRI images. *Neuroimage Clin*. (2013) 2:424–33. doi: 10.1016/j.nicl.2013.03.005

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Comparative efficacy and safety of multiple acupuncture therapies for post stroke cognitive impairment: a network meta-analysis of randomized controlled trials

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Background: Acupuncture therapy has been widely used to treat post-stroke cognitive impairment (PSCI). However, acupuncture therapy includes multiple forms. Which acupuncture therapy provides the best treatment outcome for patients with PSCI remains controversial.

Objective: We aimed to compare and evaluate the efficacy and safety of different acupuncture-related therapies for PSCI in an attempt to identify the best acupuncture therapies that can improve cognitive function and self-care in daily life for patients with PSCI, and bring new insights to clinical practice.

Method: We searched eight databases including PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, China Biomedical Literature Database (CBM), China Science and Technology Journal (VIP) database, China National Knowledge Infrastructure (CNKI) database, and Wan fang database to find randomized controlled trials (RCTs) of acupuncture-related therapies for PSCI from the inception of the database to January 2023. Two researchers independently assessed the risk of bias in the included studies and extracted the study data. Pairwise meta-analyzes for direct comparisons were performed using Rev. Man 5.4 software. Bayesian network meta-analysis (NMA) was performed using STATA 17.0 and R4.2.4 software. The quality of evidence from the included studies was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Adverse effects (AEs) associated with acupuncture therapy were collected by reading the full text of the included studies to assess the safety of acupuncture therapy.

Results: A total of 62 RCTs (3 three-arm trials and 59 two-arm trials) involving 5,073 participants were included in this study. In the paired meta-analysis, most acupuncture-related therapies had a positive effect on cognitive function and self-care of daily living in patients with PSCI compared with cognitive training. Bayesian NMA results suggested that ophthalmic acupuncture plus cognitive training (79.7%) was the best acupuncture therapy for improving MMSE scores, with scalp acupuncture plus cognitive training ranking as the second (73.7%). The MoCA results suggested that warm acupuncture plus cognitive training (86.5%) was the best acupuncture therapy. In terms of improvement in daily living self-care, scalp acupuncture plus body acupuncture (87.5%) was the best acupuncture therapy for improving MBI scores. The most common minor AEs included subcutaneous hematoma, dizziness, sleepiness, and pallor.

Conclusion: According to our Bayesian NMA results, ophthalmic acupuncture plus cognitive training and warm acupuncture plus cognitive training were the most effective acupuncture treatments for improving cognitive function, while scalp acupuncture plus body acupuncture was the best acupuncture treatment for improving the performance of self-care in daily life in patients with PSCI. No serious adverse effects were found in the included studies, and acupuncture treatment appears to be safe and reliable. However, due to the low methodological quality of the included studies, our findings need to be treated with caution. High-quality studies are urgently needed to validate our findings.

Systematic review registration: https://www.crd.york.ac.uk/prospero/#recordDetails, identifier: CRD42022378353.

KEYWORDS

acupuncture treatment, post-stroke cognitive impairment, cognitive rehabilitation, non-pharmacological treatment, network meta analysis

1. Introduction

Post-stroke cognitive impairment (PSCI), Characterized by distractibility and impaired language, memory, and executive skills, has a serious impact on the quality of life and survival time of stroke survivors (1). The prevalence of PSCI is steadily climbing as the population ages and the number of stroke survivors continues to increase. In the latest meta-analysis involving 16 studies, approximately 53.4% of stroke survivors were reported to suffer from PSCI, with the incidence of mild and severe PSCI being 36.4 and 16.5%, respectively (2). One study based on 6,504 stroke patients evaluated outcomes from the first 3 months to 5 years after stroke and found that patients with PSCI were strongly associated with an increased risk of death, dependency, depression, and hospitalization (3). However, in many national and international guidelines for stroke treatment, few details about PSCI were mentioned. It is clear that PSCI is not receiving enough attention and is not effectively addressed.

Currently, the treatment of PSCI mainly consists of pharmacological and non-pharmacological treatments. Studies have confirmed that there is no strong evidence that pharmacological interventions, including cholinesterase inhibitors and memantine, can improve cognition or slow the progression of dementia (4). In addition, one study based on 168 patients with vascular cognitive impairment found no significant improvement in cognitive function or ADL with donepezil (5). Instead, we found side effects associated with these drugs, such as gastrointestinal reactions and liver toxicity (6). Therefore, non-pharmacological treatments such as acupuncture, cognitive training, and transcranial magnetic stimulation have gradually received widespread attention. A network meta-analysis (7) published in 2022 compared five nonpharmacological treatments for improving cognitive function and self-care in patients with PSCI, and its results indicated that acupuncture was the most effective treatment for improving MoCA scores in PSCI patients.

Acupuncture, as a basic treatment tool in Chinese medicine, has been widely used for thousands of years for the prevention and treatment of various diseases (8). Acupuncture indeed has better clinical efficacy for some hard-to-treat chronic diseases, such as chronic kidney disease and low back pain (9, 10). In recent years, studies (11–13) have continued to find that acupuncture has a better effect on improving cognitive function in patients with PSCI. Relevant animal experiments are also being conducted in an attempt to explore the potential mechanism of acupuncture for PSCI. However, there are many forms of acupuncture treatment, including scalp acupuncture, warm acupuncture, abdominal acupuncture, and auricular acupuncture, etc. To date, there is still no systematic review that comprehensively compares and evaluates the efficacy of multiple acupuncture therapies. The differences in efficacy between acupuncture therapies remain unclear. Similarly, it is not clear to PSCI patients and clinicians which acupuncture technique is the best choice. Therefore, we conducted this network meta-analysis. In this study, we included 62 RCTs that critically evaluated the efficacy of eight different acupuncture techniques for the treatment of PSCI to provide evidence for the clinical selection of appropriate treatment options.

2. Methods

2.1. Registration

The protocol for this meta-analysis was registered with the International Platform for the Registration of Systematic Review (PROSPERO) under registration number CRD42022378353. This study was conducted in strict accordance with the PRISMA Extension Statement for Reports of Systematic Reviews Incorporating Meta-Analyzes of Healthcare Intervention Networks (PRISMA-NMA) (14), as detailed in Supplementary Appendix S1.

2.2. Search strategy

We searched eight databases including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), China Science and Technology Journal (VIP) database, and Wan Fang database, from their inception to January, 2023, to find eligible RCTs regarding acupuncture treatment of PSCI. The language was restricted to Chinese or English. Meanwhile, the reference lists of systematic

review articles were read to determine if there was any missing literature. The following terms were used in the search strategies: (acupuncture therapy, scalp acupuncture, warm acupuncture, electro-acupuncture) and (stroke, cerebrovascular accident, post-stroke cognitive impairment, and PSCI). The search strategy for each database was shown in Supplementary Appendix S2.

2.3. Eligibility criteria

We included studies that met the inclusion and exclusion eligibility criteria listed in Table 1.

2.4. Date extraction

Two investigators (YL and LZ) independently performed literature screening and data extraction and cross-checked the results. Any inconsistencies in the information extraction process can be resolved by the third investigator (FY-C). Extraction included basic characteristics (first author, year of publication, diagnostic criteria, sample size, gender, stroke type, age, duration of disease), details of the intervention (type of acupuncture, duration of treatment, periodicity, frequency), outcomes and adverse events (AEs).

2.5. Quality assessment

Two investigators (YL and LZ) independently assessed the quality of the included literature according to the risk of bias assessment tool (ROB2) recommended by the Cochrane Handbook. The assessments included the randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. Each assessment component was categorized as low risk, high risk, and some concern. Given that the majority of acupuncture studies were published in Chinese journals, we used the Consolidated Standards for Reporting Trials (CONSORT) reporting guidelines (15) to assess the quality of included literature. The percentages for each item in the corresponding specifications were calculated and presented. In addition, the quality of evidence for each outcome indicator was assessed using the Grading of Recommendations, Assessments, Developments and Evaluations (GRADE) system (16), which resulted in a high, moderate, low, or very low level of evidence. Disagreements encountered during the assessment process could be resolved by the third investigator (FY-C).

2.6. Statistical analysis

Paired meta-analysis was performed using Rev. Man 5.4 software (Cochrane Collaboration, Oxford, United Kingdom). Effect sizes were calculated using mean differences (MDs) and 95% confidence intervals (CI) for continuous variables. Effect sizes were calculated using odd ratios (OR) and 95%CI for dichotomous variables. Heterogeneity between included studies was assessed according to the Q test (p value) and I^2 statistic. If $p \geq 0.1$ and $I^2 \leq 50\%$, it represented acceptable heterogeneity, and a fixed-effects model was selected for meta-analysis, and conversely, a random-effects model was selected for meta-analysis.

STATA version 17.0 (Stata Corp, College Station, Texas, United States) and R version 4.2.4 (R Core Team, Vienna, Austria) were used for Bayesian framework network meta-analysis. Considering the possible heterogeneity among the included studies, we merged the data using random effects models. Given that the outcome variables chosen for this study were all continuous, mean differences (MDs) and 95% CI were selected for calculation. Markov chain Monte Carlo (MCMC) was used to calculate the model with the following parameters: four chains, 20,000 sample iterations, 5,000 burns, and a lean interval of 1. Brooks-Gelman-Rubin diagnostic plots were used to assess the convergence of the model. In addition, we also observed trajectory and density plots. The node-splitting method was used to assess the agreement between direct and indirect comparisons. $p > 0.05$ indicates the existence of the agreement. When there was a closed loop, we used the inconsistency factor (IF) to make the judgment. When the 95% CI contains 0, it indicates the existence of consistency between direct and indirect evidence. The surface under

TABLE 1 Eligibility criteria for relevant studies.

Criteria	Inclusion	Exclusion
Population	•Adults (18 years or older) who meet validated diagnostic instruments for PSCI	•Under 18 years old • Cognitive impairment caused by other diseases, such as Alzheimer's disease (AD) and Cranial Trauma
Intervention	•Various acupuncture therapies (body acupuncture, scalp acupuncture, warm acupuncture, electro-acupuncture, abdominal acupuncture, auricular bloodletting, ophthalmic acupuncture, etc.) •Single or combined use of acupuncture therapy	•Other non-pharmacological treatments not covered by the study
Comparators	•Cognitive training •The different acupuncture treatments compared with the experimental group	•Other non-pharmacological treatments not covered by the study
Outcomes	•The Minimum Mental State Examination scale (MMSE) •The Montreal Cognitive Assessment Scale (MoCA) •The Modified Barthel Index scale (MBI) •Adverse events (AEs)	•Lack of valid outcome
Languages	Chinese and English	Other languages
Study designs	Randomized controlled trials (RCTs)	Reviews, animal trials, case reports, and conference papers.

the cumulative ranking area (SUCRA) was calculated to rank each intervention probabilistically. The value of SUCRA ranged from 0 to 100%, with higher values indicating better efficacy. The following formula was used to approximate the outcome data, taking into account possible differences in baseline conditions for outcome indicators in the included studies, where the correlation coefficient R-value was 0.5.

$$\overline{MDs}_{Change} = \overline{MDs}_{Final} - \overline{MDs}_{Baseline} \quad (1)$$

$$SD_{Change} = \sqrt{\left(SD_{Baseline}\right)^2 + \left(SD_{Final}\right)^2 - \left(2 \times R \times SD_{Baseline} \times SD_{Final}\right)} \quad (2)$$

3. Results

3.1. Literature selection

We initially searched for 2,268 potentially relevant articles and excluded 1,075 articles due to duplication. The 1,094 articles were excluded by reading the titles and abstracts. The remaining 99 studies were evaluated by reading the full text. 62 studies (17–78) were ultimately included in the quantitative analysis. The PRISMA flowchart of the search process is shown in Figure 1.

3.2. Study characteristics

All 62 included studies were conducted in China, of which 59 and 3 RCTs were published in Chinese and English, respectively. These included studies were reported between 2012 and 2022. A total of 5,073 participants were included, of which 2,593 participants were in the experimental group and 2,480 participants were in the control group. Among the 62 studies, 3 (18, 53, 55) were three-arm trials and 59 were two-arm trials. The baseline data for participants in both groups were generally similar, but 5 studies (23, 25, 36, 41, 45) did not report the mean age and 17 studies (25, 31, 33, 34, 36–38, 41, 44–47, 50, 52, 57, 58, 69) did not report the mean duration of disease. 3 studies (23, 35, 36) reported patient drop-out and reported specific reasons, and the number of drop-outs ranged from 3 to 11. Treatment duration ranged from 2 weeks to 12 weeks. In terms of treatment measures, in addition to cognitive training (CT), 13 types of acupuncture-related therapies are included, which were body acupuncture (BA), scalp acupuncture (SA), body acupuncture plus cognitive training (BA+CT), scalp acupuncture plus cognitive training (SA + CT), ophthalmic acupuncture plus cognitive training (OA + CT), warm acupuncture plus cognitive training (WA + CT), electro-acupuncture plus cognitive training (EA + CT), auricular bloodletting plus cognitive training (AB+CT), abdominal acupuncture plus cognitive training (AA+CT), scalp acupuncture plus body acupuncture (SA + BA), abdominal acupuncture plus body acupuncture (AA+BA), warm acupuncture plus scalp acupuncture (WA + SA) and scalp acupuncture plus auricular bloodletting (SA + AB). Furthermore, 47 studies (17–23, 25–29, 31, 33–36, 38, 40, 41, 43–50, 52, 53, 55–57, 59, 60, 62–67, 70, 72, 73, 75, 77, 78) reported MMSE scores, 29 studies (18, 24, 28, 30–34, 37, 39, 42, 47–49, 52, 54, 58, 61–63, 67–72, 74, 76, 77) reported MoCA scores and 20 studies (22–24, 27, 30, 32–35, 41, 42, 47–50, 54, 60, 61, 73, 74) reported MBI scores. The characteristics of the included studies are shown in Table 2.

3.3. Risk of bias

According to ROB2, three studies (23, 35, 36) were rated at high risk of bias, two studies (19, 26) were rated at low risk of bias, and the remaining studies were rated at some risk of bias. The main issues included lack of description of allocation concealment, lack of blinding of outcome assessors, and lack of exploration of prospective protocols, which ultimately led to an increased risk of bias. The risk of bias assessment for the included studies is presented in Supplementary Figure S1. Many of the items in the CONSORT (18/25 items) statements did not achieve the desired reporting rate (>80%), which was shown in Supplementary Appendix 3.

3.4. Pairwise meta-analysis

After a comprehensive analysis of studies with the same treatment and outcomes, we conducted 19 direct-paired meta-analyzes to compare MMSE scores, 11 to compare MoCA scores, and 10 to compare MBI scores, respectively. As for MMSE scores，SA (two RCTs; WMD = 2.50, 95%CI: 0.67, 4.32, $p = 0.007$), BA+CT (one RCT; WMD = 5.29, 95%CI: 4.16, 6.42, P<0.00001), SA + CT (16 RCTs; WMD = 4.39, 95%CI: 3.08, 5.70, P<0.00001), OA + CT (one RCT; WMD = 5.85, 95%CI: 4.69, 7.01, P<0.00001), WA + CT (one RCT; WMD = 1.86, 95%CI: 0.16, 3.56, $p = 0.03$), AB+CT (one RCT; WMD = 2.57, 95%CI: 0.81, 4.33, $p = 0.004$), SA + BA (16 RCTs; WMD = 4.24, 95%CI: 3.28, 5.20, $p<0.00001$), SA + AB (one RCT; WMD = 3.84, 95%CI: 2.00, 5.68, $p<0.00001$) were effective than the CT group. In the comparison of different acupuncture treatments, we found that SA (one RCT; WMD = 0.88, 95%CI: 0.15, 1.61, $p = 0.02$), SA + CT (one RCT; WMD = 2.42, 95%CI: 0.74, 4.10, $p = 0.005$), SA + BA (two RCTs; WMD = 1.79. 95% CI: 1.05, 2.53, $p < 0.00001$) improved MMSE scores more than BA alone. Furthermore, SA + CT (one RCT; WMD = 2.48, 95%CI: 0.18, 4.78, $p = 0.03$) and WA + CT (one RCT; WMD = 1.22, 95%CI: 0.08, 2.36, $p = 0.04$) were more effective in improving MMSE scores compared with BA+CT. Meanwhile, SA + CT had a greater effect than SA alone (two RCTs; WMD = 3.23, 95%CI: 1.49, 4.97, $p = 0.0003$). However, there was no statistical difference in efficacy between BA and CT, EA and CT, AA+BA and CT, AA+CT and BA+CT, and SA + AB and BA+CT. In terms of MoCA scores, SA + CT (10 RCTs; WMD =3.75, 95%CI: 2.81, 4.69, P<0.00001), SA + BA (four RCTs; WMD = 3.26, 95%CI: 2.19, 4.34, P<0.00001), WA + CT (five RCTs; WMD = 3.96, 95%CI: 2.29, 5.62, P<0.00001), EA + CT (four RCTs; WMD = 3.16, 95%CI: 1.88, 4.45, $p<0.00001$), AA+CT (one CRT; WMD = 3.00, 95%CI: 0.26, 5.74, $p = 0.03$) were more effective than CT alone. Furthermore, compared with WA + CT, SA + CT (one RCT; WMD = 3.14, 95%CI: 2.15, 4.13, $p<0.00001$) and SA + BA (two RCTs; WMD = 3.61, 95%CI: 2.11, 5.11, $p<0.00001$) were more effective in improving MoCA scores. Meanwhile, SA + BA had a greater effect than BA alone (one RCT; WMD = 2.00, 95%CI: 1.37, 2.63, $p<0.00001$). However, there was no statistical difference in efficacy between

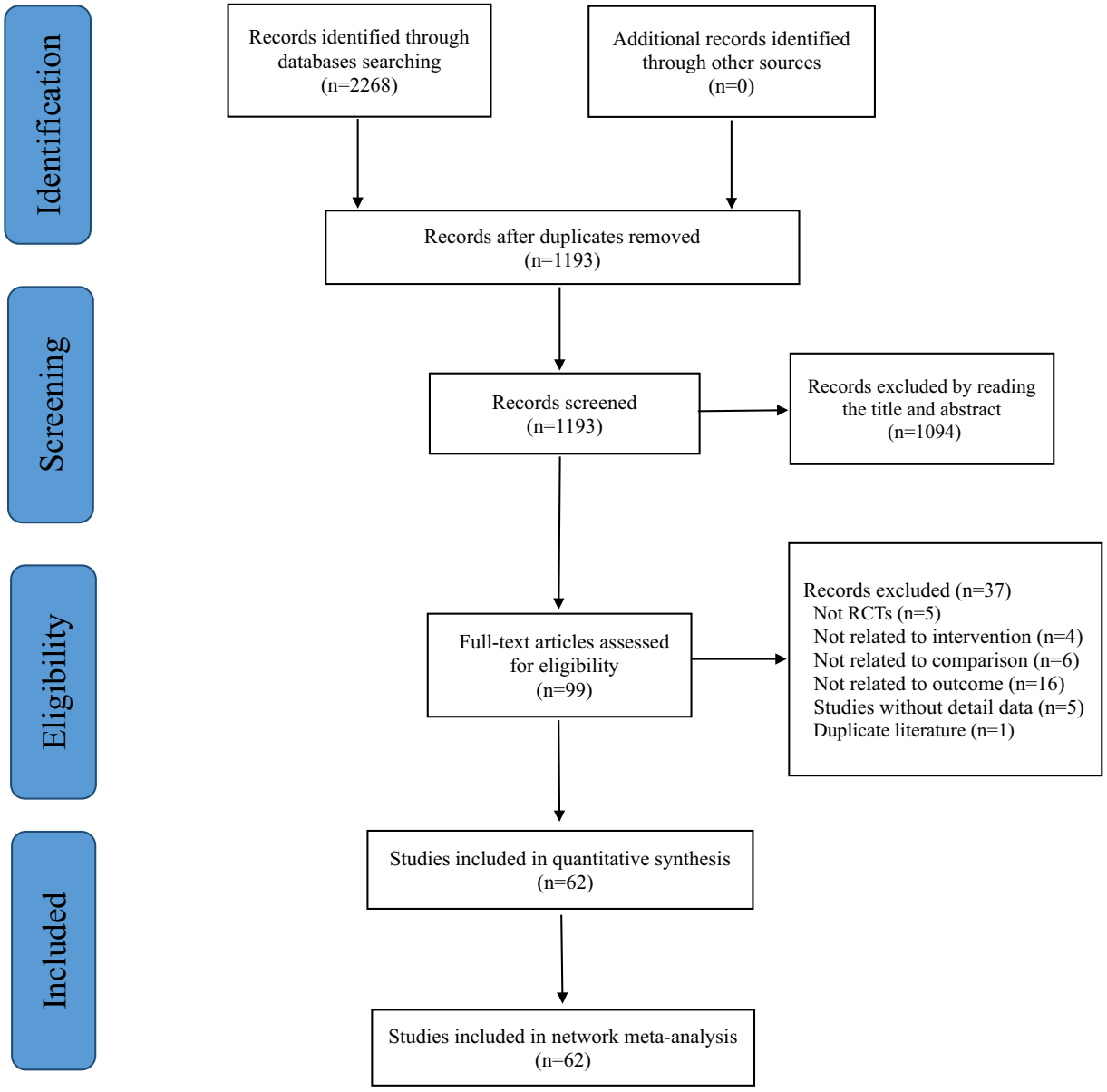

FIGURE 1
Flow chart of the literature screening process.

SA + CT and SA, SA and CT, and WA + SA and CT. For MBI scores, BA+CT (one RCT; WMD = 7.23, 95%CI: 5.39, 9.07, $p<0.00001$), SA + CT (seven RCTs; WMD = 12.83, 95%CI: 5.06, 20.60, $p = 0.001$), WA + CT (three RCTs; WMD = 10.13, 95%CI: 5.31, 14.96, $p<0.0001$), SA + BA (two RCTs; WMD = 19.13, 95%CI: 18.08, 20.18, $p<0.00001$), EA + CT (one RCT; WMD = 1.74, 95%CI: 0.13, 3.35, $p = 0.03$) and AB + CT (one RCT; WMD =13.57, 95%CI: 6.23, 20.82, $p = 0.0002$) were more effective than CT group. Furthermore, compared with BA+CT, AA+CT (one RCT; WMD =6.00, 95%CI: 6.40, 7.40, $p<0.00001$), SA + BA (two RCTs; WMD = 10.40, 95%CI: 3.14, 17.66, $p = 0.005$) and WA + CT (one RCT; WMD = 3.23, 95%CI: 0.12, 6.34, $p = 0.04$) were more effective in improving MBI scores. However, there was no statistical difference in efficacy between AA+BA and CT. The results of paired meta-analysis and heterogeneity are presented in Table 3.

3.5. Network meta-analysis

The transferability hypothesis was assessed by evaluating the baseline differences in mean age and disease duration of patients in the included studies. As shown in Figure 2A, the mean age of PSCI patients showed a high degree of similarity among the included studies. Furthermore, as shown in Figure 2B, the mean duration of disease in patients with PSCI also showed a high degree of similarity. Therefore, this study satisfies the transferability hypothesis and reliable results can be obtained.

The inconsistency test results for MMSE, MoCA, and MBI scores were all greater than 0.05 ($p = 0.9064$, 0.7492, and 0.9231), so the consistency model was selected for analysis. We adopted the node-splitting method to test the internal inconsistency of NMA. The results showed no significant differences between direct or indirect

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TABLE 2 The characteristics of the included studies.

Study	Sample size (T/C) (M/F)	Stroke type (I/H)	Mean age (Year) (T/C)	Course of disease (T/C)	Treatment (T/C)	Treatment period	Outcome	Adverse effects (AEs)	Drop-out situation (T/C)
1-Bao 2021 (17)	72 (31/41)	NA	62.4 ± 3.93	40.6 ± 8.87d	SA + BA	8 weeks	①	None	None
	72 (34/38)	NA	61.6 ± 4.75	40.4 ± 10.9d	CT				
2-Jiang 2016 (18)	51 (25/26)	31/20	62.37 ± 7.89	44.22 ± 17.00d	CT	12 weeks	①②	None	None
	52 (25/27)	37/15	61.58 ± 9.71	41.12 ± 21.71d	SA				
	52 (23/29)	35/17	62.33 ± 7.22	41.13 ± 18.80d	SA + CT				
3-Jian 2020 (19)	35 (20/15)	NA	63.00 ± 7.23	2.13 ± 0.85 m	SA + CT	12 weeks	①	NA	None
	35 (17/18)	NA	65.30 ± 8.52	2.51 ± 0.46 m	CT				
4-Bai 2012 (20)	30 (16/14)	NA	59.85 ± 6.03	11.71 ± 3.65d	SA + CT	4 weeks	①	NA	None
	30 (18/12)	NA	60.39 ± 5.67	16.93 ± 2.97d	CT				
5-Pu 2018 (21)	53 (33/20)	NA	60.37 ± 5.45	5.12 ± 1.39d	SA + BA	12 weeks	①	NA	None
	53 (34/19)	NA	59.15 ± 5.29	5.33 ± 1.40d	CT				
6-Cai 2020 (22)	43 (20/23)	NA	61.35 ± 5.63	9.65 ± 3.26d	SA + BA	4 weeks	①③	NA	None
	43 (22/21)	NA	64.23 ± 5.24	10.32 ± 2.61d	CT				
7-Zeng 2018 (23)	40 (22/18)	25/15	NA	71.00 ± 42.73d	SA + CT	4 weeks	①③	NA	6/5
	40 (24/16)	26/14	NA	68.00 ± 36.56d	CT				
8-Chen 2020 (24)	30 (13/17)	NA	62.00 ± 5.12	42.00 ± 5.52d	SA + CT	4 weeks	②③	NA	None
	30 (14/16)	NA	61.77 ± 4.81	43.40 ± 5.10d	CT				
9-Liu 2013 (25)	25 (10/15)	NA	NA	NA	EA + CT	4 weeks	①	NA	None
	25 (10/15)	NA	NA	NA	CT				
10-Chen 2020 (26)	48 (26/22)	NA	60.47 ± 2.35	42.66 ± 7.89d	SA + BA	4 weeks	①	NA	None
	48 (25/23)	NA	60.80 ± 2.19	42.50 ± 7.31d	CT				
11-Ding 2016 (27)	40 (24/16)	NA	56.24 ± 8.12	14.24 ± 9.58d	SA + CT	8 weeks	①③	NA	None
	46 (24/22)	NA	57.87 ± 9.01	11.84 ± 10.41d	CT				
12-Du 2019 (28)	30 (14/16)	NA	62.14 ± 9.48	26.00 ± 0.01d	SA + CT	8 weeks	①②	NA	None
	30 (15/15)	NA	66.49 ± 10.03	25.00 ± 0.01d	CT				
13-Duan 2021 (29)	41 (25/26)	NA	44.08 ± 5.24	3.65 ± 0.47 m	SA + BA	4 weeks	①	NA	None
	41 (23/18)	NA	43.30 ± 5.61	3.28 ± 0.19 m	CT				
14-Feng 2014 (30)	30 (16/14)	NA	64 ± 6	6.05 ± 1.29 m	WA + CT	8 weeks	②③	NA	None
	30 (21/9)	NA	72 ± 8	5.95 ± 1.42 m	CT				
15-Han 2021 (31)	30 (18//12)	22//8	54.43 ± 9.34	NA	SA + CT	8 weeks	①②	NA	None
	30 (16/14)	20//10	58.86 ± 10.47	NA	CT				
16-Hu 2019 (32)	40 (27/13)	NA	45.87 ± 10.22	28.2 ± 8.5d	WA + CT	4 weeks	②③	NA	None
	40 (24/16)	NA	46.59 ± 10.18	27.6 ± 9.1d	CT				
17-Niu 2021 (33)	75 (40/35)	NA	52.06 ± 7.98	NA	SA + CT	6 weeks	①②③	NA	None
	75 (41/34)	NA	51.89 ± 10.24	NA	CT				
18-Kong 2021 (34)	78 (40/35)	NA	52.06 ± 7.98	NA	SA + CT	6 weeks	①②③	NA	None
	78 (41/34)	NA	51.89 ± 10.24	NA	CT				
19-Leng 2020 (35)	40 (21/19)	18/22	60.65 ± 7.23	34.58 ± 8.21d	WA + CT	8 weeks	①③	NA	2/3
	40 (22/18)	16/24	61.35 ± 8.34	32.83 ± 8.35d	BA+CT				
20-Chen 2016 (36)	30 (12/18)	NA	NA	NA	SA + BA	8 weeks	①	NA	1/2
	30 (15/15)	NA	NA	NA	CT				
21-Li 2017 (37)	32 (17/15)	NA	59.15 ± 5.07	NA	WA + CT	4 weeks	②	NA	None
	30 (18//12)	NA	58.25 ± 5.47	NA	CT				

(Continued)

TABLE 2 (Continued)

Study	Sample size (T/C) (M/F)	Stroke type (I/H)	Mean age (Year) (T/C)	Course of disease (T/C)	Treatment (T/C)	Treatment period	Outcome	Adverse effects (AEs)	Drop-out situation (T/C)
22-Lin 2020 (38)	34 (22/12)	NA	66.69 ± 6.28	NA	SA + BA	8 weeks	①	None	None
	34 (21/18)	NA	67.98 ± 7.40	NA	CT				
23-Lin 2014 (39)	30 (18/12)	NA	65 ± 5	29.85 ± 18.10d	EA + CT	4 weeks	②	NA	None
	29 (19/10)	NA	67 ± 7	30.05 ± 19.89d	CT				
24-Qian 2018 (40)	35 (17/18)	NA	70 ± 6	10.14 ± 3.37	SA + CT	8 weeks	①	NA	None
	35 (20/15)	NA	69 ± 6	10.54 ± 3.85	CT				
25-Feng 2015 (41)	30 (16/14)	14/16	NA	NA	AB+CT	4 weeks	①③	NA	None
	30 (19/11)	15/15	NA	NA	CT				
26-Song 2020 (42)	35 (19/16)	26//9	60 ± 10	2.8 ± 1.4 m	SA + BA	8 weeks	②③	NA	None
	35 (21/14)	25//10	58 ± 10	2.5 ± 1.6 m	CT				
27-Sun 2019 (43)	50 (22/28)	29/21	60.21 ± 2.12	73.50 ± 5.47d	SA + BA	4 weeks	①	YES	None
	50 (23/27)	28/22	60.28 ± 2.36	73.25 ± 5.11d	BA+CT				
28-Tan 2020 (44)	50 (25/25)	NA	58.9 ± 6.5	NA	SA + BA	8 weeks	①	NA	None
	50 (26/24)	NA	58.3 ± 6.3	NA	CT				
29-Ge 2016 (45)	50 (29/21)	NA	NA	NA	SA + BA	8 weeks	①	NA	None
	50 (30/20)	NA	NA	NA	CT				
30-Tian 2021 (46)	25 (14/11)	21//4	68.19 ± 0.16	NA	SA + BA	8 weeks	①	NA	None
	25 (15/10)	20//5	68.21 ± 0.15	NA	CT				
31-Wang 2015 (47)	40 (21/19)	31/9	66.3 ± 6.1	NA	AA+CT	4 weeks	①③	NA	None
	40 (20/20)	32/8	65.6 ± 7.6	NA	BA+CT				
32-Wang 2021 (48)	40 (26/14)	NA	66 ± 8	14.62 ± 6.17	SA + CT	8 weeks	①②③	NA	None
	40 (24/16)	NA	67 ± 9	15.45 ± 6.24	CT				
33-Wang 2021 (49)	30 (18/12)	16/14	51.07 ± 8.04	38.27 ± 8.14d	SA + CT	4 weeks	①②③	NA	None
	30 (17/13)	18//12	56.57 ± 9.13	39.07 ± 9.14d	CT				
34-Wang 2017 (50)	30 (20/10)	NA	53.27 ± 11.62	NA	EA + CT	8 weeks	①③	NA	None
	30 (19/11)	NA	56.73 ± 9.32	NA	CT				
35-Wang 2015 (51)	38 (24/14)	20/18	46.89 ± 6.10	2.40,2.11 m	WA + SA	4 weeks	②	NA	None
	38 (25/13)	21/17	44.44 ± 9.92	2.38,2.16 m	CT				
36-Wang 2018 (52)	50 (24/26)	27/23	53.8 ± 11.7	NA	SA + CT	3 weeks	①②	NA	None
	50 (26/24)	29/21	54.5 ± 13.6	NA	CT				
37-Wang 2011 (53)	20 (10/10)	NA	61.39 ± 10.42	30.05 ± 19.89d	SA + CT	4 weeks	①	NA	None
	20 (12/8)	NA	58.65 ± 9.53	31.70 ± 21.75d	SA				
	20 (13/7)	NA	62.29 ± 11.18	29.85 ± 18.10d	CT				
38-Lei 2021 (54)	34 (19/15)	21/13	59.73 ± 6.82	4.08 ± 0.72 m	SA + BA	8 weeks	②③	NA	None
	34 (18/16)	20/14	59.40 ± 6.74	4.11 ± 0.70 m	BA+CT				
39-Wang 2018 (55)	40 (23/17)	NA	45.39 ± 11.42	24.05 ± 11.89	SA + CT	4 weeks	①	NA	None
	40 (28/12)	NA	42.29 ± 11.72	26.85 ± 16.10	SA				
	40 (26/14)	NA	52.65 ± 7.53	19.70 ± 11.75	CT				
40-Wang 2019 (56)	104 (62/42)	NA	62 ± 7	54.39 ± 9.57	SA + BA	4 weeks	①	NA	None
	104 (61/43)	NA	62 ± 7	55 ± 10	CT				
41-Zhang 2021 (57)	50 (24/26)	NA	63.5 ± 3.4	NA	SA + BA	6 weeks	①	NA	None
	50 (25/25)	NA	60.32 ± 7.93	NA	CT				

(Continued)

TABLE 2 (Continued)

Study	Sample size (T/C) (M/F)	Stroke type (I/H)	Mean age (Year) (T/C)	Course of disease (T/C)	Treatment (T/C)	Treatment period	Outcome	Adverse effects (AEs)	Drop-out situation (T/C)
42-Wei 2019 (58)	30 (18/12)	NA	60.32 ± 7.93	NA	EA + CT	6 weeks	②	NA	None
	30 (19/11)	NA	60.38 ± 8.01	NA	CT				
43-Zhao 2021 (59)	31 (17/14)	NA	53.61 ± 5.69	3.75 ± 1.46d	SA + AB	8 weeks	①	NA	None
	31 (20/11)	NA	54.23 ± 6.27	3.89 ± 1.50d	CT				
44-Xu 2022 (60)	45 (28/17)	30/15	67.85 ± 1.91	1.94 ± 0.34 m	BA+CT	8 weeks	①③	NA	None
	45 (30/15)	32/13	68.02 ± 2.03	2.05 ± 0.37 m	CT				
45-Zheng 2021 (61)	44 (26/18)	12/32	62 ± 6	54.7 ± 14.2d	SA + BA	8 weeks	②③	NA	None
	43 (32/11)	13/30	61 ± 7	56.9 ± 16.4d	BA+CT				
46-Yan 2022 (62)	30 (15/15)	24//6	67.4 ± 4.2	32.2 ± 9.01d	WA + CT	4 weeks	①②	NA	None
	30 (17/13)	20//10	67.2 ± 4.9	31.3 ± 10.3d	CT				
47-Yang 2018 (63)	34 (18/16)	NA	68 ± 8 7	14.7 ± 6.2	SA + CT	4 weeks	①②	NA	None
	33 (19/14)	NA	67 ± 8	15.5 ± 6.2	CT				
48-Yang 2020 (64)	17 (11/6)	10//7	65.5 ± 6.8	20.5 ± 3.0	SA + BA	4 weeks	①	NA	None
	17 (10/7)	8//9	65.8 ± 5.6	20.0 ± 3.5	CT				
49-Zhou 2021 (65)	52 (29/23)	18/34	58.17 ± 6.64	25.43 ± 3.17d	SA + BA	2 weeks	①	NA	None
	52 (27/25)	17/35	57.63 ± 7.02	25.34 ± 2.98d	BA				
50-Yang 2019 (66)	40 (24/16)	NA	51.35 ± 7.30	21.40 ± 5.38d	SA + BA	4 weeks	①	NA	None
	40 (22/18)	NA	51.72 ± 7.46	21.57 ± 5.54d	CT				
51-Yao 2019 (67)	40 (21/19)	NA	61.27 ± 5.38	42.38 ± 14.23d	EA + CT	12 weeks	②	YES	None
	38 (20/18)	NA	62.72 ± 6.48	44.23 ± 18.87d	CT				
52-Yao 2020 (68)	30 (11/19)	21//9	54.6 ± 11.8	2.5 ± 0.8 m	SA + BA	4 weeks	①②	NA	None
	30 (9/21)	18//12	57.4 ± 12.8	2.4 ± 1.0 m	CT				
53-Yu 2021 (69)	30 (18/12)	NA	59 ± 3	NA	AA+CT	4 weeks	②	NA	None
	30 (17/13)	NA	59 ± 3	NA	CT				
54-Zhan 2016 (70)	25 (14/11)	15//10	60 ± 10	78.2 ± 47.2	SA + CT	4 weeks	①②	NA	None
	25 (19/6)	13//12	60 ± 9	75.8 ± 50.2	BA+CT				
55-Zhang 2020 (71)	30 (20/10)	NA	70. 10 ± 4. 51	23. 03 ± 7. 47d	EA + CT	6 weeks	②	NA	None
	30 (18/12)	NA	69. 03 ± 4. 70	24. 63 ± 11. 77d	CT				
56-Zhang 2018 (72)	65 (45/20)	52/13	59.87 ± 9.78	77.9 ± 21.85	SA + BA	4 weeks	①②	NA	None
	65 (47/18)	50/15	59.57 ± 8.85	75.5 ± 19.16	BA				
57-Zhang 2019 (73)	35 (20/15)	25//10	59.95 ± 8.71	39.72 ± 18.73d	AA+BA	4 weeks	①③	NA	None
	35 (19/16)	16/19	61.12 ± 9.62	42.11 ± 17.56d	CT				
58-Zheng 2019 (74)	29 (18/11)	NA	63 ± 3	31.78 ± 16.15d	WA + CT	12 weeks	②③	NA	None
	28 (19/9)	NA	67 ± 7	29.85 ± 18.36d	CT				
59-Zhou 2022 (75)	75 (41/34)	NA	50.92 ± 11.16	4.01 ± 0.61d	OA + CT	6 weeks	①	NA	None
	75 (41/34)	NA	51.01 ± 13.19	3.97 ± 0.56d	CT				
60-Zhuo 2021 (76)	20 (12/8)	NA	63.25 ± 9.34	2.15 ± 1.03 m	SA + BA	3 weeks	②	NA	None
	22 (12/10)	NA	63.04 ± 9.16	2.27 ± 1.06 m	CT				
61-Zhou 2020 (77)	30 (18/12)	NA	53.76 ± 9.27	64.35 ± 31.65d	SA + BA	8 weeks	①②	NA	None
	30 (20/10)	NA	53.89 ± 9.52	64.15 ± 30.97d	CT				
62-Zhu 2014 (78)	40 (22/18)	18/22	55.56 ± 13.58	21.67 ± 15.82d	SA	4 weeks	①	NA	None
	40 (24/16)	21/19	56.37 ± 13.26	20.51 ± 13.38d	BA				

T, Treatment group; C, Control group; M, Man; F, Female; I, Ischemic Stroke; H, Hemorrhagic stroke; SA, Scale acupuncture; BA, Body acupuncture; OA, Ophthalmic acupuncture; WA, warm acupuncture; EA, Electro-acupuncture; AB, Auricular bloodletting; AA, Abdominal acupuncture; CT, Cognitive training; ①, Mental State Examination Scale (MMSE); ②, Montreal Cognitive Assessment Scale (MoCA); ③, Modified Barthel Index scale (MBI) NA, Not mentioned.

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TABLE 3 The results of the paired meta-analysis.

Comparison	WMD (95% CI)	Number of studies	Number of patients	I^2 (%)	*p*-value
MMSE					
K-A	**4.24 [3.28, 5.20]**	16	1,481	94	<0.00001
E-A	**4.39 [3.08, 5.70]**	16	1,310	91	<0.00001
D-A	**5.29 [4.16, 6.42]**	1	90	–	–
F-A	**5.85 [4.69, 7.01]**	1	150	–	–
G-A	**1.86 [0.16, 3.56]**	1	60	–	–
I-A	**2.57 [0.81, 4.33]**	1	60	–	–
N-A	**3.84 [2.00, 5.68]**	1	62	–	–
E-B	**2.42 [0.74, 4.10]**	1	104	–	–
E-C	**3.23 [1.49, 4.97]**	2	120	0	0.68
E-D	**2.48 [0.18, 4.78]**	1	50	–	–
G-D	**1.22 [0.08, 2.36]**	1	75	–	–
K-B	**1.79 [1.05, 2.53]**	2	234	17	0.27
C-A	**2.50 [0.67, 4.32]**	2	120	0	1
C-B	**0.88 [0.15, 1.61]**	1	80	–	–
B-A	0.04 [−1.63, 1.71]	1	103	–	–
H-A	4.07 [−0.45, 8.60]	2	110	96	<0.00001
L-A	2.57 [−0.14, 5.28]	1	58	–	–
J-D	0.90 [−0.20, 2.00]	1	80	–	–
K-D	0.94 [−0.18, 2.06]	1	100	–	–
MoCA					
E-A	**3.75 [2.81, 4.69]**	10	901	79	<0.00001
K-A	**3.26 [2.19, 4.34]**	4	505	0	0.71
G-A	**3.96 [2.29, 5.62]**	5	419	88	<0.00001
H-A	**3.16 [1.88, 4.45]**	4	310	0	0.92
J-A	**3.00 [0.26, 5.74]**	1	50	–	–
E-D	**3.14 [2.15, 4.13]**	1	60	–	–
K-D	**3.61 [2.11, 5.11]**	2	128	67	0.08
K-B	**2.00 [1.37, 2.63]**	1	57	–	–
E-C	2.08 [−0.32, 4.48]	1	104	–	–
C-A	−0.06 [−2.34, 2.22]	1	103	–	–
M-A	1.47 [−0.87, 3.81]	1	76	–	–
MBI					
D-A	**7.23 [5.39, 9.07]**	1	90	–	–
E-A	**12.83 [5.06, 20.60]**	7	647	97	<0.00001
G-A	**10.13 [5.31, 14.96]**	3	197	64	0.06
K-A	**19.13 [18.08, 20.18]**	2	156	46	0.17
H-A	**1.74 [0.13, 3.35]**	1	60	–	–
I-A	**13.57 [6.32, 20.82]**	1	60	–	–
J-D	**6.00 [4.60, 7.40]**	1	80	–	–
K-D	**10.40 [3.14, 17.66]**	2	155	74	0.05
G-D	**3.23 [0.12, 6.34]**	1	75	–	–
L-A	2.00 [−2.95, 6.95]	1	58	–	–

The bold font indicates a statistical difference; A, Cognitive training; B, Body acupuncture; C, Scalp acupuncture; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; F, Ophthalmic acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I, Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L, Abdominal acupuncture plus body acupuncture; M, Warm acupuncture plus scalp acupuncture; N, Scalp acupuncture plus auricular bloodletting.

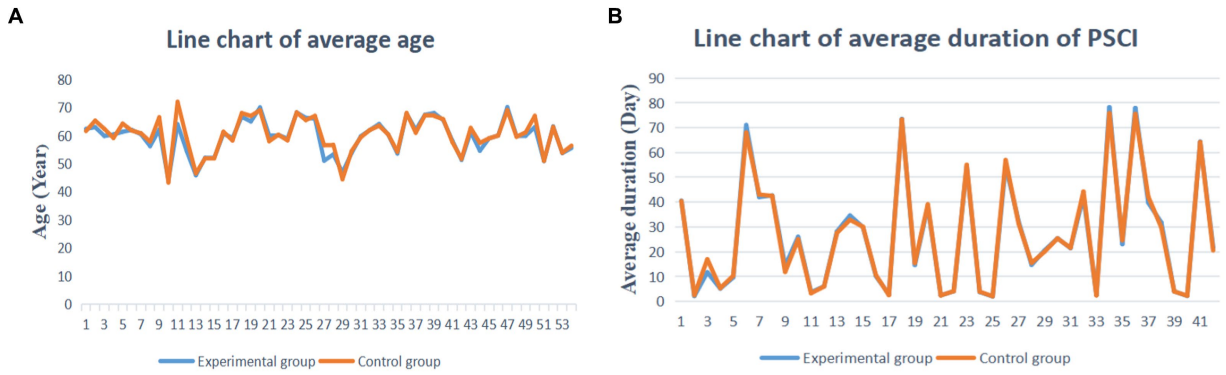

FIGURE 2
Baseline assessment. **(A)** The average age assessment. **(B)** The average duration PSCI assessment.

comparisons for each split node ($p > 0.05$), which suggests no evidence of the existence of inconsistency (Supplementary Figure S2). The results of the closed-loop inconsistency test showed that all 95% CI contained 0, which indicated that the closed-loop comparisons possessed excellent consistency (Supplementary Table S1). The Brooks-Gelman-Rubin diagnostic plots showed that the shrink factor's median and 97.5% value tended to be 1 and stabilized after 5,000 iterations, and then the Bayesian model was calculated up to 20,000 iterations (Supplementary Figure S3). Meanwhile, we observed the trajectory and density plots (Supplementary Figure S4). All these results indicate that the model has excellent convergence.

All included studies with 4,057 participants and 13 acupuncture-related therapies reported MMSE data (Figure 3A), including 3 (18, 53, 55) three-arm studies (6.4%) and 44 two-arm studies (93.6%). Among them, the CT group had the largest sample size. The two groups most commonly compared were scalp acupuncture plus cognitive training and cognitive training, and scalp acupuncture plus body acupuncture and cognitive training, respectively. 29 studies reported MoCA data involving 2,285 participants and 10 acupuncture-related therapies (Figure 3B). 20 studies reported MBI data involving 1,579 participants and 9 acupuncture-related therapies (Figure 3C).

In terms of improving MMSE scores, the results (Table 4) showed that BA+CT (MD = −3.00, 95%CI: −5.94, −0.05), SA + CT (MD = −4.50, 95%: −5.85, −3.16), OA + CT (MD = −6.31, 95%CI: −11.64, −1.01) and SA + BA (MD = −3.92, 95%CI: −5.19, −2.64) were more effective for PSCI patients compared to the CT group. In addition, SA + CT (MD = −2.94, 95%CI: −5.85, −0.04) was more effective than BA when comparing different acupuncture treatments. Regarding the improvement of MoCA score, the results (Table 4) showed that SA + CT (MD = 3.54, 95%CI: 2.44, 4.59), WA + CT (MD = 4.04, 95%CI: 2.53, 5.50), EA + CT (MD = 3.33, 95%CI: 1.29, 5.38) and SA + BA (MD = 2.84, 95%CI: 1.10, 4.56) were more effective in patients with PSCI compared to the CT group. In addition, SA + CT (MD = 3.71, 95%CI: 1.43, 5.98), WA + CT (MD = 4.20, 95%CI: 1.51, 6.88), EA + CT (MD = 3.49, 95%CI: 0.45, 6.54) and SA + BA (MD = 3.01, 95%CI: 1.00, 4.96) were more effective than BA+CT when comparing different acupuncture treatments. In terms of improving MBI scores, the results (Table 5) showed that SA + CT (MD = −12.80, 95%CI: −17.93, −7.67) and EA + CT (MD = −10.59, 95%CI: −19.05, −2.14) were more effective than CT alone.

We calculated the SUCRA values for each intervention for probability ranking (Supplementary Table S2) and constructed probability ranking histograms using R software (Figure 4). Figure 4A shows that among the 13 treatments, CT (6.2%) had the worst ability to improve MMSE scores. In addition, the top three acupuncture treatments that improved MMSE scores were OA + CT (79.7%), SA + CT (73.7%), and AA+CT (69.5%). WA + CT (86.5%), SA + CT (77.3%), and EA + CT (72.1%) were the three best acupuncture treatments for improving MoCA scores (Figure 4B). Furthermore, SA + BA (87.5%), AB+CT (75.4%), and SA + CT (72.6%) were the three most effective acupuncture treatments among the nine treatments for improving MBI scores (Figure 4C).

3.6. Adverse effect

Of the 62 studies included, six studies (17, 18, 38, 43, 61, 67) (9%) reported adverse reactions (Supplementary Table S3). Three studies (17, 18, 38) reported no adverse reactions during treatment. One study (67) reported that patients in the electroacupuncture group experienced subcutaneous hematomas after treatment, but they recovered spontaneously without systematic treatment. Two studies (43, 61) reported that patients experienced adverse effects such as dizziness, pallor, and sleepiness, which were considered to be possibly related to the first time they received acupuncture treatment. In conclusion, acupuncture treatment seems to be safe and reliable, but there is no sufficient evidence to prove it.

3.7. Publication bias

Comparative adjustment funnel plots were plotted using STATA software to assess publication bias and small sample size effects for the MMSE, MoCA, and MBI, respectively (Figure 5). The results showed that the comparative adjustment funnel plots for the MoCA and MBI scales were symmetrical, with most points evenly distributed on either side of the midline, reflecting a moderate sample size of the included studies and a low likelihood of publication bias. However, in the comparative adjusted funnel plot for the MMSE scale, most studies were more dispersed, with some of them lying outside the 95% CI range, indicating possible publication bias.

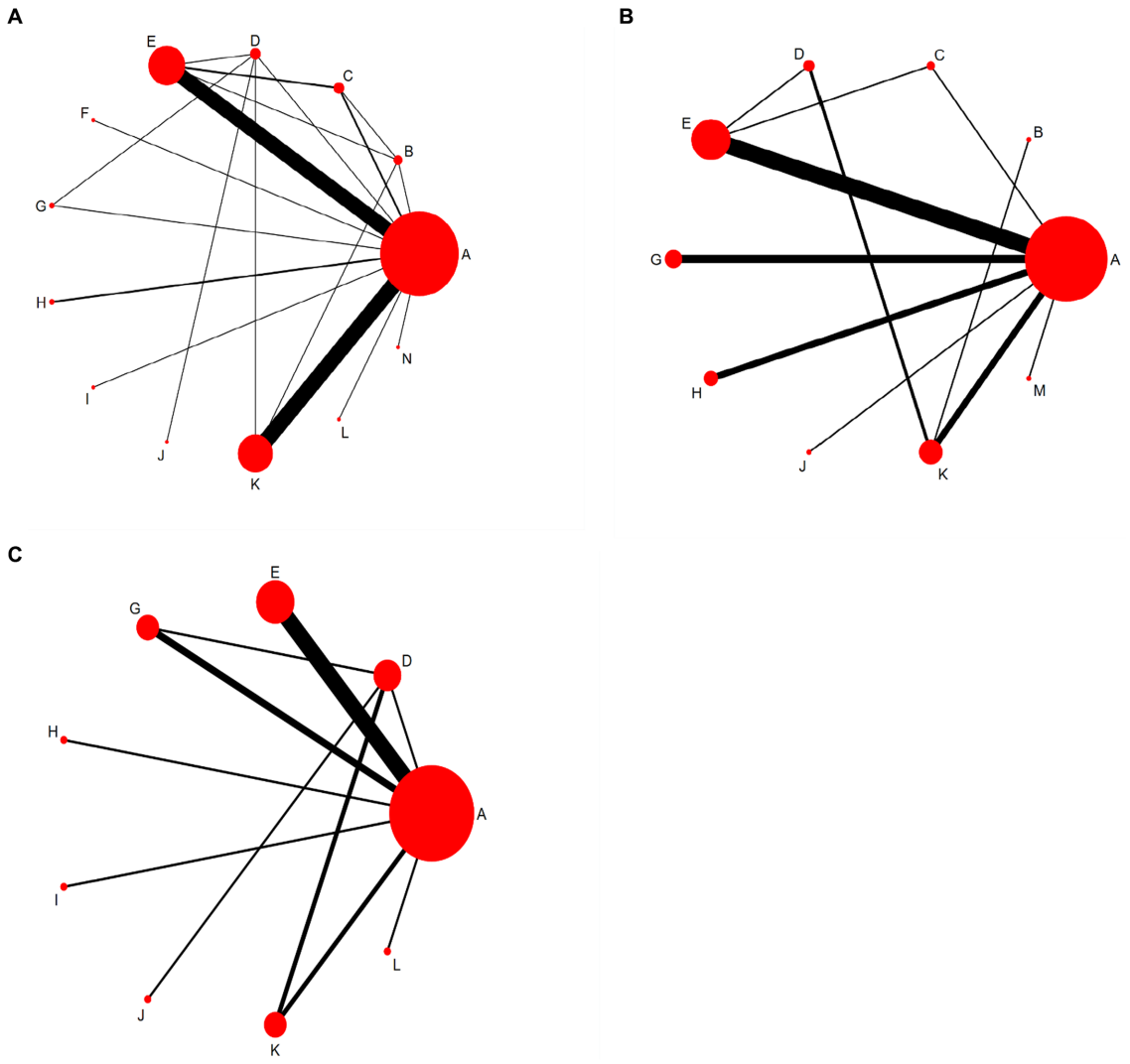

FIGURE 3
Network evidence diagram. A, Cognitive training; B, Body acupuncture; C, Scalp acupuncture; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; F, Ophthalmic acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I: Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L: Abdominal acupuncture plus body acupuncture; M: Warm acupuncture plus scalp acupuncture; N: Scalp acupuncture plus auricular bloodletting. **(A)** The Minimum Mental State Examination scale (MMSE). **(B)** The Montreal Cognitive Assessment Scale (MoCA). **(C)** The Modified Barthel Index scale (MBI).

3.8. Evidence assessment of outcome measures

According to the GRADE scores, the strength of evidence for the three scales mentioned above ranged between very low and moderate. The main reasons for the reduced quality of evidence were flaws in study design and considerable statistical heterogeneity (Supplementary Table S4).

4. Discussion

4.1. Summary of main finding

In this systematic review, a total of 62 RCTs involving 5,073 participants and 13 acupuncture-related therapies were included. The results of the paired meta-analysis showed that most acupuncture-related therapies were effective in improving global cognitive ability (measured by MMSE and MoCA) and self-care of daily living (measured by MBI) in PSCI patients. Furthermore, BA, AA+BA, and WA + SA did not show sufficient advantages compared with the CT group. Notably, only one study of these three types of acupuncture therapy was compared with the CT group. The effect size may change as the sample size increases. The results of the NMA showed that in terms of improving MMSE scores, BA+CT, SA + CT, OA + CT, and SA + BA resulted in better outcomes for patients with PSCI compared with the CT group. In addition, the efficacy of SA + CT was better than BA alone. Based on the probability ranking results, it is clear that OA + CT is the most effective in improving MMSE scores. In terms of improving MoCA scores, SA + CT, WA + CT, EA + CT, and SA + BA were capable of delivering better outcomes than the CT group. Furthermore, the efficacy of the four acupuncture-related therapies

TABLE 4 Network meta-analysis results of Minimum Mental State Examination Scale (MMSE) and Montreal Cognitive Assessment Scale (MoCA).

Treatment	MoCA													
MMSE	**A**	0.87 [−2.71, 4.40]	0.68 [−2.72, 4.11]	−0.16 [−2.41, 2.06]	**3.54 [2.44, 4.59]**	–	**4.04 [2.53, 5.50]**	**3.33 [1.29, 5.38]**	–	3.33 [−0.68, 7.36]	2.84 [1.10, 4.56]	–	1.40 [−2.41, 5.25]	–
	−1.55 [−4.29, 1.19]	**B**	−0.17 [−5.04, 4.75]	−1.02 [−4.69, 2.71]	2.68 [−0.96, 6.63]	–	3.17 [−0.65, 7.07]	2.46 [−1.64, 6.59]	–	2.47 [−2.89, 7.84]	1.97 [−1.11, 5.11]	–	0.54 [−4.67, 5.82]	–
	−2.21 [−5.31, 0.88]	−0.66 [−4.12, 2.81]	**C**	−0.85 [−4.88, 3.18]	2.85 [−0.59, 6.27]	–	3.35 [−0.41, 7.08]	2.65 [−1.37, 6.65]	–	2.64 [−2.62, 7.90]	2.16 [−1.65, 5.95]	–	0.72 [−4.39, 5.82]	–
	−3.00 [−5.94, −0.05]	−1.45 [−5.38, 2.50]	−0.78 [−4.98, 3.41]	**D**	**3.71 [1.43, 5.98]**	–	**4.20 [1.51, 6.88]**	**3.49 [0.45, 6.54]**	–	3.49 [−1.11, 8.09]	**3.01 [1.00, 4.96]**	–	1.57 [−2.84, 6.02]	–
	−4.50 [−5.85, −3.16]	**−2.94 [−5.85, −0.04]**	−2.27 [−5.42, 0.84]	−1.49 [−4.57, 1.55]	**E**	–	0.49 [−1.32, 2.31]	−0.21 [−2.50, 2.08]	–	−0.20 [−4.36, 3.91]	−0.70 [−2.63, 1.23]	–	−2.14 [−6.08, 1.86]	–
	−6.31 [−11.64, −1.01]	−4.73 [−10.75, 1.18]	−4.09 [−10.21, 2.09]	−3.30 [−9.36, 2.73]	−1.80 [−7.26, 3.68]	**F**	–	–	–	–	–	–	–	–
	−3.32 [−7.37, 0.75]	−1.76 [−6.66, 3.11]	−1.10 [−6.20, 3.97]	−0.31 [−4.38, 3.69]	1.18 [−3.02, 5.40]	2.98 [−3.68, 9.67]	**G**	−0.70 [−3.22, 1.83]	–	−0.70 [−4.93, 3.61]	−1.19 [−3.46, 1.08]	–	−2.62 [−6.71, 1.49]	–
	−3.25 [−6.99, 0.51]	−1.69 [−6.35, 2.96]	−1.03 [−5.89, 3.84]	−0.26 [−5.00, 4.55]	1.24 [−2.72, 5.26]	3.04 [−3.40, 9.60]	0.06 [−5.45, 5.62]	**H**	–	0.03 [−4.51, 4.51]	−0.48 [−3.16, 2.18]	–	−1.91 [−6.26, 2.39]	–
	−2.66 [−8.15, 2.76]	−1.10 [−7.24, 4.98]	−0.45 [−6.75, 5.83]	0.33 [−5.91, 6.51]	1.83 [−3.83, 7.43]	3.63 [−4.00, 11.20]	0.64 [−6.15, 7.45]	0.58 [−6.10, 7.15]	**I**	–	–	–	–	–
	−4.90 [−10.97, 1.13]	−3.34 [−9.91, 3.21]	−2.69 [−9.46, 4.06]	−1.90 [3.98, 2.10]	−0.40 [−6.51, 5.70]	1.40 [−6.64, 9.48]	−1.58 [−8.12, 5.07]	−1.63 [−8.82, 5.45]	−2.24 [−10.42, 5.90]	**J**	−0.49 [−4.86, 3.86]	–	−1.93 [−7.44, 3.65]	-
	−3.92 [−5.19, −2.64]	−2.36 [5.11, 0.37]	−1.70 [−4.97, 1.55]	−0.91 [−3.98, 2.10]	0.57 [−1.20, 2.39]	2.37 [−3.05, 7.86]	−0.60 [−4.80, 3.59]	−0.67 [−4.63, 3.28]	−1.25 [−6.84, 4.40]	0.98 [−5.09, 7.07]	**K**	–	−1.43 [−5.63, 2.78]	-
	−3.14 [−8.85, 2.53]	−1.59 [−7.84, 4.72]	−0.93 [−7.31, 5.61]	−0.11 [−6.52, 6.29]	1.36 [−4.46, 7.20]	3.18 [−4.56, 10.97]	0.18 [−6.79, 7.17]	0.11 [−6.69, 6.96]	−0.47 [−8.37, 7.46]	1.76 [−6.53, 10.07]	0.77 [−5.06, 6.62]	**L**	–	–
	–	–	–	–	–	–	–	–	–	–	–	–	**M**	–
	−3.41 [−8.83, 2.02]	−1.85 [−7.98, 4.24]	−1.19 [−7.44, 5.03]	−0.39 [−6.60, 5.73]	1.08 [−4.50, 6.71]	2.89 [−4.69, 10.42]	−0.07 [−6.93, 6.67]	−0.14 [−6.79, 6.38]	−0.73 [−8.40, 6.96]	1.49 [−6.61, 9.60]	0.50 [−5.08, 6.09]	−0.27 [−8.14, 7.58]	-	**N**

The bold font indicates a statistical difference; A, Cognitive training; B, Body acupuncture; C, Scalp acupuncture; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; F, Ophthalmic acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I, Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L, Abdominal acupuncture plus body acupuncture; M, Warm acupuncture plus scalp acupuncture; N, Scalp acupuncture plus auricular bloodletting.

was better than BA+CT. Based on the probability ranking results, it is clear that WA + CT is the most effective acupuncture therapy for improving MoCA scores. Regarding the improvement of MBI scores, SA + CT and EA + CT were more effective than CT alone. Furthermore, no statistically significant differences were found in the comparison of the various acupuncture therapies. Based on the probability ranking, it is clear that SA + BA is the most effective acupuncture measure for improving MBI scores in PSCI patients. Although the certainty of the evidence was rated as very low to moderate due to deficiencies in methodological quality and strong heterogeneity among studies, this review provides an up-to-date overview of the available RCTs of different types of acupuncture for PSCI.

4.2. Clinical practice applicability

Different from Alzheimer's disease, there are still no symptomatic medications approved by authoritative official regulatory authorities

TABLE 5 Network meta-analysis results of Modified Barthel Index scale (MBI).

Treatment	A								
MBI	−7.31 [−20.42, 5.81]	D							
	−12.80 [−17.93, −7.67]	−5.49 [−19.57, 8.59]	E						
	−1.58 [−22.03, 18.88]	−3.29 [−18.89, 12.32]	2.20 [−7.69, 12.09]	G					
	−10.59 [−19.05, −2.14]	6.91 [−11.56, 25.38]	12.40 [−1.58, 26.38]	10.19 [−5.23, 25.71]	H				
	−0.40 [−13.14, 12.61]	−7.01 [−26.49, 12.47]	−1.52 [−16.81, 13.77]	−3.73 [−20.43, 13.98]	−13.92 [−33.33, 5.49]	I			
	−14.23 [−28.72, 0.08]	−4.98 [−17.97, 8.00]	0.51 [−18.63, 19.64]	−1.70 [−21.98, 18.58]	−11.89 [−34.45, 10.67]	2.03 [−21.36, 25.42]	J		
	−12.29 [−30.72, 6.14]	−7.77 [−24.38, 8.83]	−2.28 [−13.69, 9.12]	−4.49 [−17.72, 8.74]	−14.68 [−31.21, 1.84]	−0.76 [−18.40, 16.88]	−2.79 [−23.85, 18.27]	K	
	−3.93 [−23.21, 15.35]	6.31 [−12.75, 25.36]	11.80 [−2.95, 26.54]	9.59 [−6.61, 25.80]	−0.60 [−19.58, 18.38]	13.32 [−6.64, 33.28]	11.29 [−11.75, 34.33]	14.08 [−3.09, 31.26]	L

The bold font indicates a statistical difference; A, Cognitive training; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I, Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L, Abdominal acupuncture plus body acupuncture.

for the treatment of PSCI (79). As a result, the focus of many medical associations has gradually shifted to whether nonpharmacologic interventions can help patients with PSCI improve cognitive function and maintain normal daily living independence (80). Based on clinical evidence, acupuncture is a relatively resource-intensive intervention that appears to be desirable for chronic conditions such as cognitive impairment that require long-term treatment (81). Studies (12, 13) have been conducted to demonstrate the effectiveness of acupuncture in the treatment of PSCI. However, acupuncture therapy encompasses a variety of forms and previous studies have tended to view acupuncture therapy as a whole. As for which acupuncture therapy can bring the best outcome for PSCI patients, it is still not clear. In clinical applications, ineffective acupuncture treatment inevitably delays optimal treatment time and wastes medical resources. Therefore, we conducted this study in an attempt to identify the best acupuncture treatment to improve cognitive function and self-care in daily life for patients with PSCI, providing new insights for clinical practice. We initially proposed pharmacological treatment and acupuncture techniques alone as the treatment measures for the control group. Unfortunately, we found that cholinesterase inhibitors are only used in China for the treatment of PSCI. Therefore, cognitive training and the acupuncture technique alone were finally set as the treatment measures for the control group in this study. The comparison between acupuncture therapy and cognitive training is meaningful because most guidelines on the treatment of PSCI include cognitive training as a treatment to improve PSCI patients.

The potential mechanisms of acupuncture for the treatment of PSCI have now been extensively studied. Therefore, we categorized the mechanisms into the following six aspects: (1) acupuncture can reduce the expression of inflammatory factors by inhibiting the degradation of IkB kinase or inhibiting the entry of NF-kB into the cell nucleus, which can result in the improvement of cognitive function (82), (2) acupuncture antagonizes neuronal apoptosis by increasing the transactivation activity of the PI3K/AKL signaling pathway (83), (3) acupuncture ameliorates neurological deficits by inhibiting the expression of autophagy-related proteins LC3-II and Beclin-1 in brain tissue (84), (4) acupuncture promotes axonal regeneration and improves synaptic plasticity by promoting the expression of PSD-95 and SYN proteins (85), (5) acupuncture improves neurological deficits and learning memory by upregulating the expression of VEGF and NGFs vascular endothelial factors (86), and (6) acupuncture reduces nerve cell damage by increasing the expression activity of endogenous oxidants such as SOD and GSH-PX proteins (87).

4.3. Study strengths and limitations

To the best of our knowledge, this study is the first network meta-analysis to comprehensively assess the efficacy and safety of different acupuncture therapies for PSCI based on currently available evidence. This study was conducted in strict accordance with PRISMA-NMA guidelines. Eight Chinese and English databases were searched to ensure the adequacy of the number of included studies, and references to systematic reviews of relevant topics were also reviewed. We used explicit inclusion and exclusion criteria, data extraction, and risk of bias assessment, and assessed the methodological quality of the included studies using the CONSORT statement guidelines. From the mesh evidence map, we found that only a small number of studies compared different acupuncture therapies directly. Therefore, in the absence of direct evidence, we used the method of network meta-analysis to provide indirect evidence. Finally, according to the nodal split model, it is clear that there is no significant difference between direct or indirect comparisons for each split node ($p > 0.05$), while the Brooks-Gelman-Rubin diagnostic plots for each outcome indicator show that the median and 97.5% values of the contraction factor converge to 1, which indicates that our findings are stable and reliable.

However, there are some limitations of this study that need to be considered. Firstly, acupuncture therapy is a unique non-pharmacological treatment in China, most of the literature related to acupuncture is published in Chinese databases. Therefore,

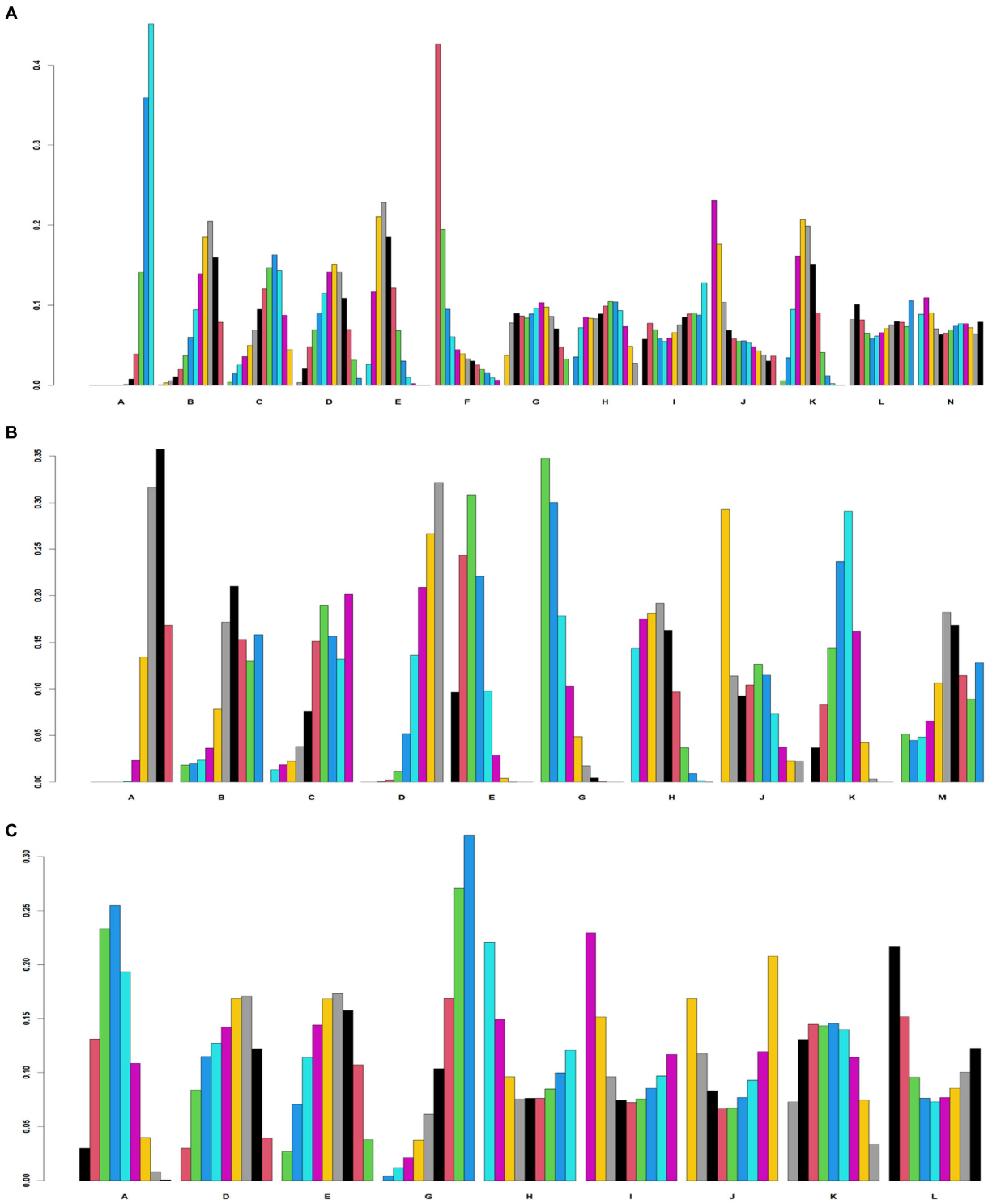

FIGURE 4
Probability ranking diagram. A, Cognitive training; B, Body acupuncture; C, Scalp acupuncture; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; F, Ophthalmic acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I, Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L, Abdominal acupuncture plus body acupuncture; M, Warm acupuncture plus scalp acupuncture N: Scalp acupuncture plus auricular bloodletting. **(A)** Minimum Mental State Examination scale (MMSE). **(B)** Montreal Cognitive Assessment Scale (MoCA). **(C)** Modified Barthel Index scale (MBI).

a comprehensive search of Chinese databases is necessary. Unfortunately, most of the included studies were of low quality in terms of experimental design, mainly in the form of a lack of description of allocation concealment, blinding of outcome assessors, and detailed descriptions of prospective plans, which partly contributed to the overall quality of the evidence being rated as low. Seventy-two percent did not achieve the expected reporting rate (>80%) as assessed by the CONSORT statement. In addition, we found

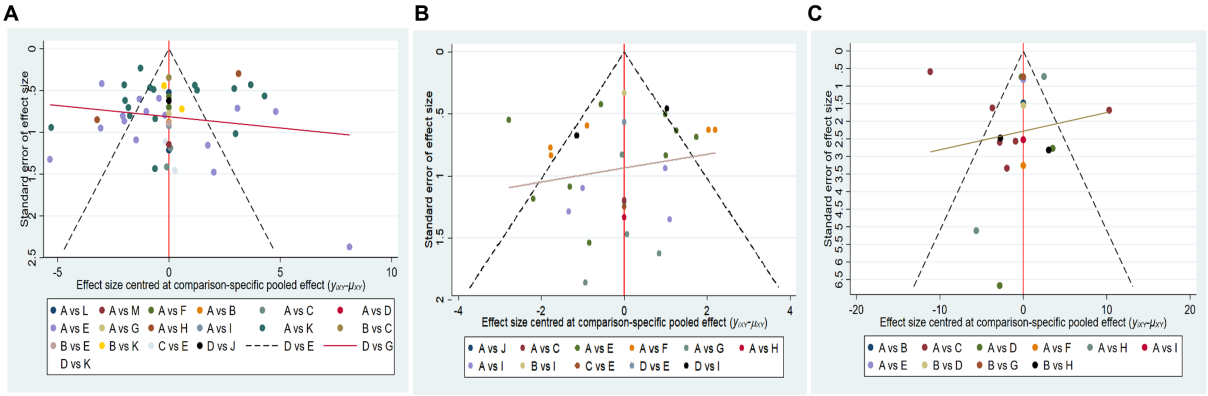

FIGURE 5
Comparative adjustment funnel plots. A, Cognitive training; B, Body acupuncture; C, Scalp acupuncture; D, Body acupuncture plus cognitive training; E, Scalp acupuncture plus cognitive training; F, Ophthalmic acupuncture plus cognitive training; G, Warm acupuncture plus cognitive training; H, Electro-acupuncture plus cognitive training; I, Auricular bloodletting plus cognitive training; J, Abdominal acupuncture plus cognitive training; K, Scalp acupuncture plus body acupuncture; L, Abdominal acupuncture plus body acupuncture; M, Warm acupuncture plus scalp acupuncture; N, Scalp acupuncture plus auricular bloodletting. **(A)** Minimum Mental State Examination scale (MMSE). **(B)** Montreal Cognitive Assessment Scale (MoCA). **(C)** Modified Barthel Index scale (MBI).

a high level of heterogeneity in some comparisons in the results of the paired meta-analysis. Through a review of the literature, we found that this heterogeneity may stem from clinical heterogeneity. Although we compared the same kinds of acupuncture therapies with cognitive training, some factors, such as acupuncture depth, retention time, and acupoint selection, still differed. Differences in the skill level of acupuncture therapists during clinical practice are among the factors that contribute to clinical heterogeneity. Furthermore, given that only thirteen trials in this review were pre-registered, the prospective registration of study protocols before conducting studies should be strongly urged so that others can follow their studies. Moreover, with regard to blinding, it is difficult to blind acupuncture therapists due to the inherent characteristics of acupuncture as a non-pharmacological therapy. However, it is feasible and necessary to blind participants and outcome assessors.

5. Conclusion

Based on the available evidence, most acupuncture therapies have positive effects on cognitive function and self-care in daily life in PSCI patients compared to cognitive training. Acupuncture-related therapies may be an effective alternative intervention for the treatment of PSCI. Ophthalmic acupuncture plus cognitive training may be the treatment of choice for improving MMSE scores in PSCI patients. Warm acupuncture plus cognitive training was the preferred therapy for improving MoCA scores, while scalp acupuncture plus body acupuncture was the preferred therapy for improving MBI scores. The methodological quality of the literature included in this study was low and the results should be treated with caution. Future high-quality studies are needed for further validation of our findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

YL, LZ, and FC conceived and designed the study and edited the final manuscript. XL and JH designed the research methodology. MB and XS developed the search strategy and performed data extraction. YL and LZ performed data analysis and wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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References

1. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Ann Transl Med*. (2014) 2:80. doi: 10.3978/j.issn.2305-5839.2014.08.05

2. Barbay M, Diouf M, Roussel M, Godefroy O. Systematic review and Meta-analysis of prevalence in post-stroke neurocognitive disorders in hospital-based studies. *Dement Geriatr Cogn Disord*. (2018) 46:322–34. doi: 10.1159/000492920

3. Obaid M, Douiri A, Flach C, Prasad V, Marshall I. Can we prevent Poststroke cognitive impairment? An umbrella review of risk factors and treatments. *BMJ Open*. (2020) 10:e037982. doi: 10.1136/bmjopen-2020-037982

4. Quinn TJ, Richard E, Teuschl Y. European stroke organisation and European academy of neurology joint guidelines on post-stroke cognitive impairment. *Eur J Neurol*. (2021) 28:3883–920. doi: 10.1111/ene.15068

5. Dichgans M, Markus HS, Salloway S. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in Cadasil. *Lancet Neurol*. (2008) 7:310–8. doi: 10.1016/s1474-4422(08)70046-2

6. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology*. (2021) 190:108352. doi: 10.1016/j.neuropharm.2020.108352

7. Li Z, Yang L, Qiu H. Comparative efficacy of 5 non-pharmacological therapies for adults with post-stroke cognitive impairment: a Bayesian network analysis based on 55 randomized controlled trials. *Front Neurol*. (2022) 13:977518. doi: 10.3389/fneur.2022.977518

8. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med*. (2002) 136:374–83. doi: 10.7326/0003-4819-136-5-200203050-00010

9. Berman BM, Langevin HM, Witt CM. Acupuncture for chronic low Back pain. *N Engl J Med*. (2010) 363:454–61. doi: 10.1056/NEJMct0806114

10. Kim KH, Lee MS, Kim TH. Acupuncture and related interventions for symptoms of chronic kidney disease. *Cochrane Database Syst Rev*. (2016) 2016:CD009440. doi: 10.1002/14651858.CD009440.pub2

11. Liu Y, Chen F, Qin P. Acupuncture treatment vs. cognitive rehabilitation for post-stroke cognitive impairment: a systematic review and Meta-analysis of randomized controlled trials. *Front Neurol*. (2023) 14:1035125. doi: 10.3389/fneur.2023.1035125

12. Zhou L, Wang Y, Qiao J. Acupuncture for improving cognitive impairment after stroke: a Meta-analysis of randomized controlled trials. *Front Psychol*. (2020) 11:549265. doi: 10.3389/fpsyg.2020.549265

13. Kuang X, Fan W, Hu J. Acupuncture for post-stroke cognitive impairment: a systematic review and Meta-analysis. *Acupunct Med*. (2021) 39:577–88. doi: 10.1177/09645284211009542

14. Hutton B, Salanti G, Caldwell DM. The Prisma extension statement for reporting of systematic reviews incorporating network Meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. (2015) 162:777–84. doi: 10.7326/m14-2385

15. Schulz KF, Altman DG, Moher D. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)*. (2010) 340:c332. doi: 10.1136/bmj.c332

16. Guyatt GH, Oxman AD, Vist GE. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*. (2008) 336:924–6. doi: 10.1136/bmj.39489.470347.AD

17. Bao X, Li L, Liu H. Effect of acupuncture combined with rehabilitation on cognitive and motor functions in Poststroke patients. *Anat Rec*. (2021) 304:2531–7. doi: 10.1002/ar.24700

18. Jiang C, Yang SL, Tao J. Clinical efficacy of acupuncture treatment in combination with Rehacom cognitive training for improving cognitive function in stroke: a 2 X 2 factorial design randomized controlled trial. *J Am Med Dir Assoc*. (2016) 17:1114–22. doi: 10.1016/j.jamda.2016.07.021

19. Xiong J, Zhang Z, Ma Y. The effect of combined scalp acupuncture and cognitive training in patients with stroke on cognitive and motor functions. *NeuroRehabilitation*. (2020) 46:75–82. doi: 10.3233/nre-192942

20. Bai JLB, Tang Q. Effect of cluster needling of scalp point combined with cognitive Trajning on cognitive impairment after cerebral infarction. *Chin J Rehabil Med*. (2012) 27. doi: 10.3870/zgkf.2012.05.003

21. Y P. Analysis of the effect of acupuncture on cognitive dysfunction after cerebral infarction. *Shenzhen J Integr Med*.. (2018) 28. doi: 10.16458/j.cnki.1007-0893.2018.24.016,

22. Qq C. Efficacy of acupuncture combined with cognitive rehabilitation training for post-stroke cognitive impairment and its effect on cytokines. *Reflexology Rehabil Med*. (2020) 5. doi: 10.19589/j.cnki.issn2096-7950.2020.09.045

23. Zeng LLZX, Huang Z. Clinical effects of Jin's 3-needle combined with cognitive rehabilitation training in the treatment of convalescent cerebral apoplexy with cognitive impairment. *Shandong. J Tradit Chin Med*. (2018) 37. doi: 10.16295/j.cnki.0257-358x.2018.05.005

24. Chen AZLZ, Lan L. Effect of prolonged head-acupuncture combined with cognitive rehabilitation training platform on cognitive function after stroke. *Chinese J Rehabilitation Med*. (2020) 5. doi: 10.19787/j.issn.1008-1879.2020.06.009

25. Fx LJ. Electroacupuncture of Baihui and Shenting points with rehabilitation training clinical study on cognitive impairment after stroke. *Chin Med. J*. (2013) 28:608–10. doi: 10.16368/j.issn.1674-8999.2013.04.020

26. Chen XYNQ. Effect of acupuncture combined with rehabilitation training on cognitive dysfunction and serum cytokines in stroke patients. *Reflexology Rehabil Med*. (2020) 29:40–2. doi: 10.19589/j.cnki.issn2096-7950.2020.13.040

27. Ding XZH. Effect of head injection combined with motor relearning on cognitive impairment in post-stroke patients. *Hebei Chin Med*. (2016) 38. doi: 10.3969/j.issn.1002-2619.2016.04.033

28. Du RRZY. The efficacy of acupuncture therapy combined with occupational function training on cognitive dysfunction after ischemic stroke. *Chinese J Rehabilitation Med*. (2019) 10. doi: 10.19787/j.issn.1008-1879.2019.02.006

29. Duan LZZX. Study on the effect of combining rehabilitation training with nourishing kidney and marrow acupuncture in patients with cognitive impairment after stroke. *Heilongjiang Med J*. (2021) 45. doi: 10.3969/j.issn.1004-5775.2021.20.004

30. Feng XDWM. Clinical efficacy of supervised Moxibustion on post-stroke cognitive impairment. *Chin J Rehabil Theory Pract*. (2014) 20. doi: 10.3969/j.issn.1006-9771.2014.10.015

31. Han HYWZ. The effect of scalp acupuncture combined with cognitive training on cognitive dysfunction after stroke. *J Med Inform*. (2021) 34. doi: 10.3969/j.issn.1006-1959.2021.15.050

32. Jx H. Clinical observation of 40 cases of cognitive dysfunction after cerebral hemorrhage treated with warm acupuncture. *J Ethnobiol Ethnomedicine*. (2019) 28:102–104.

33. Niu LQH. Cognitive function training combined with long stay acupuncture at head point series clinical study on cognitive dysfunction after cerebral infarction. *Res Integrat Tradition Chin Western Med*. (2021) 13:377–80. doi: 10.3969/j.issn.1674-4616.2021.06.005

34. Kong YFQH, Niu YQ. Clinical study on cognitive dysfunction after cerebral infarction treated with cephalic plexus acupuncture and long stay acupuncture with cognitive function training. *J Tradit Chin Med*. (2021) 37:1464–1466.

35. Leng JWF, Guo W. Efficacy of long-time Moxibustion "Baihui" for post-stroke urinary incontinence with cognitive Dysfunction. *Rehabil Med*. (2020) 30:103–7. doi: 10.3724/SP.J.1329.2020.02004

36. Chen LZWJ, Wang LJ. Acupuncturing five Zang -organs Yu combined with head-needling for cognitive function after stroke and the influence of plasma homocysteine. *JCAM*. (2016) 9:88–90. doi: 10.16808/j.cnki.issn1003-7705.2016.09.041

37. Q L. Curative effect observation of warm needling method on patients with cognitive impairment after stroke. *China Med Dev Inform*. (2017) 23. doi: 10.15971/j.cnki.cmdi.2017.20.002

38. Lin BRL, Yao JM. Clinical effects of acupuncture with rehabilitation training for cognitive dysfunction after cerebral infarction. *Chronic Pathematology J*. (2020) 20. doi: 10.16440/j.cnki.1674-8166.2020.01.056

39. Lin ZCCL, Tao J. Effect of Electroacupuncture at Baihui point on auditory P300 in patients with cognitive impairment after cerebral infarction. *Shanghai J Acupuncture Moxibustion*. (2014) 33. doi: 10.13460/j.issn.1005-0957.2014.01.0014

40. Qian LFYQ, Luo KT. The effect of Bai Changliu acupuncture with rehabilitation training on ischemic stroke with cognitive dysfunction in qi deficiency and blood stasis type. *Shanghai J Acupuncture Moxibustion*. (2018) 37. doi: 10.13460/j.issn.1005-0957.2018.05.0499

41. Feng XDFH. Effective observation of ear Acupoint bloodletting combined with rehabilitation training on cognitive impairment after stroke. *CJCM*. (2015) 7:49–50. doi: 10.3969/j.issn.1674-7860.2015.14.025

42. Song YZF, Huang WH. Therapeutic observation of acupuncture based on brain-kidney correlated theory combined with rehabilitation training for post-stroke cognitive impairment. *Shanghai J Acupuncture Moxibustion*. (2020) 39. doi: 10.13460/j.issn.1005-0957.2020.06.0657

43. Xq S. Analysis of the therapeutic effect of nourishing the kidney and benefiting the marrow acupuncture method with rehabilitation training on patients with cognitive impairment after stroke. *Modern Drug Applications China*. (2019) 13. doi: 10.14164/j.cnki.cn11-5581/r.2019.05.093

44. Tan SLX, Liu CQ. Effect evaluation of acupuncture and rehabilitation training on cognitive dysfunction after cerebral infarction. *Clinical Res Chin Med*. (2020) 12. doi: 10.3969/j.issn.1674-7860.2020.06.034

45. Sh G. Evaluation of the efficacy of acupuncture with rehabilitation training in the treatment of cognitive dysfunction after cerebral infarction. *China Foreign Med Treat*. (2016) 18:167–8. doi: 10.16662/j.cnki.1674-0742.2016.18.167

46. Tian YLSY, Feng XY. The efficacy of acupuncture combined with cognitive rehabilitation training in the treatment of post-stroke cognitive dysfunction. *Clin Med*. (2021) 41. doi: 10.19528/j.issn.1003-3548.2021.01.049

47. Wang CXLX, Yu KF. Effect of ventral acupuncture combined with early rehabilitation training on motor function and cognitive impairment in patients with cerebrovascular disease. *Modern J Integrat Chin Western Med*. (2015) 24. doi: 10.3969/j.issn.1008-8849.2015.19

48. Wang FGS, Yang L. Efficacy of acupuncture combined with cognitive training for cognitive dysfunction after ischemic stroke. *Shanghai J Acupuncture Moxibustion*. (2021) 40. doi: 10.13460/j.issn.1005-0957.2021.07.0795

49. Wang HZY, Cai SF. Effect of indwelling scalp acupuncture combined with occupational therapy on patients with cognitive dysfunction after stroke. *J Neurol Neurorehabil*. (2021) 17. doi: 10.12022/jnnr.2020-0092

50. Wang HLFX, Chen Z. Clinical efficacy of electro-acupuncturing on Baihui and Zusanli points plus rehabilitation training on post-stroke cognitive impairment. *Clinic Res Chin Med*. (2017) 9. doi: 10.3969/j.issn.1674-7860.2017.05.035

51. Wang LNFX, Liu CM. Effect of needle warming Moxibustion on cognitive dysfunction after stroke. *Chin J Rehabil Theory Pract*. (2015) 21. doi: 10.3969/j.issn.1006-9771.2015.02.018

52. Wang WLX, Zhu LS. Effect of long-time indwelling needle of Sculp acupuncture at early stage combined with rehabilitation training on cognitive disorder of stroke patients. *J Tradit Chin Med*. (2018) 50. doi: 10.13457/j.cnki.jncm.2018.03.044

53. Wang YZL, Li SR. Effect of cranial acupuncture plexus combined with cognitive training on cognitive dysfunction in patients with cerebral infarction. *Theory Prac Rehabil China*. (2011) 17:316–318. doi: 10.3969/j.issn.1006-9771.2011.04

54. Lei YFZG. Effect of computer-assisted cognitive training combined with Ziwu-Liu injection acupuncture on the rehabilitation effect of cognitive dysfunction after stroke. *J External Therapy TCM*. (2021) 4:72–4. doi: 10.3969/j.issn.1006-978X.2021.04.031

55. Wang YXMW, Zhang HS. Effect of cluster needling of scalp acupuncture combined with cognitive rehabilitation on cognitive impairment after cerebral infarction. *Chin Med Herald*. (2018) 24. doi: 10.13862/j.cnki.cn43-1446/r.2018.17.025

56. Wang ZGZH, Wang XW. Efficacy of acupuncture plus cognitive rehabilitation training for post-stroke cognitive impairment and its effect on cytokines. *Shanghai J Acupuncture Moxibustion*. (2019) 38. doi: 10.13460/j.issn.1005-0957.2019.10.1098

57. Zj Z. Evaluation of the efficacy of acupuncture with rehabilitation training in the treatment of cognitive dysfunction after cerebral infarction. *Heilongjiang Trad Chin Med*. (2021) 4:94–5.

58. Wei RPZJ, Cong WD. Analysis of the efficacy of acupuncture for cognitive function and Nhiss and Adl scores after cerebral infarction. *Jilin Chin Med*. (2019):10. doi: 10.13463/j.cnki.jlzyy.2019.10.029

59. Zhao JYGY. Clinical efficacy of auricular Acupoint therapy combined with Zhisan acupuncture and Cephalopuncture in patients with cognitive dysfunction after stroke. *RARM*. (2021) 2:7–9.

60. Xu WXFL, Luo JC. Effect of acupuncture at eight points of the nape combined with cognitive rehabilitation training for patients with post-stroke cognitive impairment. *J Nurs Sci*. (2022) 37. doi: 10.3870/j.issn.1001-4152.2022.14.050

61. Zheng CJXW, Duan C. Combination of acupuncture and computer-assisted cognitive training for post-stroke cognitive dysfunction: a randomized controlled study. *Chin Acupuncture Moxibustion*. (2021) 41:247–51. doi: 10.13703/j.0255-2930.20200311-k0001

62. Yan HLZC, Wu HB. Clinical observation on cognitive impairment after stroke treated with Moxibustion and Moxibustion of the Duoyuan Group of Points Combined with cognitive function training. *J Anhui Univ Trad Chin Med*. (2022) 41. doi: 10.3969/j.issn.2095-7246.2022.03.011

63. Yang FLK, Yang XB. Clinical observation of long-time needle retaining at Baihui (Gv 20) on post-stroke cognitive disorder of qi deficiency and blood stasis. *Chin Acupuncture Moxibustion*. (2018) 38:1151–6. doi: 10.13703/j.0255-2930.2018.11.004

64. Gd Y. Observation of clinical efficacy of acupuncture combined with cognitive rehabilitation training for cognitive dysfunction in stroke patients and the effect on serum cytokines. *Reflexology Rehabil Med*. (2020):8. doi: 10.19589/j.cnki.issn2096-7950.2020.08.024

65. Zhou JRWB. A randomized controlled study on the effect of Tongdu and Tonifying acupuncture on the cognitive function of patients after stroke. *J External Therap TCM*. (2021) 30:26–7. doi: 10.3969/j.issn.1006-978X.2021.05.012

66. Yang YZH. Clinical efficacy and impact on daily living activities of cognitive dysfunction after stroke treated with acupuncture method of Tonifying kidney and benefiting marrow together with rehabilitation training. *Clin J Acupuncture Moxibustion*. (2019) 35:24–27. doi: 10.3969/j.issn.1005-0779.2019.07.008

67. Yao JJLS, Yu JF. Acupuncture combined with cognitive rehabilitation training for cognitive dysfunction after ischemic stroke. *Asia-Pacific Trad Med*. (2019) 15. doi: 10.11954/ytctyy.201909040

68. Yao RGZ, Zhang KW. Clinical study of Jin san acupuncture therapy for post-stroke cognitive impairment. *Acupuncture Tuina Med*. (2020) 18:40–6. doi: 10.1007/s11726-020-1155-2

69. Yu LYCM, Ma M. Effect of Bo's abdominal acupuncture therapy on the resting-state Fmri in patients with cognitive impairment after stroke. *Shanghai J Acupuncture Moxibustion*. (2021) 40. doi: 10.13460/j.issn.1005-0957.2021.11.1293

70. Zhan JPR, Guo YH. Acupuncture of Baihui and Shenting combined with basic treatment and conventional rehabilitation for cognitive impairment after stroke: a randomized controlled study. *Chin Acupuncture Moxibustion*. (2016) 36. doi: 10.13703/j.0255-2930.0216.08.007

71. Zhang JBWR, Yang H. Head acupuncture combined with computer-assisted training for cognitive impairment after cerebral infarction in the elderly magnetic resonance spectroscopy imaging. *Chin J Gerontol*. (2020) 40. doi: 10.3969/j.issn.1005-9202.2020.19.011

72. Zhang JZL, Chen XY. Clinical efficacy of nourishing the kidney and benefiting the marrow acupuncture method with rehabilitation training in 65 cases of post-stroke cognitive impairment. *World J Int Chin Western Med*. (2018) 13. doi: 10.13935/j.cnki.sjzx.180318

73. Zhang YYSB, Huang GL. The efficacy of Sanjiao acupuncture combined with computer-assisted cognitive training in the treatment of cognitive impairment after acute stroke. *Shandong. J Tradit Chin Med*. (2019) 38. doi: 10.16295/j.cnki.0257-358x.2019.12.007

74. Zheng MJY, Chen Y. Exploration of Tongdu Yiyang Moxibustion on improving cognitive dysfunction after cerebral infarction based on event-related electric potential P300. *Acta Chin Med*. (2019) 34:1546–50. doi: 10.16368/j.issn.1674-8999.2019.07.366

75. Zhou HXQZ, Kong YF. Clinical study on cognitive impairment after ischemic stroke treated with eye acupuncture combined with cognitive function training. *J Pract Tradit Chin Med*. (2022) 38:711–733.

76. Zhuo JBZC, Zhang LY. Clinical study of heart-brain acupuncture method combined with cognitive rehabilitation to improve cognitive impairment during recovery from cerebral infarction. *Yunnan. J Tradit Chin Med*. (2021) 42:24–27. doi: 10.3969/j.issn.1007-2349.2021.06.008

77. Zhou LZZ. Evaluation of the efficacy of acupuncture with rehabilitation training in the treatment of cognitive dysfunction after cerebral infarction. *RARM*. (2020) 1:7–9.

78. Zhu YLHC, Xing JL. 4o cases of post-stroke cognitive dysfunction treated with the "treatment from the governor" method of acupuncture. *J Anhui Univ Chinese Med*. (2014) 33:50–2. doi: 10.3969/j.issn.20957246.2014.02.019

79. van der Flier WM, Skoog I, Schneider JA. Vascular Cognitive Impairment. *Nat Rev Dis Primers*. (2018) 4:18003. doi: 10.1038/nrdp.2018.3

80. Yao S, Liu Y, Zheng X. Do nonpharmacological interventions prevent cognitive decline? A systematic review and Meta-analysis. *Transl Psychiatry*. (2020) 10:19. doi: 10.1038/s41398-020-0690-4

81. Wonderling D, Vickers AJ, Grieve R. Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care. *BMJ (Clinical research ed)*. (2004) 328:747. doi: 10.1136/bmj.38033.896505.EB

82. Kong LHSG, Liu SH. Effect of acupuncture on the expression and content of nuclear transcription factor-Kb in hippocampal tissue of rats with cerebral ischemia-reperfusion. *Acupuncture Res*. (2006) 31:140–4+93. doi: 10.13702/j.1000-0607.2006.03.003

83. Gao MLB, Tan X. Effects of acupuncture Baihui and Sishencong on learning memory ability and cell apoptosis in ischemia-reperfusion injury model rats. *World Chin Med*. (2021) 16:1226–30. doi: 10.3969/j.issn.1673-7202.2022.08.009

84. Xu SYLW, Hong H. Effect of acupuncture on the expression of autophagy-related proteins Lc3-ii and Beclin1 in cerebral ischemia-reperfusion rats. *J Nanjing Univ Chin Med*. (2021) 37:270–4. doi: 10.14148/j.issn.1672-0482.2021.0270

85. Xie ZRXD, Tang YN. Effect of acupuncture on the expression of Synaptophysin and postsynaptic Mitogen-95 in serum and brain tissue of Mcao rats. *China J Trad Chin Med Inform*. (2021) 28:81–5. doi: 10.19879/j.cnki.1005-5304.202005293

86. Zhang YKTL. Effects of acupuncture on learning memory ability and vascular endothelial growth factor expression in cerebral ischemia-reperfusion rats. *J Huazhong Univ Sci Technol*. (2013) 42:70–3.

87. Lin YKLR, Chen B. Oxidative stress mechanisms underlying the effect of acupuncture on learning memory in a rat model of focal cerebral ischemia-reperfusion. *Chin J Rehabil Med*. (2015) 30:755–60.

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ICTs and interventions in telerehabilitation and their effects on stroke recovery

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Telerehabilitation (TR) is a new model to provide rehabilitation services to stroke survivors. It is a promising approach to deliver mainstream interventions for movement, cognitive, speech and language, and other disorders. TR has two major components: information and communication technologies (ICTs) and stroke interventions. ICTs provide a platform on which interventions are delivered and subsequently result in stroke recovery. In this mini-review, we went over features of ICTs that facilitate TR, as well as stroke interventions that can be delivered via TR platforms. Then, we reviewed the effects of TR on various stroke disorders. In most studies, TR is a feasible and effective solution in delivering interventions to patients. It is not inferior to usual care and in-clinic therapy with matching dose and intensity. With new technologies, TR may result in better outcomes than usual care for some disorders. One the other hand, TR also have many limitations that could lead to worse outcomes than traditional rehabilitation. In the end, we discussed major concerns and possible solutions related to TR, and also discussed potential directions for TR development.

KEYWORDS

telerehabilitation, telehealth, stroke, information and communication technologies, rehabilitation

1. Introduction

Stroke is a leading cause of death and disability globally (1). The occurrence of stroke is increasing rapidly in terms of absolute numbers due to population aging (2). Worldwide in 2019, there are 143 million stroke survivors suffering from various symptoms such as hemiplegia, aphasia and depression, which greatly impair their independency and cause tremendous burden to patients, their family and the society (3, 4). Extensive studies demonstrated that proper rehabilitation programs can ease stroke symptoms, reduce long-term disability, and improve quality of life (5, 6). Patients should start rehabilitation as early as possible in order to prevent chronic damage to the brain (7), and continue to do so even after recovery is slower than before (8). Traditionally, rehabilitation services are provided by healthcare professionals in clinic settings. But this is difficult for patients living in remote areas, especially in low- and middle-income countries. They have no access to rehabilitation services or they have to take extra time and efforts to travel a long distance. In this situation, telerehabilitation (TR) can offer an alternative way to deliver services (9).

By using information and communication technologies (ICTs), TR is able to minimize the barrier of distance between patients and rehabilitation providers (10). The role of ICTs is to ensure traditional in-clinic rehabilitation services delivered remotely to patients as effectively as possible. TR is not a new subspeciality (9); instead, it covers all aspects of rehabilitation, including

"evaluation, assessment, monitoring, prevention, intervention, supervision, education, consultation, and coaching (11)." There are a number of advantages to use TR for stroke patients. TR can save time and money, make the access to healthcare professionals easier, and provide extra training opportunities for interventions requiring higher dose. It also helped to decrease infection rates of certain diseases, and may provide emotional support to patients for being at home (12, 13).

In this mini-review, we will focus on two major components of TR: ICTs and stroke interventions, as well as outcomes of TR for various stroke conditions. ICTs serve as platforms on which interventions are delivered. Both of them are the keys to feasibility, effectiveness and safety of TR as well as to patients' satisfaction and adherence. Previous reviews regarding stroke and TR are mainly focused on one aspect, such as upper limb rehabilitation or application of virtual reality (14, 15). So, we think it is necessary to provide an overall picture in order to summarize key factors in this topic. In the end, we also discussed existing issues and potential future development.

2. Information and communication technologies in telerehabilitation

ICTs are the foundation of TR, allowing stroke survivors to achieve optimal recovery outcomes by utilizing home-based therapies (16). There are a number of ICTs available, including text, audio, visual, mobile-based, computer-based, web-based, sensors and wireless devices (17). The major purpose of ICTs is to provide a platform for patients to receive rehabilitation services as if in clinical settings. The platform should be safe, user friendly and feasible to apply stroke interventions to all users with high tolerance for error (18). When possible, the platform should be easily modified to deliver personalized service. The considerations of building up a TR platform involve a variety of factors, such as effectiveness of intervention, customer support, cost, accessibility, usability and acceptability (19). For example, low-cost platform may be not effective enough but can be afforded by most people; while high-cost platform usually is more complicated with a higher learning curve resulting in less use.

Telephone is one of the earliest TR methods and still frequently used today. In a recent study by Cha et al. (20), nurse-initiated phone call interventions are able to increase physical activities of subacute patients after hospital discharge. Calls to discuss patients' conditions may also increase their adherence to therapy and satisfaction with it (21). It is also used in goal setting programs for self-management of daily activities and stroke knowledge education (22). These results suggest that low-cost solutions, such as telephone and text, are still viable in plenty of situations.

Videoconferencing is an upgrade option of telephone service, providing both audio and visual communication between patients and healthcare professionals. Videoconferencing can be mobile-based or computer-based to support face-to-face information exchange. Li et al. (23). investigated feasibility, validity, and reliability of using videoconferencing for functional assessments of stroke patients after hospital discharge, and telephone service and home visit were used as controls. The functional status of patients was measured at the end of 2 weeks and 3 months. The authors found that patients offered videoconferencing and home visit have similar scores in functional status. Videoconferencing has higher validity and reliability than telephone based on measures from this study. Patients in videoconferencing group also showed high satisfaction and confidence. The results suggest that videoconferencing is a better solution than telephone.

Mobile-based, computer-based and web-based ICTs are usually integrated into interventions in the form of games, virtual reality (VR) and other trainings. They can deliver user training data to healthcare professionals for evaluation (17). They also can be combined with videoconferencing for better outcomes. Wearable sensors are used to collect patients' data in order to monitor their status including falls, heart rate, blood pressure, respiratory rate and blood oxygen levels (24). In a study by Asano et al. (25), 61 patients performed rehabilitation training though tablet-based TR system followed by a review through videoconferencing. Sensers were used to obtain their physiological signals to find adverse effects from TR for safety reason. Nasrabadi et al. (26) developed an activity recognition system based on inertial measurement units (IMU) for TR. The system can be used to track body motion during movement-based therapies in order to detect wrong actions and to assess training effectiveness. Accelerometer, gyroscope and electromyograph (EMG) sensors are also frequently used to track body motion and muscle activities. Furthermore, artificial intelligence (AI) approach was increasingly used in stroke rehabilitation. For example, machine learning methods were adopted as a promising support tool for clinicians to predict functional recovery of stroke patients (27). Major technologies used in TR were summarized in Figure 1.

3. Interventions and related technologies in telerehabilitation

According to a highly cited review article, interventions for stroke recovery were divided into four types. They are training interventions, technological interventions, pharmacological interventions and neuromodulation interventions (28). Among them, pharmacological interventions are not directly associated to TR. Thus, we will consider only the other three types of interventions below.

Both training interventions and technological interventions are related to physical activity and exercise. The former is in the form of strength or/and task-oriented trainings, while the latter consists of serious gaming, VR and robotics. These interventions are not mutually exclusive. Instead, they can be combined together to achieve optimal outcomes for stroke recovery. For example, Lee et al. (29) studied the role of a smart glove in upper limb function recovery. Participants were asked to perform task-oriented actions in a VR environment. The control group takes usual care plus recreational activities. As a result, the intervention group demonstrated better outcomes for all measures. Hao et al. (15) reviewed effects of VR-based TR systems including totally 260 stroke patients. The VR-TR group showed similar outcomes to in-person rehabilitation group in terms of upper limb and balance functions. Rozevink et al. (30) studied the effects of an upper limb robot-assisted serious game therapy in a TR setting. Their system significantly improved motor function of patients with high satisfaction and adherence.

Neuromodulation interventions include electrical stimulation and magnetic stimulation for the purpose to enhance neural pathways of different human body systems (24). Electrical stimulation (ES) is a popular and well-established intervention for stroke therapy, and it can be broken down into several subcategories, such as functional

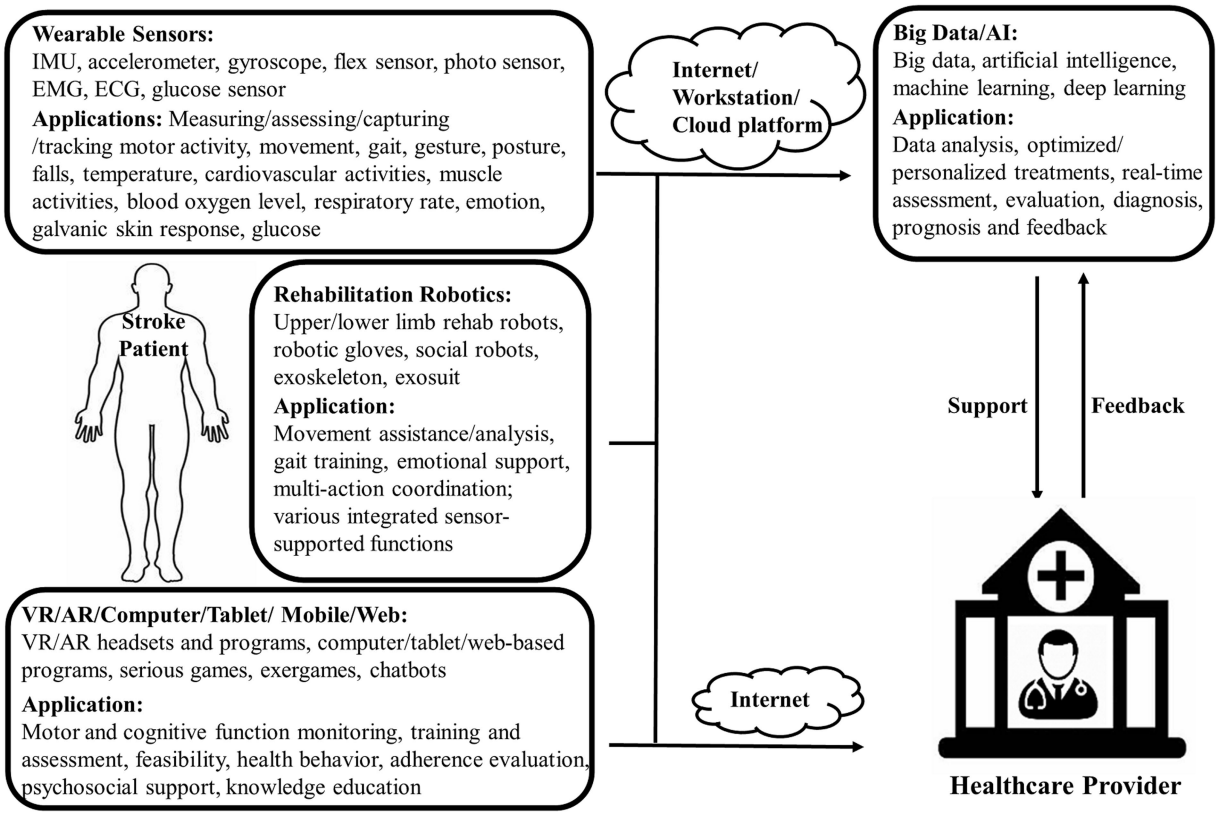

FIGURE 1
Overview of major technologies in telerehabilitation systems.

electrical stimulation (FES) for peripheral nerve system and transcranial direct current stimulation (tDCS) for central nerve system (31, 32). The effectiveness of ES for stroke recovery has been extensively studied with positive results (33, 34). But these interventions require sufficient knowledge and experience in order to operate ES devices properly. Additionally, there are also safety concerns. As a result, there are very few studies combining ES and TR for stroke recovery. Hermann et al. (35) examined the efficacy of FES treatment for post-stroke arm disorder, while Ko et al. (36) reported the use of home-based tDCS for cognitive training. Their data suggest that using ES in TR is promising. On the hand, transcranial magnetic stimulation (TMS) has been widely used to treat various stroke conditions (37, 38). But it has not been used in TR in our literature search, possibly because TMS device is very expensive and complex. The use of neuromodulation interventions in TR is just starting to receive attention, and further studies are needed to examine their outcomes.

4. Effects of telerehabilitation on post-stroke functional impairments

4.1. Movement disorders

Majority stroke survivors suffer from movement disorders (39), and rehabilitation practices are the key to help patients to regain their lost abilities (28). In a random clinical trial (RCT), 124 patients with arm motor disorders were equally divided into two groups – TR group and in-clinic therapy group. All patient received thirty six 72-min sessions of identical interventions in the form of daily functional games, exercise videos, and stroke education. The results demonstrated that both groups have significant gains in arm functionality based on Fugl-Meyer (FM) scores with high satisfaction, and there is no significant difference between the two groups. But in-clinic therapy group showed better adherence compared to TR group (40). In a similar study, the authors found that early TR after stroke is suitable for intensive arm motor trainings with excellent feasibility, safety and efficacy (41). Stzurm et al. (42) developed a computer game-assisted TR platform to improve compliance and accessibility of rehabilitation programs for individuals. They found that the TR service resulted significant improvement of patients' hand-arm functions which were evaluated by Wolf Motor Function Test and a customized computer-based system. Additionally, robotic rehabilitation for motor recovery via TR service substantially improved the upper limb function of patients with high satisfaction (43, 44).

For lower limb related disorders, Held et al. (45) developed an autonomous TR system for balance and gait recovery. During a 12-week period, patients play exercise games in a VR environment for 40 min per session. Their results suggest the TR system is safe, feasible and able to provide intensive therapy at home for lower limb trainings. Lin et al. (46) recruited 24 chronic stroke patients who were asked to perform a 50-min balance training session, and three times each week. The authors found that TR increased balance abilities of patients in terms of Berg Balance Scale, and there is no difference in training

effect and satisfaction between TR group and conventional therapy group. In another study, patients reported high acceptability and satisfaction of a serious game-based TR system for ankle movements (47).

TR also plays an important role in the recovery of activities of daily living (ADL) after stroke, which is a key indicator of one's functional status. In a systematic review, the authors conclude that there is no significant difference between TR intervention group and in-person physical therapy group, as well as usual care group (10). These studies suggest that TR is a feasible and effective way to improve motor functions of stroke patients, and its effects are not inferior to traditional therapies. But augmented TR training may be not effective in improving physical function compared with usual care (48).

4.2. Cognitive disorders

Post-stroke cognitive disorders may result in tremendous reduction in quality of life and independence on ADL, and they can also lead to poor adherence to treatments (49). In a study by Faria et al. (50), 36 chronic stroke patients were recruited, and divided into two groups – adaptive VR-based TR group and paper-and-pencil-based control group with task generator. Both groups performed equivalent cognitive trainings for 12 sessions over 1 month. The results showed that the TR group had significant improvement in cognitive functions compared to control group. In another study, VR-based cognitive TR also resulted better outcomes than traditional rehabilitation for stroke patients in terms of global cognitive level, attentive, memory and linguistic skills (51). Additionally, Lawson et al. demonstrated feasibility of TR in cognitive trainings as well as its non-inferiority compared with their previous in-person rehabilitation trainings (52). Bernini et al. (53, 54) also showed TR is not inferior to in-person rehabilitation with satisfiable user experience for general cognitive disorders. Overall, TR system is feasible for cognitive trainings, and has similar or better performance compared to traditional cognitive training methods.

4.3. Speech and language disorders

Aphasia has an occurrence rate of 30% in hospitalized stroke patients. It often leads to social isolation and low mood, and was rated as one of the worst diseases that has negative impact on quality of life (55). Meltzer et al. evaluated the effectiveness of TR for communication disorders by conducting identical treatments with 44 patients for TR group and in-person group. After 10-week treatment, all patients had significant improvement on evaluated indices, and the gain is similar for both groups. Their findings suggest that TR is highly effective for communication disorders (56). In another study, Maresca et al. conducted a RCT consisting of 30 patients with aphasia, who were assigned to either control group trained with a conventional treatment or experimental group trained with tablet-based TR platform. After 6-month treatment, the experimental group demonstrated significant improvement in all evaluations expect writing, and performed much better than control group (57). Similarly, a web-based application demonstrated TR is effective way for aphasia training (58). Ora et al. also conducted a RCT consisting of a TR group and a control group with 31 patients for each. Both of them received usual care, but TR group also received additional 5-h training per week. As a result, there is no significant difference between the two groups for assessed indicis after 4 weeks (59). In a another study by the same authors, TR were shown to be a feasible and acceptable way for aphasia training (60). A review suggests intensity of therapy is the key for aphasia trainings (61), thus TR may serve as a complementary intervention for better outcomes.

4.4. Other disorders

Approximately 50% of stroke patients have swallowing disorders, and TR composed of motion and muscle exercises can effectively improve swallow functions with high patient satisfaction (62). Wearable EMG sensors can monitor swallowing activities and subsequently detect dysphagia in remote settings (63). TR is also used to reduce post-stroke depression, and telephone intervention demonstrated similar effects in reducing depression to usual care or in-person intervention (64).

5. Discussion

As shown in Table 1, TR demonstrated considerable feasibility and effectiveness for stroke recovery. It is not inferior to usual care and in-clinic therapy with matched intensity, duration, and frequency. It also has a high satisfaction rate among stroke patients. But TR is probably not suitable for every patient because of technical barriers and various personal reasons. TR treatments have a higher dropout rate than traditional rehabilitation programs because some patients, especially those with cognitive disorders, have difficulties in completing the training session remotely (50). Additionally, without healthcare professionals standing aside, many patients have less confidence and motivation to conduct interventions, which subsequently results in low adherence and poorer clinical outcomes. Furthermore, some interventions requiring large, expensive or dangerous devices may be not suitable for home settings. There are also some concerns in interpreting TR outcomes. First, inclusion and exclusion criteria for participants are not perfect due to limited availability of patients (40). Second, cohort studies lack control groups, which may lead to wrong conclusions (42). Third, satisfaction and other self-reported data are not subjective (41). On the other hand, a recent survey research regarding telemedicine showed that majority physicians and patients still prefer in-person care, because they do not trust the quality of TR. Lack of physical exam and intervention accuracy were cited as key reasons (65). The results also suggest that self-reported satisfaction rate from patients may be questionable.

To address above-mentioned issues, technological advances are the key. Intelligent devices requiring less efforts from patients can overcome technical barriers in usability. VR and haptic devices can be used to create an environment mimicking clinic setting to increase confidence and motivation of patients (66, 67). Additionally, many devices for stroke interventions can be redesigned to adapt TR platforms. For example, FES and tDCS devices have already been used for neuromodulation in TR (68), but the number of studies is very limited mainly for safety reasons.

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TABLE 1 Representative references of telerehabilitation studies.

Study population	Objective	Characteristics of telerehabilitation	Assessment methods	Key findings
124 patients with movement disorders within 4 weeks of stroke (25)	To evaluate the efficacy of a telerehabilitation system	Tablet-based telerehabilitation program including limb strengthening and balance exercises plus videoconference reviews. 60 min per session, 5 times per week over 3 months.	Comparison: usual rehabilitation care. Measures: results were assessed with scores of the late-life function and disability instrument (LLFDI), walking test and modified Barthel index etc.	The intervention and control groups self-reported similar improvements in functional outcomes. No significance was found between them.
124 stroke patients with arm motor disorders within 6 weeks of stroke (40)	To study the efficacy of home-based telerehabilitation vs. in-clinic therapy	Arm motor therapy including exercises and functional trainings plus stroke education through videoconference with the therapist using the computer-based TR system. 70 min per session, totally 36 sessions over 4 weeks.	Comparison: in-clinic therapy with matched intensity, duration, and frequency. Measures: results were assessed Fugl-Meyer score, NIHSS score, modified Rankin scale score.	Both TR and in-clinic rehabilitation produced substantial gains in arm motor function. No significance was found between them.
16 stroke patients with a recent hemiparetic stroke (41)	To evaluate feasibility, safety, and potential efficacy of providing intense TR therapy early after stroke	Functional games, exercise videos, education, and daily assessments via videoconference with the therapist via the computer-based TR system. 70 min per session, totally 18 TR sessions over 6 weeks.	Comparison: 18 in-clinic rehabilitation sessions for the same group of patients with the same intervention program, which are performed alternately with TR. Measures: same as previous one.	TR is feasible and safe in stroke recovery at less than 1 month from onset.
10 single stroke patients with upper limb disorders between 4 months and 2 years (42)	To determine the feasibility and acceptability of a game-assisted home exercise program.	Game-assisted repetitive task practice exercise program consisting of 7 object manipulation tasks. Before TR program, participants received three to four initial clinically supervised therapy sessions. 145–60 min per session, 4 times per week over 6 weeks.	Comparison: same group of patients, before and after interventions. Measures: feasibility and acceptability were based on retention rate, compliance and semi-structured interviews. Quantitative analysis included the Wolf Motor Function and a computerized performance-based assessment.	Feasible trial procedures, acceptable game-assisted task-oriented home training with a high compliance rate and positive outcomes.
14 patients with upper limb disorders at least 6 months after stroke (43)	To assess the effects of robotic home-based treatment rehabilitation	Customized upper limb home-based robotic rehabilitation programs including circle drawing, point-to-point practice, shoulder horizontal abduction, and other exercises.	Comparison: same group of patients, before and after interventions. Measures: NIHSS score, Fugl-Meyer score, Barthel Index, modified Ashworth scale etc.	Significant improvements in MAS of elbow and computer-based exercise performance
15 patients with lower limb disorders 3–74 months after stroke (45)	To study the safety, usability and patient acceptance of an autonomous telerehabilitation system for balance and gait.	Autonomous rehabilitation based on virtual rehabilitation was provided at the participants' home. 10 to 40 min per day for 12 weeks based on patient conditions.	Comparison: same group of patients, before and after interventions. Measures: compliance and acceptance of the system measured with the technology acceptance model (TAM).	The TR system is safe, feasible and can help to intensive rehabilitative therapy at home.

(Continued)

TABLE 1 (Continued)

Study population	Objective	Characteristics of telerehabilitation	Assessment methods	Key findings
32 patients with movement disorders at least 6 months after stroke (46)	To examine the possible effects of therapeutic exercises performed by an App on trunk control, balance, and gait in stroke survivors.	Videoconference with the therapist via the computer-based TR system with wireless sensors to monitor patient conditions. 10 min of standing exercise and 10 min of 3D interactive games, 50 min per session per day for 4 weeks.	Comparison: usual care. Measures: assessed with berg balance scale (BBS), Barthel index (BI), and self-reported telerehabilitation satisfaction of the participants	No significant difference between groups could be demonstrated. Some unwillingness to use TR system.
95 first-ever stroke patients within 2 weeks of discharge (48)	To investigate whether augmented TR intervention improved physical function compared with usual care	Telephone and text-based TR services with personalized treatment plans consisting of 5 sessions per week for 6 months.	Comparison: usual care. Measures: Stroke Impact Scale (SIS3.0), hand grip strength, balance test etc.	Augmented TR Intervention may be effective in preventing deterioration but no significant difference from usual care in improving physical function.
36 patients with cognitive disorders at least 6 months after stroke (50)	To test effectiveness of VR rehabilitation intervention for cognitive disorders	Customized application Reh@City v2.0 providing adaptive cognitive training experience through everyday tasks VR simulation. 90 min per session for 2 months	Comparison: content-equivalent paper-and-pencil training. Measures: general cognitive functioning; attention; WMS-III; self-reported evaluation.	TR showed higher effectiveness with improvements in different cognitive domains and self-perceived cognitive deficits in everyday life, but with higher dropout rate.
40 patients with cognitive disorders, 3–6 months after stroke (51)	To evaluate the efficacy of a VR-based TR system	VR-based cognitive training system with home tablet. 50 min per session, 3 sessions per weeks for 6 months	Comparison: standard cognitive training. Measures: Montreal overall cognitive assessment, attentive matrices, phonemic fluency etc.	TR has significant improvement in global cognitive level, as well as in the attentive, memory and linguistic skills.
46 patients with cognitive disorders at least 3 months after stroke (52)	To determine usability of a TR-based cognitive training system.	Zoom-based TR via videoconference plus traditional in-person rehabilitation. 120 min per week for 6 weeks for TR.	Comparison: before and after interventions, and previous patients in similar conditions. Measures: Goal Attainment Scaling (GAS), Comprehensive Assessment of Prospective memory (CAPM), adherence, self-reported questionnaires.	TR is a feasibility an option for remote delivery of compensatory memory skills training after a stroke.
40 patients with mild or major cognitive disorders (53)	To compare the same rehabilitation program performed at home and at hospital	Computer-based intervention based on traditional paper-and-pencil exercises at home via videoconference. 45 min per session, 3 sessions per week for 6 weeks.	Comparison: in-person cognitive intervention with the same computer-based exercises. Measures: exhaustive neuropsychological battery before and after the intervention.	Effects of TR are not inferior to in-clinic rehabilitation. No significance between two groups.
46 patients with cognitive disorders at least 3 months after stroke	To determine usability and user experience of a TR-based cognitive training system.	Zoom-based TR via videoconference plus traditional in-person rehabilitation. 120 min per week for 6 weeks for TR.	Comparison: before and after interventions, and previous patients in similar conditions. Measures: Goal Attainment Scaling (GAS), Comprehensive Assessment of Prospective memory (CAPM), adherence, self-reported questionnaires.	The study supports the feasibility and potential effectiveness of TR options for remote delivery of compensatory memory skills training after a stroke

(Continued)

TABLE 1 (Continued)

Study population	Objective	Characteristics of telerehabilitation	Assessment methods	Key findings
40 patients with cognitive disorders, 3–6 months after stroke (51)	To evaluate the efficacy of a VR-based TR system	VR-based cognitive training system with home tablet. 50 min per session, 3 sessions per weeks for 6 months	Comparison: standard cognitive training. Measures: Montreal overall cognitive assessment, attentive matrices, phonemic fluency etc.	TR has significant improvement in global cognitive level, as well as in the attentive, memory and linguistic skills.
44 patients with communication disorders at least 6 months after stroke (56)	To evaluate the effectiveness of TR for communication disorders.	Tablet-based home exercises and realistic, customized treatment plans tailored to the needs of each individual client. Weekly 60-min sessions for 10 weeks	Comparison: in-person rehabilitation. Measures: western aphasia battery aphasia quotient, cognitive-linguistic quick test, communication effectiveness index, confidence ratings etc.	No significant difference of all except self-rated confidence having higher score for in-person group.
30 patients with aphasia due to stroke (57)	To evaluate the effectiveness of a TR training for aphasia using a VR system.	Virtual reality rehabilitation system. 50 min per session, 5 sessions per week for 6 months. and included 2 phases	Comparison: traditional linguistic treatment using paper-pencil tools. Measures: neuropsychological evaluation including token test, aphasic depression rating scale etc. before and after intervention.	The experimental group improves in all the investigated areas, except for writing, while the control group only improves in comprehension, depression, and quality of life
32 patients with aphasia at least 6 months after stroke (58)	To investigate an intensive asynchronous computer-based treatment delivered remotely with clinician oversight to people with aphasia.	A web-based TR application – Web ORLA® (Oral Reading for Language in Aphasia) which provides repeated choral and independent reading aloud of sentences with a virtual therapist. 90 min per day, 6 days per week for 6 weeks	Comparison: commercially available computer games. Measures: Western Aphasia Battery; Communicative Abilities in Daily Living Test.	Improved language outcomes following intensive, web-based delivery of ORLA® to individuals with chronic aphasia.
62 post-stroke patients with aphasia (59)	To study effects of augmented rehabilitation via TR for speech-language disorders	TR via videoconference in addition to usual care. 5 h per week for 4 weeks.	Comparison: usual care alone. Measures: Norwegian Basic Aphasia Assessment, Verb and Sentence Test score.	TR via videoconference may be a viable rehabilitation model. But additional TR training has no additional gains.

With additions of remote control and extensive safety mechanisms, ES devices have potential to be used in TR more frequently. To address the lack of physical exam and accuracy in TR, wearable sensors can be used to acquire a variety of parameters of patients and to monitor their health conditions and activities (69, 70). Thus, healthcare professionals can detect adverse effects during TR and make better intervention plans.

With further development of technologies, fully digitalized TR system may be possible. TR-based interventions, which combine serious games, immersive VR, rehabilitation robots and various sensors, have possibility to achieve better outcomes. Patients' data can be collected with sensors and analyzed though machine learning approach. Traditional measures for evaluating intervention outcomes, such as Berg balance scale, can be performed automatically with proper devices (71, 72). Besides technology aspects, new TR models should also be considered. Community health workers and caregivers have received much attention (73, 74), but their roles in TR were not fully explored. They can serve as a bridge between healthcare professionals and patients to overcome certain communication-related issues and technical barriers. Overall speaking, TR is still in its developing stage, and further studies are needed to provide evidence for optimal use of TR.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1234003/full#supplementary-material

References

1. Owolabi MO, Thrift AG, Mahal A, Ishida M, Martins S, Johnson WD, et al. Primary stroke prevention worldwide: translating evidence into action. *Lancet Public Health*. (2022) 7:e74–85. doi: 10.1016/S2468-2667(21)00230-9

2. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res*. (2017) 120:439–48. doi: 10.1161/CIRCRESAHA.116.308413

3. Warlow CP. Epidemiology of stroke. *Lancet*. (1998) 352:S1. doi: 10.1016/S0140-6736(98)90086-1

4. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

5. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, et al. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst Rev*. (2014) 2014:Cd001920. doi: 10.1002/14651858.CD001920.pub3

6. Kuriakose D, Xiao ZC. Pathophysiology and treatment of stroke: present status and future perspectives. *Int J Mol Sci*. (2020) 21:7609. doi: 10.3390/ijms21207609

7. Ostrowska PM, Śliwiński M, Studnicki R, Hansdorfer-Korzon R. Telerehabilitation of post-stroke patients as a therapeutic solution in the era of the Covid-19 pandemic. *Healthcare*. (2021) 9:654. doi: 10.3390/healthcare9060654

8. Boyd LA, Hayward KS, Ward NS, Stinear CM, Rosso C, Fisher RJ, et al. Biomarkers of stroke recovery: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *Int J Stroke*. (2017) 12:480–93. doi: 10.1177/1747493017714176

9. Winters JM. Telerehabilitation research: emerging opportunities. *Annu Rev Biomed Eng*. (2002) 4:287–320. doi: 10.1146/annurev.bioeng.4.112801.121923

10. Laver KE, Adey-Wakeling Z, Crotty M, Lannin NA, George S, Sherrington C. Telerehabilitation services for stroke. *Cochrane Database Syst Rev*. (2020) 1:Cd010255. doi: 10.1002/14651858.CD010255.pub3

11. Shem K, Irgens I, Alexander M. Chapter 2—getting started: mechanisms of telerehabilitation In: M Alexander, editor. *Telerehabilitation*. New Delhi: Elsevier (2022). 5–20.

12. Digital Technologies, Web and Social Media Study Group of the Italian Society of NeurologyIodice F, Romoli M, Giometto B, Clerico M, Tedeschi G, et al. Stroke and digital technology: a wake-up call from COVID-19 pandemic. *Neurol Sci*. (2021) 42:805–9. doi: 10.1007/s10072-020-04993-3

13. Prvu Bettger J, Resnik LJ. Telerehabilitation in the age of COVID-19: an opportunity for learning health system research. *Phys Ther*. (2020) 100:1913–6. doi: 10.1093/ptj/pzaa151

14. Moulaei K, Sheikhtaheri A, Nezhad MS, Haghdoost AA, Gheysari M, Bahaadinbeigy K. Telerehabilitation for upper limb disabilities: a scoping review on functions, outcomes, and evaluation methods. *Arch Public Health*. (2022) 80:196. doi: 10.1186/s13690-022-00952-w

15. Hao J, Pu Y, Chen Z, Siu KC. Effects of virtual reality-based telerehabilitation for stroke patients: a systematic review and meta-analysis of randomized controlled trials. *J Stroke Cerebrovasc Dis*. (2023) 32:106960. doi: 10.1016/j.jstrokecerebrovasdis.2022.106960

16. Neibling BA, Jackson SM, Hayward KS, Barker RN. Perseverance with technology-facilitated home-based upper limb practice after stroke: a systematic mixed studies review. *J Neuroeng Rehabil*. (2021) 18:43. doi: 10.1186/s12984-021-00819-1

17. Edwards D, Williams J, Carrier J, Davies J. Technologies used to facilitate remote rehabilitation of adults with deconditioning, musculoskeletal conditions, stroke, or traumatic brain injury: an umbrella review. *JBI Evid Synth*. (2022) 20:1927–68. doi: 10.11124/JBIES-21-00241

18. Krishnan G. Telerehabilitation: an overview. *Telehealth Med Today*. (2021) 6:285. doi: 10.30953/tmt.v6.285

19. Nikolaev VA, Nikolaev AA. Recent trends in telerehabilitation of stroke patients: a narrative review. *NeuroRehabilitation*. (2022) 51:1–22. doi: 10.3233/NRE-210330

20. Cha S, Chang WK, Cho HM, Jung YS, Kang M, Paik NJ, et al. The effect of a telephone-based intervention on physical activity after stroke. *PLoS One*. (2022) 17:e0276316. doi: 10.1371/journal.pone.0276316

21. Rochette A, Korner-Bitensky N, Bishop D, Teasell R, White CL, Bravo G, et al. The YOU CALL-WE CALL randomized clinical trial: impact of a multimodal support intervention after a mild stroke. *Circ Cardiovasc Qual Outcomes*. (2013) 6:674–9. doi: 10.1161/CIRCOUTCOMES.113.000375

22. Wan LH, Zhang XP, Mo MM, Xiong XN, Ou CL, You LM, et al. Effectiveness of goal-setting telephone follow-up on health Behaviors of patients with ischemic stroke: a randomized controlled trial. *J Stroke Cerebrovasc Dis*. (2016) 25:2259–70. doi: 10.1016/j.jstrokecerebrovasdis.2016.05.010

23. Li L, Huang J, Wu J, Jiang C, Chen S, Xie G, et al. A Mobile health app for the collection of functional outcomes after inpatient stroke rehabilitation: pilot randomized controlled trial. *JMIR Mhealth Uhealth*. (2020) 8:e17219. doi: 10.2196/17219

24. Eng JJ, Pastva AM. Advances in remote monitoring for stroke recovery. *Stroke*. (2022) 53:2658–61. doi: 10.1161/STROKEAHA.122.038885

25. Asano M, Tai BC, Yeo FYT, Yen SC, Tay A, Ng YS, et al. Home-based tele-rehabilitation presents comparable positive impact on self-reported functional outcomes as usual care: the Singapore tele-technology aided rehabilitation in stroke (STARS) randomised controlled trial. *J Telemed Telecare*. (2021) 27:231–8. doi: 10.1177/1357633X19868905

26. Nasrabadi AM, Eslaminia AR, Bakhshayesh PR, Ejtehadi M, Alibiglou L, Behzadipour S. A new scheme for the development of IMU-based activity recognition systems for telerehabilitation. *Med Eng Phys*. (2022) 108:103876. doi: 10.1016/j.medengphy.2022.103876

27. Campagnini S, Arienti C, Patrini M, Liuzzi P, Mannini A, Carrozza MC. Machine learning methods for functional recovery prediction and prognosis in post-stroke rehabilitation: a systematic review. *J Neuroeng Rehabil*. (2022) 19:54. doi: 10.1186/s12984-022-01032-4

28. Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. *Lancet Neurol*. (2020) 19:348–60. doi: 10.1016/S1474-4422(19)30415-6

29. Lee HS, Lim JH, Jeon BH, Song CS. Non-immersive virtual reality rehabilitation applied to a task-oriented approach for stroke patients: a randomized controlled trial. *Restor Neurol Neurosci*. (2020) 38:165–72. doi: 10.3233/RNN-190975

30. Rozevink SG, van der Sluis CK, Garzo A, Keller T, Hijmans JM. HoMEcare aRm rehabiLItatioN (MERLIN): telerehabilitation using an unactuated device based on serious games improves the upper limb function in chronic stroke. *J Neuroeng Rehabil*. (2021) 18:48. doi: 10.1186/s12984-021-00841-3

31. Cheung VCK, Niu CM, Li S, Xie Q, Lan N. A novel FES strategy for poststroke rehabilitation based on the natural organization of neuromuscular control. *IEEE Rev Biomed Eng*. (2019) 12:154–67. doi: 10.1109/RBME.2018.2874132

32. Veldema J, Gharabaghi A. Non-invasive brain stimulation for improving gait, balance, and lower limbs motor function in stroke. *J Neuroeng Rehabil*. (2022) 19:84. doi: 10.1186/s12984-022-01062-y

33. Lee JH, Baker LL, Johnson RE, Tilson JK. Effectiveness of neuromuscular electrical stimulation for management of shoulder subluxation post-stroke: a systematic review with meta-analysis. *Clin Rehabil*. (2017) 31:1431–44. doi: 10.1177/0269215517700696

34. Andreopoulou G, Busselli G, Street T, Bulley C, Safari R, van der Linden ML, et al. Is functional electrical stimulation effective in improving walking in adults with lower limb impairment due to an upper motor neuron lesion? An umbrella review. *Artif Organs*. (2023). doi: 10.1111/aor.14563

35. Hermann VH, Herzog M, Jordan R, Hofherr M, Levine P, Page SJ. Telerehabilitation and electrical stimulation: an occupation-based, client-centered stroke intervention. *Am J Occup Ther*. (2010) 64:73–81. doi: 10.5014/ajot.64.1.73

36. Ko MH, Yoon JY, Jo YJ, Son MN, Kim DS, Kim GW, et al. Home-based transcranial direct current stimulation to enhance cognition in stroke: randomized controlled trial. *Stroke*. (2022) 53:2992–3001. doi: 10.1161/STROKEAHA.121.037629

37. Kim WS, Kwon BS, Seo HG, Park J, Paik NJ. Low-frequency repetitive transcranial magnetic stimulation over Contralesional motor cortex for motor recovery in subacute ischemic stroke: a randomized sham-controlled trial. *Neurorehabil Neural Repair*. (2020) 34:856–67. doi: 10.1177/1545968320948610

38. Xi X, Wang H, Han L, Ding M, Li J, Qiao C, et al. Meta-analysis of repetitive transcranial magnetic stimulation combined with task-oriented training on upper limb function in stroke patients with hemiplegia. *Medicine*. (2023) 102:e33771. doi: 10.1097/MD.0000000000033771

39. Kim J, Thayabaranathan T, Donnan GA, Howard G, Howard VJ, Rothwell PM, et al. Global stroke statistics 2019. *Int J Stroke*. (2020) 15:819–38. doi: 10.1177/1747493020909545

40. Cramer SC, Dodakian L, le V, See J, Augsburger R, McKenzie A, et al. Efficacy of home-based telerehabilitation vs in-clinic therapy for adults after stroke: a randomized clinical trial. *JAMA Neurol*. (2019) 76:1079–87. doi: 10.1001/jamaneurol.2019.1604

41. Edwards D, Kumar S, Brinkman L, Ferreira IC, Esquenazi A, Nguyen T, et al. Telerehabilitation initiated early in post-stroke recovery: a feasibility study. *Neurorehabil Neural Repair*. (2023) 37:131–41. doi: 10.1177/15459683231159660

42. Szturm T, Imran Z, Pooyania S, Kanitkar A, Mahana B. Evaluation of a game based tele rehabilitation platform for in-home therapy of hand-arm function post stroke: feasibility study. *PM R*. (2021) 13:45–54. doi: 10.1002/pmrj.12354

43. Bressi F, Campagnola B, Cricenti L, Santacaterina F, Miccinilli S, di Pino G, et al. Upper limb home-based robotic rehabilitation in chronic stroke patients: a pilot study. *Front Neurorobot*. (2023) 17:1130770. doi: 10.3389/fnbot.2023.1130770

44. Hu J, Zou J, Wan Y, Yao Q, Dong P, Li G, et al. Rehabilitation of motor function after stroke: a bibliometric analysis of global research from 2004 to 2022. *Front Aging Neurosci*. (2022) 14:1024163. doi: 10.3389/fnagi.2022.1024163

45. Held JP, Ferrer B, Mainetti R, Steblin A, Hertler B, Moreno-Conde A, et al. Autonomous rehabilitation at stroke patients home for balance and gait: safety, usability and compliance of a virtual reality system. *Eur J Phys Rehabil Med*. (2018) 54:545–53. doi: 10.23736/S1973-9087.17.04802-X

46. Lin KH, Chen CH, Chen YY, Huang WT, Lai JS, Yu SM, et al. Bidirectional and multi-user telerehabilitation system: clinical effect on balance, functional activity, and satisfaction in patients with chronic stroke living in long-term care facilities. *Sensors*. (2014) 14:12451–66. doi: 10.3390/s140712451

47. Lim H, Marjanovic N, Luciano C, Madhavan S. Feasibility and acceptability of game-based cortical priming and functional lower limb training in a remotely supervised home setting for chronic stroke: a case series. *Front Rehabil Sci*. (2022) 3:775496. doi: 10.3389/fresc.2022.775496

48. Saywell NL, Vandal AC, Mudge S, Hale L, Brown P, Feigin V, et al. Telerehabilitation after stroke using readily available technology: a randomized controlled trial. *Neurorehabil Neural Repair*. (2021) 35:88–97. doi: 10.1177/1545968320971765

49. Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: still an incomplete picture. *Int J Stroke*. (2013) 8:38–45. doi: 10.1111/j.1747-4949.2012.00972.x

50. Faria AL, Pinho MS, Bermúdez i Badia S. A comparison of two personalization and adaptive cognitive rehabilitation approaches: a randomized controlled trial with chronic stroke patients. *J Neuroeng Rehabil*. (2020) 17:78. doi: 10.1186/s12984-020-00691-5

51. Torrisi M, Maresca G, de Cola MC, Cannavò A, Sciarrone F, Silvestri G, et al. Using telerehabilitation to improve cognitive function in post-stroke survivors: is this the time for the continuity of care? *Int J Rehabil Res*. (2019) 42:344–51. doi: 10.1097/MRR.0000000000000369

52. Lawson DW, Stolwyk RJ, Ponsford JL, McKenzie DP, Downing MG, Wong D. Telehealth delivery of memory rehabilitation following stroke. *J Int Neuropsychol Soc*. (2020) 26:58–71. doi: 10.1017/S1355617719000651

53. Bernini S, Panzarasa S, Sinforiani E, Quaglini S, Cappa SF, Cerami C, et al. HomeCoRe for telerehabilitation in mild or major neurocognitive disorders: a study protocol for a randomized controlled trial. *Front Neurol*. (2021) 12:752830. doi: 10.3389/fneur.2021.752830

54. Bernini S, Panzarasa S, Quaglini S, Costa A, Picascia M, Cappa SF, et al. HomeCoRe system for telerehabilitation in individuals at risk of dementia: a usability and user experience study. *Front Med*. (2023) 10:1129914. doi: 10.3389/fmed.2023.1129914

55. Doogan C, Dignam J, Copland D, Leff A. Aphasia recovery: when, how and who to treat? *Curr Neurol Neurosci Rep*. (2018) 18:90. doi: 10.1007/s11910-018-0891-x

56. Meltzer JA, Baird AJ, Steele RD, Harvey SJ. Computer-based treatment of poststroke language disorders: a non-inferiority study of telerehabilitation compared to in-person service delivery. *Aphasiology*. (2018) 32:290–311. doi: 10.1080/02687038.2017.1355440

57. Maresca G, Maggio MG, Latella D, Cannavò A, de Cola MC, Portaro S, et al. Toward improving poststroke aphasia: a pilot study on the growing use of telerehabilitation for the continuity of care. *J Stroke Cerebrovasc Dis*. (2019) 28:104303. doi: 10.1016/j.jstrokecerebrovasdis.2019.104303

58. Cherney LR, Lee JB, Kim KYA, van Vuuren S. Web-based Oral Reading for language in aphasia (web ORLA(®)): a pilot randomized control trial. *Clin Rehabil*. (2021) 35:976–87. doi: 10.1177/0269215520988475

59. Øra HP, Kirmess M, Brady MC, Partee I, Hognestad RB, Johannessen BB, et al. The effect of augmented speech-language therapy delivered by telerehabilitation on poststroke aphasia-a pilot randomized controlled trial. *Clin Rehabil*. (2020) 34:369–81. doi: 10.1177/0269215519896616

60. Øra HP, Kirmess M, Brady MC, Sørli H, Becker F. Technical features, feasibility, and acceptability of augmented telerehabilitation in post-stroke aphasia-experiences from a randomized controlled trial. *Front Neurol*. (2020) 11:671. doi: 10.3389/fneur.2020.00671

61. Brady MC, Kelly H, Godwin J, Enderby P, Campbell PCochrane Stroke Group. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev*. (2016) 2016:Cd000425. doi: 10.1002/14651858.CD000425.pub4

62. Hota S, Inamoto Y, Oguchi K, Kondo T, Otaka E, Mukaino M, et al. Outcomes of dysphagia following stroke: factors influencing Oral intake at 6 months after onset. *J Stroke Cerebrovasc Dis*. (2021) 30:105971. doi: 10.1016/j.jstrokecerebrovasdis.2021.105971

63. Kantarcigil C, Kim MK, Chang T, Craig BA, Smith A, Lee CH, et al. Validation of a novel wearable electromyography patch for monitoring submental muscle activity during swallowing: a randomized crossover trial. *J Speech Lang Hear Res*. (2020) 63:3293–310. doi: 10.1044/2020_JSLHR-20-00171

64. Kirkness CJ, Cain KC, Becker KJ, Tirschwell DL, Buzaitis AM, Weisman PL, et al. Randomized trial of telephone versus in-person delivery of a brief psychosocial intervention in post-stroke depression. *BMC Res Notes*. (2017) 10:500. doi: 10.1186/s13104-017-2819-y

65. SteelFisher GK, McMurtry CL, Caporello H, Lubell KM, Koonin LM, Neri AJ, et al. Video telemedicine experiences in COVID-19 were positive, but physicians and patients prefer in-person care for the future. *Health Aff*. (2023) 42:575–84. doi: 10.1377/hlthaff.2022.01027

66. Liu Y, Guo S, Yang Z, Hirata H, Tamiya T. A home-based tele-rehabilitation system with enhanced therapist-patient remote interaction: a feasibility study. *IEEE J Biomed Health Inform*. (2022) 26:4176–86. doi: 10.1109/JBHI.2022.3176276

67. Berton A, Longo UG, Candela V, Fioravanti S, Giannone L, Arcangeli V, et al. Virtual reality, augmented reality, gamification, and telerehabilitation: psychological impact on Orthopedic Patients' rehabilitation. *J Clin Med*. (2020) 9:2567. doi: 10.3390/jcm9082567

68. Chung J, Kim CT, Lee J, Lee E, Jung KI, Yoo WK, et al. Factors affecting participation in telerehabilitation using transcranial direct current stimulation for patients with poststroke paralysis in South Korea. *Telemed J E Health*. (2023). doi: 10.1089/tmj.2022.0452

69. Malik AN, Tariq H, Afridi A, Rathore FA. Technological advancements in stroke rehabilitation. *J Pak Med Assoc*. (2022) 72:1672–4. doi: 10.47391/JPMA.22-90

70. Langerak AJ, Regterschot GRH, Selles RW, Meskers CGM, Evers M, Ribbers GM, et al. Requirements for home-based upper extremity rehabilitation using wearable motion sensors for stroke patients: a user-centred approach. *Disabil Rehabil Assist Technol*. (2023):1–13. doi: 10.1080/17483107.2023.2183993

71. Dubois A, Mouthon A, Sivagnanaselvam RS, Bresciani JP. Fast and automatic assessment of fall risk by coupling machine learning algorithms with a depth camera to monitor simple balance tasks. *J Neuroeng Rehabil*. (2019) 16:71. doi: 10.1186/s12984-019-0532-x

72. Lin BS, Zhang Z, Peng CW, Lin CC, Lin CH, Lin BS. Automatic assessment system based on IMUs and machine learning for predicting berg balance scale. *IEEE Sensors J*. (2022) 22:19919–30. doi: 10.1109/JSEN.2022.3200986

73. Bhattacharjya S, Lenker J, Ghosh R. Assessing the usefulness of an mHealth strategy to support implementation of multi-faceted adaptive feeding interventions by community-based rehabilitation workers. *Assist Technol*. (2023) 35:228–34. doi: 10.1080/10400435.2022.2028936

74. Vloothuis JDM, Mulder M, Nijland RHM, Goedhart QS, Konijnenbelt M, Mulder H, et al. Caregiver-mediated exercises with e-health support for early supported discharge after STROKE (CARE4STROKE): a randomized controlled trial. *PLoS One*. (2019) 14:e0214241. doi: 10.1371/journal.pone.0214241

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Web-based psychoeducational interventions for managing cognitive impairment–a systematic review

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Objective: Web-based rehabilitation, a branch of telerehabilitation, is carried out over the internet, unrestricted by time or place. Even though web-based interventions have been reported as feasible and effective in cases of mood disorders, for example, such evidence on the effectiveness of web-based cognitive rehabilitation remains unclear. This systematic review summarizes current knowledge on web-based psychoeducational programs aiming to manage cognitive deficits in patients with diseases that affect cognition.

Methods: Using the Ovid database and the Web of Science, we systematically searched the Cochrane Database of Systematic Reviews, Medline, and PsycINFO to identify eligible studies. The review protocol (CRD42021257315) was pre-registered with the PROSPERO International Prospective Register of Systematic Reviews. The search was performed 10/13/2022. Two reviewers independently screened titles, abstracts, and full-texts, and extracted data for the selected studies. Two independent reviewers assessed the methodological quality.

Results: The search retrieved 6,487 articles. Four studies with different patient groups (stroke, traumatic brain injury, brain tumor, and cancer) met the inclusion criteria of this systematic review. The studies examined systematic cognition-focused psychoeducational rehabilitation programs in which the patient worked independently. Three studies found positive effects on subjective cognitive functions, executive functions, and self-reported memory. No effects were found on objective cognitive functions. However, the studies had methodological weaknesses (non-randomized designs, small sample sizes, vaguely described interventions). Overall, adherence and patient satisfaction were good/excellent.

Conclusion: Web-based cognitive intervention programs are a new approach to rehabilitation and patient education. The evidence, although scarce, shows that web-based interventions are feasible and support subjective cognitive functioning. However, the literature to date is extremely limited and the quality of the studies is weak. More research with high-quality study designs is needed.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=257315, identifier: CRD42021257315.

KEYWORDS

web-based, cognition, psychoeducation, rehabilitation, telerehabilitation, systematic review

1. Introduction

Digitalized health care services have the advantage of providing patients with access to treatment, irrespective of time and place (1–3). Web-based rehabilitation, a branch of telerehabilitation, is carried out at a patient's home over the internet. Online platforms and secure network connections also offer a new way to deliver cognitive and neuropsychological rehabilitation. The potential advantages of telerehabilitation in clinical practice are the possibility to offer services to larger population, reduce waiting times and to personalize rehabilitation but also to be cost-effectiveness (4). Still, the traditional way of carrying out neuropsychological rehabilitation is face-to-face at inpatient or outpatient clinics, but these services are regionally uneven and insufficient (5, 6).

Managing cognitive impairment in neurological disorders often requires intensive neuropsychological rehabilitation to improve cognitive functions as well as emotional and psychosocial wellbeing. A significant proportion of stroke patients show cognitive impairment despite good clinical recovery (7) and cognitive symptoms are also common after traumatic brain injury and encephalitis (8, 9). Rehabilitation for cognitive impairment has shown to be effective after brain injuries (10), and psychoeducation and compensatory strategy training (training of sets of conscious mental processes and techniques to compensate cognitive deficiencies) have been found to be the most efficient approaches for rehabilitation (11–13). Cognitive training (practice on a set of tasks designed to reflect particular cognitive functions) is also a common approach in cognitive rehabilitation, especially in online programs (14). Despite some near-transfer effect of attention and working memory training far-transfer and long-time effects of cognitive training are considered poor (15–17).

Psychoeducational framework is an established and essential approach originating from psychosocial treatment of psychiatry broadened to somatic diseases to provide support and information on the condition of patients and aims to improve functional abilities, mood, and quality of life (18, 19). Neurological patients benefit from sharing knowledge about symptoms, recovery, and symptom management (12, 20–22) and even patients with minor strokes have expressed the need for it after discharge (23). Information about stroke not only increases patients' understanding of the condition and its effects, but also enhances patients' contentment and diminishes depressive symptoms (21). Patients with mild cognitive symptoms also benefit from metacognitive and memory strategy training (11) and patients with mild traumatic brain injury cognitive strategy training was related to positive behavioral changes and better subjective and objective cognitive performance (24).

Considering the overlap and variety of the terminology in literature, in this review neuropsychological and cognitive rehabilitation is referred as broad neurocognitive rehabilitation. The interest in this study is in the neuropsychological or cognitive interventions combining psychoeducation (sharing knowledge) with cognitive strategy training (compensatory strategy training) leaving cognitive training interventions (practicing particular functions, "brain training") outside when being the only approach of the intervention.

To date, the knowledge about structured web-based cognitive intervention programs, including psychoeducation and cognitive strategy training, is still scattered; only a few, mainly small-scale feasibility studies have been reported and deemed applicable to neurological patients (25–28). Web-based programs are also used to teach neurological patients self-management, but evidence of their effectiveness is limited (29). Web-based intervention programs have become evidence-based treatments for mood disorders (30), and have also been used for motor rehabilitation after stroke, for example (31). Yet, the effectiveness of cognitive or neuropsychological online rehabilitation programs is unclear.

The aim of this study was to systematically review the current knowledge on the effectiveness and feasibility of web-based psychoeducational interventions among adolescent and adult patients whose cognitive functions are affected by a somatic health condition.

2. Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (32). The review protocol (CRD42021257315) was pre-registered with the PROSPERO International Prospective Register of Systematic Reviews.

We used a PICO (population, intervention, comparison, outcome) framework to formulate the study design and search strategy. We asked: In adolescent or adult patients whose cognition is affected by a somatic health condition (P), are web-based psychoeducational interventions (I), in comparison to other interventions or no intervention at all (C), feasible and effective in improving subjective and/or objective cognitive functioning (O)? The search was targeted at adolescents or adults participating in a psychoeducational cognitive program or an intervention delivered remotely online and carried out independently by the patient. Subjective cognitive complaints, as evaluated by the patient's self-report (subjective cognitive functioning) and/or objective cognitive functions, as defined by performance in neuropsychological tests (objective cognitive functioning), were considered an outcome. We also considered data on adherence and program acceptability/feasibility.

2.1. Eligibility criteria

The trials were selected if they met the following criteria: (1) The intervention program was structured, delivered over the internet, and carried out by the patient independently; (2) The program focused on cognitive impairment; (3) The program included psychoeducation and cognitive strategic skill training; (4) The age group was from adolescence to working-aged participants; (5) The participants had a somatic health condition that affected their cognition; (6) The outcome was subjective and/or objective cognitive functioning.

Exclusion criteria were as follows: (1) The participants had a progressive neurodegenerative condition; (2) Solely cognitive training as approach; (3) The article was written in a language other

than English; (4) Studies reported only the perspectives of health-care professionals or the future development of technology; (5) Studies reported only the feasibility of the programs.

Considering the novelty of the research field, no limitations were applied to sample sizes or study design, although we did primarily search for randomized controlled studies (RCTs). In addition to RCTs, we also included observational studies and single, one-arm studies without control groups. However, study protocol papers and case studies were excluded, as were abstracts and conference papers.

2.2. Information sources

The search was conducted in MEDLINE®, PsycINFO, the Cochrane Database of Systematic Reviews databases using the Ovid database search and the Web of Science database. Additional studies were identified from the reference lists of the relevant studies and accessed via the Google Scholar database. The initial search was performed in May 2021 and repeated in September 2021 and April 2022. The date of the last search was 10/13/2022. The searches were not subject to any time restrictions.

2.3. Search strategy

The search consisted of terms describing cognition or neurology, telehealth technology, and rehabilitation {e.g., [(web-based, internet-based or digital) and (cogniti* or neuropsycholog* or memory) and (rehabilitation or program*)]}. The search strategy was adapted to the requirements of the databases searched. The full search strategy is included in Supplementary material. Search results were exported directly to EndNote X9 and duplicates were removed. We manually added additional identified records.

2.4. Selection process

The screening process is described in the PRISMA flow diagram in Figure 1. Author OV conducted the screening. The

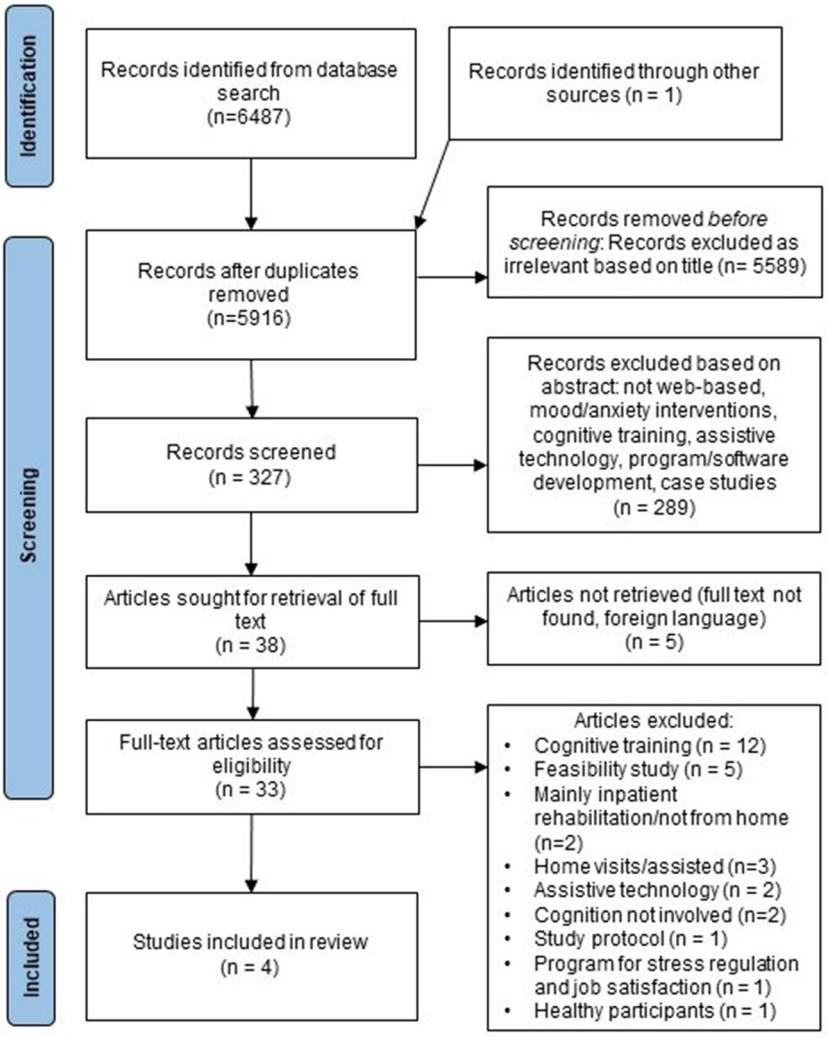

FIGURE 1
Flow chart of systematic review.

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titles of the identified papers were first reviewed for obvious exclusions. Abstracts were screened on the basis of their titles. If, after the abstract was read, it was unclear whether the article should be selected, the full text was reviewed. The selected full text articles were reviewed by authors OV and E-LK for eligible articles.

2.5. Quality assessment

Two reviewers (OV, E-LK) performed the quality assessment. Disagreements were discussed until consensus was reached. We applied the quality assessment tool created by Kallio et al. (33), which has previously been used to appraise research on cognitive training. In this rating system, the criteria is applied to randomized intervention trials used by Cochrane and collaborators (34) as well as the Delphi list (35), which is a criteria list for the quality assessment of randomized clinical trials.

The quality criteria are detailed in Table 1. Each criterion was worth 1 point. The methodological quality of the research was considered high when a study scored 8–10 points, while scores of 5–7 indicated moderate quality and scores <5 indicated low quality (24).

3. Results

3.1. Studies

The initial search returned 6,487 records. Thirty-three full-text articles were assessed for eligibility and the screening process identified four eligible articles (Figure 1). The reviewers (OV, ELK) were in full agreement on which studies met the inclusion criteria. Two studies were RCTs with wait-list control groups (38, 39), one was a quasi-experimental study with an active control group (37) and one was a single-arm study without a control group (36). Due to a lack of studies and the variability of the interventions, we were unable to perform a meta-analysis on this data.

3.2. Participants

Table 2 presents the characteristics of the studies selected by the review. They included 452 participants in total, with the numbers of participants varying from 13 (36) to 318 (37). In three studies the participants were adults (37–39), and in one study adolescents (36). The mean age of the study participants ranged from 14 to 63. The participants in the intervention groups were heterogenous by diagnosis: stroke (37), TBI (36), brain tumor (38), and cancer patients (39).

3.3. Interventions

In two studies (RCTs) the intervention protocol had been described in previous papers (28, 40). The interventions lasted 4–16 weeks, but the data on the frequencies of the sessions or the total

TABLE 1 Quality assessment.

Study	1: Randomization method is performed	2: Inclusion and exclusion criteria are satisfactorily described	3. Groups are comparable at baseline	4: The study has sufficient statistical power to detect an effect (n > 25/group)	5: The intervention is adequately described	6: The measurements and outcome measures are valid and well defined	7: Those assessing the outcomes were blinded to the treatment allocation	8: Outcomes of the dropouts are described, and the analysis takes them into account	9: Intention-to-treat (ITT) analysis is applied	10: Appropriate statistical analyses are used	Total criteria met
Babcock et al. (36) USA	-	+	-	-	+/-	+	-	-	n/a	+/-	2
Brouns et al. (37) The Netherlands	-	+	+	+	-	+	-	-	+	+	6
van der Linden et al. (38) The Netherlands	+	+	-	-	+/-	+	-	+	-	+/-	4
Mihuta et al. (39) Australia	+	+	+	+	+/-	+	-	+	+	+	8

+, Criterion fulfilled; +/-, criterion partly fulfilled; -, criterion not fulfilled.

Study	Intervention	Study design	Participants	Intervention methods	Assessments	Outcomes and effects	Adherence/ drop-out
Babcock et al. (36) USA	Smart 4 weeks, 8 modules Independently	Pre-post design, single arm study $N = 13$ adolescents + parent	Age 14.3 TBI (max 96 h from occurrence)	Symptom monitoring, activity tracking, skill training, feedback, psychoeducation	Baseline, follow-ups 1, 2, 4 weeks	Outcome (measure): *primary* symptom burden (HBI), functional disability (FDI), executive functioning (brief-BRIEF), *secondary* behavior problems (CBCL, YSR), concussion knowledge (CDC), symptom monitoring (PCSS) Effect: *primary* significant improvement in functional disability and executive functions [parent-rated FBI, 0.5 (1.2), $n = 11$, $p = 0.009$, parent-rated brief-BRIEF 31.8 (7.2), $n = 11$, $p = 0.03$], significant improvement in symptom burden [parent-rated HBI 7.9 (7.5), $n = 11$, $p = 0.004$, self-report HBI 9.7 (10.1), $n = 9$, $p = 0.0005$] *secondary* no significant changes	100/38%
Brouns et al. (37) The Netherlands	Fast@home 16 weeks, 4 modules Some independently, some assisted (not specified)	Quasi-experimental study $N = 318$ [IG $N = 165$ (eRehab addition to conventional rehabilitation), CG $= 54$] [conventional rehabilitation]	Age 62.6 (IG), 58.6 (CG) Stroke (max 6 m from occurrence)	Cognitive and physical exercises, activity tracking, psychoeducation	Baseline, follow-ups 3 + 6 m	Outcome (measure): *primary* disability (SIS) *secondary* quality of life (EQ5D), mental and physical health (SF-12), fatigue (FSS), self-management (PAM-13), participation (USER-P), physical activity (IPAQ-SF) Effect: *primary* significant improvement in communication [SIS IG: 88.9 (12.1), $n = 54$, CG: 87.4 (8.9), $n = 153$, $p = 0.019$], memory [SIS IG: 87.7 (11.5), $n = 54$ CG: 82.1 (10.3), $n = 153$, $p = 0.031$], meaningful activities [(only change scores reported) SIS IG: 16.2 (17.2), $n = 54$, CG: 1.6 (19.2), $n = 153$, $p = 0.040$], and physical strength [SIS IG: 69.2 (10.4), $n = 54$, CG:67.6 (22.4) $n = 153$, $p = 0.008$] at 6 m follow-up *secondary* no significant changes	n/a
van der Linden et al. (38) The Netherlands	ReMind 10 weeks, 6 modules Independently, telephone checkup every 2 weeks	RCT $N = 45$ [IG $N = 20$ CG $N = 25$ (wait list, no other rehabilitation)]	Age 45.7 (IG), 52.6 (CG) Brain tumor [low grade glioma, meningioma] (3 m after surgery)	Psychoeducation, strategy training, attention retraining	Baseline, follow-ups 3 + 9 m	Outcome (measure): *primary* objective cognitive performance (CNS VS, WAIS-III digit span, verbal fluency) *secondary* subjective cognitive functioning (CFQ), executive functions (BRIEF-A), fatigue (MFI-20), mood (HADS) *tertiary* enrolment, attrition, adherence, patient satisfaction Effect: *primary* no significant changes *secondary* no significant changes *tertiary* recruitment difficulties, patient satisfaction good/excellent	85–91/21%
Mihuta et al. (39) Australia	EReCog 4 weeks, 4 modules Independently	RCT $N = 76$ [IG $N = 40$ CG $N = 36$ (wait-list, no other rehabilitation)]	Age 55.1 (IG), 56.9 (CG) Cancer (96.9% breast cancer, primary treatment completed min. 6 m ago)	Strategy training, relaxation, exercises, discussion, psychoeducation	Baseline, follow-ups 4 w + 3 m	Outcome (measure): *primary* subjective cognitive functioning (FACT-cog-3) *secondary* additional subjective cognitive functioning (BAPM), objective cognitive functioning (WebNeuro), psychosocial wellbeing (KPDS, BIPQ, EORTC-QLQ-C30), program satisfaction Effect: *primary* non-significant trend in improving perceived cognitive impairment [IG: 50.5 (12.7), $n = 32$, GC: 48.2 (15.0), $n = 33$, $p = 0.089$] *secondary* significant reduction in self-reported prospective memory failures at post-treatment [IG: 1.78 (0.46), $n = 32$, GC: 1.79 (0.53), $n = 33$, $p < 0.05$] and 3 m follow-up [IG: 1.67 (0.52), $n = 32$, GC: 1.66 (0.50), $n = 33$, $p = 0.025$], program satisfaction good/excellent	87/13%

HBI, Health and Behavior Inventory (range 20–80, low score = better health/behavior); FDI, Functional Disability Inventory (range 0–60, low score = better functioning); Brief-BRIEF, 24-item Behavior Rating Inventory of Executive Functioning (range 24–72, low score = better behavior); CBCL, Child Behavioral Checklist (range 0–226, low score = better behavior); YSR, Youth Self Report (range 0–224, low score = better behavior); CDC Head's Up Concussion quiz (range 0–11, high score = better knowledge); PCSS, Post-concussion symptom scale (range 0–126, low score = better health); SIS, Stroke Impact Scale (range 0–100, high score = better performance); EQ5D, EuroQol-5D-3L (range 1–15, low score = better health); SF-12, Short-Form Health Survey (range 0–100, low score = better health); FSS, Fatigue Severity Scale (range 9–63, low score = better functioning); PAM-13, Patient Activation Measure Short Form 13 (0–100, low score = better self-management); USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation (range 0–100, low score = better participation); IPAQ-SF, International Physical Activity Questionnaire Short Form (range 0<, high score = better activity); CNS VS, Central Nervous System Vital Signs (standardized z-scores, range >-2, 5-2, 5<, high score = better performance); WAIS-III, Wechsler Adult Intelligence Scale 3rd version (standardized z-scores, range >-2, 5-2, 5<, high score = better performance); CFQ, The Cognitive Failure Questionnaire (range 0–100, low score = better functioning); BRIEF-A, Behavior Rating Inventory of Executive Function (range 0–100, low score = better behavior); MFI-20, Multidimensional Fatigue Inventory (range 20–100, low score = better functioning); HADS, Hospital Anxiety and Depression Scale (range 0–21, low score = better health); FACT-Cog-3, Functional Assessment of Cancer Therapy—Cognitive Scale (range 0–148, high score = better performance); BAPM, Brief Assessment of Prospective Memory (range 0–5, low score = better functioning); WebNeuro (standardized z-scores, range >-2, 5-2, 5<, high score = better performance); KPDS, Kessler Psychological Distress Scale (range 10–50, low score = better health); BIPQ, Brief Illness Perception Questionnaire (range 0–80, low score = better functioning); EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (range 0–100, high score = better quality of life).

duration of the interventions were lacking or unclearly described in all the studies.

As required by the inclusion criteria, psychoeducation was included in all the studied interventions, and it was combined with strategy training (38, 39), strategy exercises outside the program (36, 39), and cognitive training (37). In one study (27) the strategy training was fill-in exercises within the program. Execution or form of the strategy training or exercises in other studies was not reported (28, 30). Studies with exercises outside the program did not report if completing the exercises outside the program was monitored in some way (28, 30). A physical activity tracker, exercises (36, 37) and relaxation were also used (39).

All the studies described the contents of the interventions on a general level, and contents was divided into different themed modules. The availability of the modules varied. In one study, availability was dependent on symptom burden (36). In the study by Mihuta et al. (39), completing each module before continuing to the next was compulsory. In the study by Brouns et al. (37), the psychoeducation module was reportedly available to all the participants and the other modules (cognitive training, physical exercises) were tailored individually, although how this was done was not reported. One study did not report on the availability of the modules or contents (38). The intervention for adolescents was also open to their parents (36).

Two interventions were conducted independently, with reminder emails (36, 39). In one study, the researcher made telephone checkups every 2 weeks (38). One intervention was conducted alongside conventional rehabilitation and did not report on the therapist's role in the web-based intervention (37). Two interventions were used as an application on a tablet (37, 38), and the others via an internet website (36, 39).

3.4. Outcomes/effects

Table 2 presents all the outcome measures and effects. The main outcome measures were subjective cognitive functioning (36–39), objective cognitive functioning (38, 39) and psychological wellbeing (39). Symptom monitoring (36), fatigue (37, 38), and satisfaction with the program (38, 39) were also evaluated. One study of adolescent TBI patients also included parent-rated evaluation (36).

Some self-reported improvements were found in subjective cognitive functioning. The study of adolescent TBI patients reported a significant improvement after the intervention in self-reported measure of functional/physical abilities and parent-rated measure to assess executive functions (36). A study of stroke patients found significant improvement in self-reported stroke impact scale assessing communication, memory, and meaningful activities at 6-month follow-up (37). A significant reduction in self-reported measure of prospective memory failures at post-treatment and 3-month follow-up was found in a study of cancer patients (39). Same study reported also a non-significant trend in decreasing subjective perceived cognitive impairment (39).

No effects on objective cognitive performance were found post treatment (38, 39). However, one study found a significant difference in favor of the intervention in a computerized neuropsychological test battery 1 year after brain tumor surgery (38).

One study reported a significant decrease in adolescents' self-reported and parent-rated TBI symptom burden (36). No significant differences were found in fatigue (37, 38).

3.5. Adherence to and satisfaction with program

Completion rate of the web-based interventions was high in three studies; 85–100% of the participants who started the intervention program also completed it (36, 38, 39). The adherence to exercises was high (85–91%) in one study (27). One study did not report the adherence rate (37). Satisfaction with the program was described as good or excellent in two studies (27, 28) and participants' appreciation and satisfaction with web-based intervention was 7.7 on a 10-point scale in one study (39).

3.6. Quality assessment

As shown in Table 1, only one of the selected studies was rated as a high-quality study (39). One study were considered to be of moderate quality (37) and two studies to be low quality (36, 38). Two of the four studies were not RCTs and did not fulfill the intervention description criterion (36, 37). Notable methodological limitations were small sample sizes ($n < 25$/group) and the incomparability of the groups at baseline (36, 38). All the studies failed to meet the criteria with blinding.

4. Discussion

The aim of this systematic review was to collect and evaluate the current evidence on the effectiveness and feasibility of web-based psychoeducational interventions combined with cognitive strategy training for managing cognitive impairment.

Overall, to date, the literature on digitalized cognitive or neuropsychological rehabilitation is very limited and only four studies fulfilled the inclusion criteria. Two of these studies were RCTs (38, 39), one a quasi-experimental study (37) and one a single-arm study (36). The psychoeducational content of the interventions was commonly combined with cognitive strategy training (36, 38, 39). The studies were heterogeneous in terms of age, diagnosis, and design. The diversity and heterogeneity of the interventions and populations in selected studies may hinder the comparison.

Sporadic findings in this review suggest that web-based cognitive interventions may improve self-reported subjective cognitive functioning. At 6-month follow-up, the study of stroke patients showed self-evaluated improvement in communication, memory, and meaningful activities in favor of the intervention group (37). Patients with cognitive impairment after oncological treatment showed a significant reduction in self-reported prospective memory failures post treatment and 3-month follow-up (39). The TBI adolescents self-reported recovery of

functional/physical disability and executive functions parent-rated after the intervention (36). However, the study did not have a control group. Two studies indicated that some of the rehabilitation effects were maintained for longer thanks to the web-based intervention (37, 38).

On the basis of this review, the web-based interventions had no effects on objective cognitive functioning (neuropsychological test performance). However, in one study, at 9-month follow-up, fewer brain tumor participants showed cognitive impairment in the intervention group (38). The authors emphasized the uncertainty of the finding but cautiously propose that the intervention program had small beneficial effects (38).

Profound methodological problems were found in the quality of the designs of the selected studies (see Table 1). Only two studies were RCTs and only one of these was assessed as high quality. Most studies had small sample sizes and in all the studies the size of the intervention groups was under 54. In two studies, sampling was done through self-selection, which might result in biased selection—-as participants might be more motivated to take part in rehabilitation activities. Studies used self-reported outcome measures which might prone to bias to willingness to please. These might have led to an increased risk of positive findings. In addition, in some cases, information and precise descriptions of the interventions were lacking according to the Template for Intervention Description and Replication (TIDieR) checklist (41). The TIDieR checklist is recommended for use in intervention studies to describe the intervention for good reporting policy (42).

In addition to methodological issues, studies selected in this systematic review sets few notable limitations to larger scale conclusions. Due to data reported in the studies, moderation analysis and recommendations of populations benefitting from web-based interventions could not be made. There are also lack of comparison with other interventions which leaves unclear whether web-based rehabilitation programs are superior to other intervention approaches. Also, sustainability of the effects remains unclear only one study having over 6-month follow-up (27). In all, the ability to generalize from these studies remain dubious.

A few interesting studies arose that did not fulfill the inclusion criteria. A web-based program for cognitive aging of healthy adults (excluded for not having somatic condition affecting cognition) had small to moderate effects on the self-reported feeling of stability in memory functioning and locus of control over memory in an RCT study design (43). Participants also reported fewer cognitive mistakes, less worry about cognition and dementia, and better ability to cope with cognitive loads. EpilepsyJourney, a web-based program for adolescent epilepsy patients with cognitive symptoms and behavioral problems, was believed to improve executive functions and emotional and behavioral functioning in a pre-post design study (44). The program consisted of problem-solving interventions with psychoeducational modules and support from a health care professional via video (excluded for not carrying out independently). The results of these studies could be interpreted as parallel to the sporadic findings reported in this review.

In all, despite methodological flaws, the psychoeducational components of the interventions may have contributed to the increased feeling of control over subjective cognitive functioning and may have alleviated symptom-induced anxiety—the participants received reliable information about their cognition and how to manage cognitive deficits, which is believed to be effective and necessary among neurological patients (11–13, 23).

Although the evidence of the effectiveness of web-based interventions to date is scarce, in this review they were found to be a feasible approach to arranging cognitive rehabilitation, as in previous studies (26–28, 30). It seems that completion and adherence to web-based rehabilitation may be good or even excellent in patient groups with cognitive deficits. Web-based interventions were also considered to be safe, as no adverse outcomes of TBI symptoms were reported (36).

While this review followed robust methodology and a systematic search strategy to identify relevant trials, it does have limitations. We restricted our search to English language publications only, which may have excluded some relevant studies. Despite the voluminous search strategy, the search terms used might have led to the exclusion of some interesting studies due to the novelty of the field and the as-of-yet unestablished terminology related to telerehabilitation solutions. We also relied on published reports only, which may lead to publication bias.

Web-based interventions for neurological patients have several benefits. They have the potential to reach large populations and to be used widely—-accessibility and adherence is excellent and irrespective of time, and they can even be conducted at home (only a technical device with an internet connection is needed). As the aging of the population and shortage of health care resources increases, interventions carried out independently online will become more essential. Overall, the use of telerehabilitation services will increase in future healthcare, and thus we need evidence of their advantages and weaknesses. If proven to be effective, telerehabilitation services may also broaden the variety of neuropsychological interventions and have the potential to equalize regional differences, make rehabilitation more cost-effective (4), and reduce waiting times for rehabilitation services.

4.1. Conclusion

To our knowledge, this is the first systematic review on psychoeducational web-based intervention programs for cognitive deficits in patient populations with cognitive impairment due to an injury or a treatment that affects brain functions. According to the evidence of this review, it appears that adolescent and working-aged patients are able and willing to use web-based psychoeducational programs, and that these interventions may increase patients' sense of control over their cognitive functioning. However, research on intervention studies in telerehabilitation is only in its early stages and therefore evidence of its effectiveness is still very limited and weak. Well-designed web-based intervention studies are crucial for increasing the evidence-base of this new research area, which is extremely contemporary and cautiously promising.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

OV: drafting the manuscript. OV, E-LK, AW, and HJ: writing the final version. E-LK, AW, HJ, and MH: supervision. OV and E-LK: selection of studies and quality assessment of studies. All authors: conception of the manuscript. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1249995/full#supplementary-material

References

1. Betts S, Feichter L, Kleinig Z, O'Connell-Debais A, Thai H, Wong C, et al. Telerehabilitation versus standard care for improving cognitive function and quality of life for adults with traumatic brain injury: a systematic review. *Internet J Allied Health Sci Pract.* (2018) 16:16. doi: 10.46743/1540-580X/2018.1753

2. Laver KE, Adey-Wakeling Z, Crotty M, Lannin NA, George S, Sherrington C. Telerehabilitation services for stroke. *Cochrane Database Syst Rev.* (2020) 1:CD010255. doi: 10.1002/14651858.CD010255.pub3

3. Tchero H, Tabue Teguo M, Lannuzel A, Rusch E. Telerehabilitation for stroke survivors: systematic review and meta-analysis. *J Med Internet Res.* (2018) 20:e10867. doi: 10.2196/10867

4. Lloréns R, Noé E, Colomer C, Alcañiz M. Effectiveness, usability, and cost-benefit of a virtual reality-based telerehabilitation program for balance recovery after stroke: a randomized controlled trial. *Arch Phys Med Rehabil.* (2015) 96:418–25.e2. doi: 10.1016/j.apmr.2014.10.019

5. Chimatiro GL, Rhoda AJ. Scoping review of acute stroke care management and rehabilitation in low and middle-income countries. *BMC Health Serv Res.* (2019) 19:789. doi: 10.1186/s12913-019-4654-4

6. Kasten E, Barbosa F, Kosmidis MH, Persson BA, Constantinou M, Baker GA, et al. European clinical neuropsychology: role in healthcare and access to neuropsychological services. *Healthcare*. (2021) 9:734. doi: 10.3390/healthcare9060734

7. Jokinen H, Melkas S, Ylikoski R, Pohjasvaara T, Kaste M, Erkinjuntti T, et al. Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol.* (2015) 22:1288–94. doi: 10.1111/ene.12743

8. McKeon GL, Robinson GA, Ryan AE, Blum S, Gillis D, Finke C, et al. Cognitive outcomes following anti-N-methyl-D-aspartate receptor encephalitis: a systematic review. *J Clin Exp Neuropsychol.* (2018) 40:234–52. doi: 10.1080/13803395.2017.1329408

9. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am.* (2014) 37:1–11. doi: 10.1016/j.psc.2013.11.004

10. van Heugten C, Gregório GW, Wade D. Evidence-based cognitive rehabilitation after acquired brain injury: a systematic review of content of treatment. *Neuropsychol Rehabil.* (2012) 22:653–73. doi: 10.1080/09602011.2012.680891

11. Cicerone KD, Goldin Y, Ganci K, Rosenbaum A, Wethe JV, Langenbahn DM, et al. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Phys Med Rehabil.* (2019) 100:1515–33. doi: 10.1016/j.apmr.2019.02.011

12. Turner-Stokes L, Pick A, Nair A, Disler PB, Wade DT. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. *Cochrane Database Syst Rev.* (2015) 2015:Cd004170. doi: 10.1002/14651858.CD004170.pub3

13. Wilson B, Winegardner J, van Heugten C, Ownsworth T. *Neuropsychological Rehabilitation: The International Handbook (1st ed.)*. London (GB): Routledge (2017). doi: 10.4324/9781315629537

14. Cacciante L, Pietà CD, Rutkowski S, Cieślik B, Szczepańska-Gieracha J, Agostini M, et al. Cognitive telerehabilitation in neurological patients: systematic review and meta-analysis. *Neurolo Sci.* (2022) 43:847–62. doi: 10.1007/s10072-021-05770-6

15. Melby-Lervåg M, Hulme C. Is working memory training effective? a meta-analytic review. *Dev Psychol.* (2013) 49:270–91. doi: 10.1037/a0028228

16. Cortese S, Ferrin M, Brandeis D, Buitelaar J, Daley D, Dittmann RW, et al. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry.* (2015) 54:164–74. doi: 10.1016/j.jaac.2014.12.010

17. Lindeløv JK, Dall JO, Kristensen CD, Aagesen MH, Olsen SA, Snuggerud TR, et al. Training and transfer effects of N-back training for brain-injured and healthy subjects. *Neuropsychol Rehabil.* (2016) 26:895–909. doi: 10.1080/09602011.2016.1141692

18. de Souza Tursi MF, von Werne Baes C, de Barros Camacho FR, de Carvalho Tofoli SM, Juruena MF. Effectiveness of psychoeducation for depression: a systematic review. *Aust N Z J Psychiatry.* (2013) 47:1019–31. doi: 10.1177/0004867413491154

19. Lukens EP, McFarlane WR. Psychoeducation as evidence-based practice: considerations for practice, research, and policy. *Brief Treat Crisis Interv.* (2004) 4:205–25. doi: 10.1093/brief-treatment/mhh019

20. Caplain S, Chenuc G, Blancho S, Marque S, Aghakhani N. Efficacy of psychoeducation and cognitive rehabilitation after mild traumatic brain injury for preventing post-concussional syndrome in individuals with high risk of poor prognosis: a randomized clinical trial. *Front Neurol.* (2019) 10:929. doi: 10.3389/fneur.2019.00929

21. Forster A, Brown L, Smith J, House A, Knapp P, Wright JJ, et al. Information provision for stroke patients and their caregivers. *Cochrane Database Syst Rev.* (2012) 11:Cd001919. doi: 10.1002/14651858.CD001919.pub3

22. Kontou E, Kettlewell J, Condon L, Thomas S, Lee AR, Sprigg N, et al. A scoping review of psychoeducational interventions for people after transient ischemic attack and minor stroke. *Top Stroke Rehabil.* (2021) 28:390–400. doi: 10.1080/10749357.2020.1818473

23. Kjærhauge Christiansen L, Rasmussen AM, Mouritzen HS, Østervig Buus AA, Grønkjær M. Quickly home again: patients' experiences of early discharge after minor stroke. *Scand J Caring Sci.* (2021) 35:1187–95. doi: 10.1111/scs.12937

24. Caplan B, Bogner J, Brenner L, Storzbach D, Twamley EW, Roost MS, et al. Compensatory cognitive training for operation enduring freedom/operation iraqi freedom/operation new dawn veterans with mild traumatic brain injury. *J Head Trauma Rehabil.* (2017) 32:16–24. doi: 10.1097/HTR.0000000000000228

25. Bergquist T, Gehl C, Mandrekar J, Lepore S, Hanna S, Osten A, et al. The effect of internet-based cognitive rehabilitation in persons with memory impairments after severe traumatic brain injury. *Brain Injury.* (2009) 23:790–9. doi: 10.1080/02699050903196688

26. Cadilhac DA, Andrew NE, Busingye D, Cameron J, Thrift AG, Purvis T, et al. Pilot randomised clinical trial of an eHealth, self-management support intervention (iVERVE) for stroke: feasibility assessment in survivors 12-24 months post-event. *Pilot Feasibility Stud.* (2020) 6:172. doi: 10.1186/s40814-020-00706-x

27. Gandy M, Karin E, McDonald S, Meares S, Scott AJ, Titov N, et al. A feasibility trial of an internet-delivered psychological intervention to manage mental health and functional outcomes in neurological disorders. *J Psychosom Res.* (2020) 136:110173. doi: 10.1016/j.jpsychores.2020.110173

28. van der Linden SD, Sitskoorn MM, Rutten GJM, Gehring K. Feasibility of the evidence-based cognitive telerehabilitation program remind for patients with primary brain tumors. *J Neurooncol.* (2018) 137:523–32. doi: 10.1007/s11060-017-2738-8

29. Spreadbury JH, Young A, Kipps CM. A comprehensive literature search of digital health technology use in neurological conditions: review of digital tools to promote self-management and support. *J Med Internet Res.* (2022) 24:e31929. doi: 10.2196/31929

30. Andrews G, Basu A, Cuijpers P, Craske MG, McEvoy P, English CL, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. *J Anxiety Disord.* (2018) 55:70–8. doi: 10.1016/j.janxdis.2018.01.001

31. Cogollor JM, Rojo-Lacal J, Hermsdörfer J, Ferre M, Arredondo Waldmeyer MT, Giachritsis C, et al. Evolution of cognitive rehabilitation after stroke from traditional techniques to smart and personalized home-based information and communication technology systems: literature review. *JMIR Rehabil Assist Technol.* (2018) 5:e4. doi: 10.2196/rehab.8548

32. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

33. Kallio EL, Öhman H, Kautiainen H, Hietanen M, Pitkälä K. Cognitive training interventions for patients with alzheimer's disease: a systematic review. *J Alzheimers Dis.* (2017) 56:1349–72. doi: 10.3233/JAD-160810

34. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* (2019) 366:l4898. doi: 10.1136/bmj.l4898

35. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol.* (1998) 51:1235–41. doi: 10.1016/S0895-4356(98)00131-0

36. Babcock L, Kurowski BG, Zhang N, Dexheimer JW, Dyas J, Wade SL. Adolescents with mild traumatic brain injury get smart: an analysis of a novel web-based intervention. *Telemed J E Health.* (2017) 23:600–7. doi: 10.1089/tmj.2016.0215

37. Brouns B, van Bodegom-Vos L, de Kloet AJ, Tamminga SJ, Volker G, Berger MAM, et al. Effect of a comprehensive eRehabilitation intervention alongside conventional stroke rehabilitation on disability and health-related quality of life: a pre-post comparison. *J Rehabil Med.* (2021) 53:jrm00161. doi: 10.2340/16501977-2785

38. van der Linden SD, Rutten GM, Dirven L, Taphoorn MJB, Satoer DD, Dirven CMF, et al. eHealth cognitive rehabilitation for brain tumor patients: results of a randomized controlled trial. *J Neurooncol.* (2021) 154:315–26. doi: 10.1007/s11060-021-03828-1

39. Mihuta ME, Green HJ, Shum DHK. Web-based cognitive rehabilitation for survivors of adult cancer: a randomised controlled trial. *Psychooncology.* (2018) 27:1172–9. doi: 10.1002/pon.4615

40. Mihuta ME, Green HJ. The implementation of web-based cognitive rehabilitation in adult cancer survivors: examining participant engagement, attrition and treatment fidelity. *Support Care Cancer.* (2018) 26:499–506. doi: 10.1007/s00520-017-3855-9

41. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ.* (2014) 348:g1687. doi: 10.1136/bmj.g1687

42. Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ.* (2008) 336:1472–4. doi: 10.1136/bmj.39590.732037.47

43. Reijnders JS, Geusgens CA, Ponds RW, van Boxtel MP. "Keep your brain fit!" effectiveness of a psychoeducational intervention on cognitive functioning in healthy adults: a randomised controlled trial. *Neuropsychol Rehabil.* (2017) 27:455–71. doi: 10.1080/09602011.2015.1090458

44. Modi AC, Mara CA, Schmidt M, Smith AW, Turnier L, Wade SL. Pilot executive functioning intervention in epilepsy: behavioral and quality of life outcomes. *J Pediatr Psychol.* (2021) 46:363–74. doi: 10.1093/jpepsy/jsaa119

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A rehabilitative approach beyond the acute stroke event: a scoping review about functional recovery perspectives in the chronic hemiplegic patient

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Background: Stroke is a main cause of disability worldwide and its neuro-rehabilitative management is not limited to the acute phase but requires continuity in the rehabilitation approach especially in the chronic phase. The aim of this scoping review was to highlight the different treatment opportunities available in neurorehabilitation, effective for patients with chronic stroke sequelae, not only in terms of maintaining motor function but also improving it.

Methods: The literature search was conducted using the following databases: MEDLINE (PubMed), PEDro, Scopus, Web of Science (WOS), Cochrane from 2012 to February 2023. We selected Randomized Clinical Trials in English dealing with neurorehabilitation strategies in chronic hemiplegic patients after stroke focusing on motor function, muscular strength, gait, postural balance, spasticity, and quality of life.

Results: According to the inclusion criteria, 47 articles were selected for our review. All of them were analyzed following the primary outcome and the rehabilitation technique used. Despite the different protocols used within the same technique and despite the chronicity of the disease, all studies report an improvement after the rehabilitation treatment of motor function and quality of life.

Conclusion: The literature analyzed invites us to reflect respect to neurorehabilitation approach to the patient with chronic stroke sequelae often considered to have as its objective the maintenance of the present motor function and contain disability: instead, the review reports how, even in chronicity, the patient always reports margins of statistically and clinically significant improvement. The chronic stroke rehabilitation over 6 months has been proved effective in obtaining recovery in different settings.

KEYWORDS

chronic stroke, motor impairment, stroke sequelae, rehabilitation, hemiplegic patient, recovery

1. Introduction

Stroke is one of the leading causes of death worldwide (1, 2) and it often leads to severe neurologically based disability in adults (3). Its consequences can affect cognitive, psychological, social and physical integrity: the assessment should consider the patient comprehensively in order to allow the best possible return to everyday life. Motor impairment is the most frequently recorded disability after a stroke episode (4), for this reason patient's rehabilitation is essential to achieve a good recovery (5). In agreement with the literature, chronic stroke phase begins 6 months after the acute event: it is considered that the best recovery plateau is reached at this point, in fact there is much evidence in favor of the improvements achieved in the acute and subacute phases. It is estimated that 80% of stroke patients achieve their maximum recovery within the first 3 months, reaching 95 and 100%, respectively, after the first semester and 1 year (6, 7). One of the causes might be the tendency to give more importance to the reacquisition of walking than to the fine motor skills, for instance it is estimated that upper limb motor impairment persists in 55–75% of chronic stroke patients (8, 9). However, stroke patients often need a longer period of rehabilitation, after the first phase that is provided in a hospitalization context, whereas the patient needs to experiment and integrate the motor and cognitive skills re-acquired after the stroke in his/her social context, both family and work. As a matter of fact, an important unresolved point concerns the timing of the stroke rehabilitation: it is common practice to limit the intensive treatment to the first 3 months after the acute event and consider the subsequent rehabilitation proposals as maintaining the present functional conditions and prevent secondary complications. However, several studies offer evidence in support of a rehabilitation continuity in chronic hemiplegic patients (10–12) aimed at ensuring the achievement of further objectives in the long term, as well as maintaining the already achieved results in day hospital or rehabilitative outpatient setting. For example, it is essential to avoid the risk of falling in stroke patients, and therefore improve stability and balance (13, 14) even some time after the onset of symptoms. Neuronal plasticity plays an important role in motor recovery, as well as the equilibrium between excitatory and inhibitory signals in the brain pathways (15, 16).

Various processes such as restitution, substitution and compensation can explain how it is possible to notice some improvements in the recovery of the upper limbs even years after the acute event (17–20). Restitution means a reacquisition of the lost abilities; substitution refers to the replacement of the motor paths while motor compensation requires the adaptation of other motor elements (21). As an actual fact, international guidelines recommend a rehabilitation program continuation after discharge from the post-acute care center (22–24), lasting at least a few weeks up to months as required by residual impairment.

Different neurorehabilitation techniques are followed in chronic post-stroke patient, such as traditional physiotherapy, mirror therapy, Neuromuscular Electrical Stimulation (NMES), orthoses and robotic, virtual reality (VR). From the literature, it is often clear how neuro-rehabilitative exercise is often associated with innovative techniques such as VR or robotic training for gait recovery and it is not possible to indicate which technique or protocol is better than the other: there is a great heterogeneity in the protocols and setting (outpatient, at home, remotely in tele-rehabilitation).

At present time, an ideal neurorehabilitation approach among all the various therapy possibilities has not been established. The clinical and research question should be: "What is the best neuro-rehabilitative approach for patient with chronic stroke?" evaluating the resources of the social and family context too (presence or not of the care giver, accessibility to care).

Considering these premises, the following review lends itself to identify Randomized Controlled Trials (RCT) suggesting the possibility of achieving goals in rehabilitative interventions starting 6 months or more after the acute event, particularly regarding residual motor deficits.

Because the neuro-rehabilitative approach beyond the acute stroke event may not only have as its objective the maintenance of the motor function but the improvement of the function in social life.

The aim of this scoping review was to highlight the different treatment opportunities available in neurorehabilitation, effective for patients with chronic stroke sequelae, not only in terms of maintaining motor function but also improving it.

2. Materials and methods

2.1. Eligibility criteria

The Preferred Reporting Items for Systematic Reviews extension for Scoping Reviews (PRISMAScR) checklist was followed for writing this scoping review (25, 26).

All randomized controlled trials published from 2012 to January 2023 written in English and specifically dealing with the topic of "rehabilitation strategies in chronic hemiplegic patient after stroke" were considered as eligible if they reflected the following PCC framework: (i) Population: males and females with diagnosis of chronic stroke ($\geq$ 6 months), age > 18 years old. (ii) Concept: rehabilitative techniques specifically addressed to treat motor impairment in chronic stroke patients according to International Guidelines (23). (iii) Context: sequelae, such as motor function, muscular strength, gait, postural balance, spasticity and quality of life, secondary to a chronic stroke.

We excluded pilot studies, studies without full-text available, without specified acute post-event period (6 months), with a PEDRO score under 5, (27) involving less than or equal to 10 patients, non-inferiority studies and studies which were not focused on the outcomes measures we meant to analyze.

2.2. Search strategy

A literature search was conducted (December 2022–January 2023) using the following databases: MEDLINE (PubMed), PEDro, Scopus, Web of Science (WOS), Cochrane. Keywords used were "chronic stroke AND rehabilitation, chronic stroke AND physiotherapy, chronic stroke AND recovery, chronic stroke AND exercise." Searches were supplemented by hand searching of additional articles meeting eligibility criteria that were cited in reference lists.

2.3. Evidence screening and selection

All articles identified in the research were imported into Microsoft Excel. Two independent reviewers searched databases by using the same method to guarantee suitable cross-checking of the results. The authors evaluated the studies collected by the searches based on the inclusion and exclusion criteria established and selected them according with eligibility criteria. The authors independently checked the titles, abstracts, and full text of suitable studies.

2.4. Data extraction and analysis

Data extracted from selected studies were: Authors and date of study, type of interventions, outcomes, population, who delivered the intervention; study design and authors conclusions. All data required to answer the study questions were published in the articles. Any disagreements regarding the data collection were solved by discussion until consensus.

3. Results

3.1. Study selection

As shown in the study flow chart (Figure 1) the literature search identified 883 records. After removing duplicates, the research resulted in 478 records. A total of 99 records were screened based on their titles and abstracts. Then 39 were discarded following application of the inclusion and exclusion criteria. Finally, 47 were considered relevant for qualitative analysis.

3.2. Characteristics of included studies

Characteristics of included studies are summarized in Table 1.

The included studies were heterogeneous because they have treated different rehabilitative techniques. Following our inclusion criteria, in our research we focused on various domains such as function, balance, walking abilities, spasticity and quality of life. Later we decided to analyze these RCTs dividing them in three different groups based on the principal aim: lower limb, upper limb and other outcomes; then we settled the studies in subgroups by the used rehabilitative technique. The mean and standard deviation values of the studies Pedro Score were, respectively, 6.68 and 1.04.

3.2.1. Lower limb recovery

3.2.1.1. Robotic technology

In Calabrò et al. work, the protocol with Ekso, an exoskeleton, showed a significant improvement at 10 Meter Walking Test (10MWT), Cortico-Spinal Excitability (CSE) and Sensory-Motor Integration (SMI) in the affected side, overall gait quality, hip and knee muscle activation and Frontoparietal Effective Connectivity (FPEC)

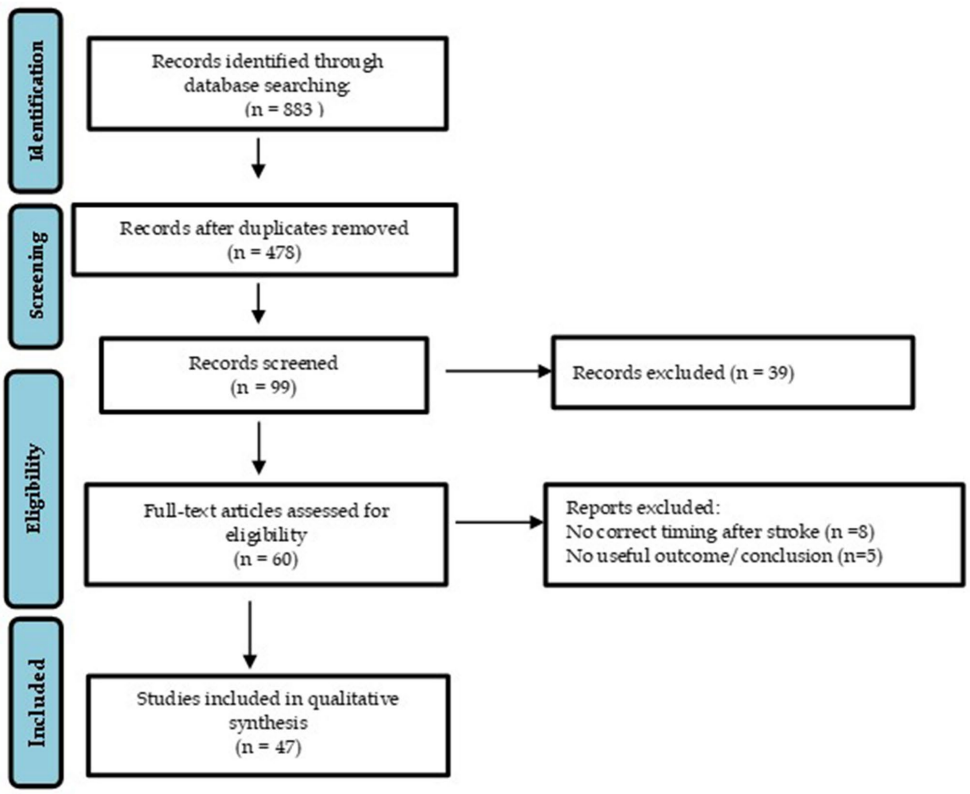

FIGURE 1
Flow chart.

TABLE 1 General characteristics of included studies.

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Calabrò et al. (28)	40 patients allocated to: EGT group (Ekso Gait Training) ($n = 20$) OGT group (Overground Gait Training) ($n = 20$)	Ekso gait training	Patients underwent 60 min of conventional physiotherapy followed by 45 min of Ekso gait training or conventional gait training, five times/week for 8 weeks.	10 Meter Walk Test (10MWT), Rivermead Mobility Index (RMI), Timed Up and Go (TUG). Gait pattern (surface electromyography-sEMG from lower limbs), FPEC (frontoparietal effective connectivity) by using EEG, corticospinal excitability (CSE) and sensory-motor integration (SMI) by using transcranial magnetic stimulation paradigm over the affected and unaffected hemisphere.	T0 = baseline T1 = post-intervention	Ekso™ gait training seems promising in gait rehabilitation for post-stroke patients, besides OGT	7/10
Kooncumchoo et al. (29)	30 patients allocated to: I-Walk machine group ($n = 15$) overground gait training (control) group ($n = 15$).	I Walk machine: specific tool for assisting walking and controlling walking patterns (staircase walking) with an adjustable number of repetitive walking steps (0–120 steps/min)	30 min of upper limb and hand movement and sit-to-stand training. The experimental group received 30 min of I-Walk training, while the control followed a 30-min overground training program. All the individuals were trained 3 days/week for 8 weeks.	Fugl–Meyer Assessment (FMA), 6-Minute Walk Test (6 MWT), 10-Meter Walk Test (10 MWT), Timed Up and Go (TUG)	T0 = baseline T1 = 2 weeks T2 = 4 weeks T3 = 6 weeks T4 = post-intervention	The I-Walk training machine improves gait speed but slightly decreases the range of motion compared to conventional PT training	6/10
Wu et al. (30)	30 patients allocated to: Resistance group ($n = 14$) or, Assistance group ($n = 14$)	A custom-designed, cable-driven robotic gait training system used on a treadmill	Subjects trained 3 times a week for 6 weeks. Each training session was 45 min excluding setup time.	Self-selected and fast overground walking velocity on a 10-m instrumented walkway (GaitMat IIa), 6-Minute Walk Test (6MWT), Modified Ashworth Scale (MAS), Berg Balance Scale (BBS), Activities-specific Balance Confidence (ABC) Scale, Medical Outcomes Study 36-Item Short-Form Health Survey	T0 = baseline T1 = post-intervention T2 = 8-weeks follow up	Applying a controlled resistance or an assistance load to the paretic leg during treadmill training may induce improvements in walking speed in individuals post-stroke. Resistance training was not superior to assistance training in improving locomotor function in individuals post-stroke.	8/10
Lee et al. (31)	30 patients allocated to: experimental group (15), control group (15)	Afferent electrical stimulation (AES) combined with mirror therapy	Patients received 60 min sessions 5 times/week for 4 weeks	Handheld Dynamometer; Modified Ashwort Scale (MAS), Berg Balance Scale (BBS); GAITRite	T0 = baseline T1 = post-intervention	Mirror therapy with afferent electrical stimulation may effectively improve muscle strength and gait and balance abilities in hemiplegic stroke survivors	6/10
Arya et al. (32)	36 patients allocated to: experimental group ($n = 19$), control group ($n = 17$)	Activity-based MT comprised movements such as ball-rolling, rocker board, and pedaling. The activities were provided on the less-affected side in front of the mirror while hiding the affected limb.	Thirty sessions consisting of 1 hour each (3–4/week) were provided across the 3 months. The experimental group received MT protocol and conventional therapy for 30 min each. The control group was provided the conventional management for 1 h to match the dose	Brunnstrom Recovery Stages (BRS), Fugl-Meyer Assessment Lower Extremity (FMA-LE), Rivermead Visual Gait Assessment (RVGA), and 10-Meter Walking Test (10-MWT)	T0 = baseline T1 = post-intervention	Activity-based MT facilitates motor recovery of the lower limb as well as reduces gait deviations among chronic post-stroke hemiparetic subjects	8/10

(Continued)

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Son et al. (33)	20 patients allocated to: self-observation training group ($n = 10$) or control group ($n = 10$)	Self-Observation training	30-min exercise therapy regimen, 5 days a week for 4 weeks. The self-observation training group additionally watched videoclips of their balance and functional gait training and performed physical training twice over a 10-min time span. Each self-observation training session was performed for 30 min, 3 times a week for 4 weeks	Surface Electromyography, Timed Up and Go (TUG), 10-Meter Walking Test (10MWT)	T0 = baseline T1 = post-intervention	Self-observation training improved lower limb muscle activity and dynamic balance in patients with chronic stroke	6/10
Bang et al. (34)	30 patients allocated to: action observational training group ($n = 15$), control group ($n = 15$)	Action Observational training (treadmill video)	Participants underwent training for 40 min per day, five times a week for 4 weeks.	Timed Up and Go Test (TUG), 10-Mt Walking Test (10MWT), 6-Minutes Walking Test (6MWT), maximal flexed knee angle in the swing phase during walking	T0 = baseline T1 = post-intervention	Action observational training is an effective method for improvement of the walking ability in chronic stroke patients	7/10
Cho et al. (35)	28 patients allocated to: experimental group ($n = 15$), control group ($n = 13$)	Motor imagery training was conducted using visual and kinematic imagery separately. Visual imagery is a process in which an individual imagines their physical movement from an external perspective, and kinematic imagery is a process in which an individual imagines internal sensory information during physical movement.	Imagery training was applied for 15 min, following gait training using a treadmill for 30 min. All interventions included gait training; imagery training was performed 3 times a week for 6 weeks.	Functional Reach Test, Timed Up-and Go Test (TUG), 10-mt Walking Test (10MWT) and Fugl-Meyer Assessment (FMA)	T0 = baseline T1 = post-intervention	Gait training with motor imagery training improves the balance and gait abilities of chronic stroke patients significantly better than gait training alone.	6/10
Dickstein et al. (36)	23 patients allocated to: experimental group ($n = 12$), control group ($n = 11$)	Integrated Motor imagery practice	The participants underwent 15-min sessions conducted 3 times a week for 4 weeks.	10-M Walking Test (10MWT), Falls Efficacy Scale Swedish version (FESS), Step Activity Monitor (SAM)	T0 = baseline T1 = post-intervention T2 = 2-weeks follow up	Home delivery of integrated motor imagery practice was feasible and exerted a positive effect on walking in the home	6/10
In et al. (37)	25 patients allocated to: VRRT group ($n = 13$), control group ($n = 12$)	Virtual reality reflection therapy (VRRT) on lower limbs	Participants received 30 min a day of conventional stroke rehabilitation program followed by 30 min of VRRT program or placebo/5 days a week for 4 weeks	Berg Balance Scale (BBS), Functional Reaching Test (FRT), Timed up and go (TUG), Balance system, 10 Mt Walking Test (10MWT)	T0 = baseline T1 = post-intervention	VRRT has beneficial effects on balance and gait ability in people with chronic stroke	5/10

(Continued)

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Kayabinar et al. (38)	30 patients allocated to: VR + RAGT group (virtual reality + robot-assisted gait training, $n = 15$); RAGT (robot-assisted gait training, $n = 15$)	Virtual reality augmented added to robot-assisted gait training	The participants underwent a total of 12 sessions, 2 days a week for 6 weeks.	Functional Gait Assessment (FGA), Rivermead Mobility Index (RMI), Berg Balance Scale (BBS), The Fall Efficacy Scale International (FES-I), Functional Independence Measure (FIM)	T0 = baseline T1 = post-intervention	VR augmented RAGT improved dual-task gait speeds and dual-task performance of chronic stroke patients; however, there was no difference between the two groups after the treatment. Although functional improvements were determined with VR combined RAGT approach, it was not superior to RAGT only treatment	6/10
Llorens et al. (39)	20 patients allocated to: experimental group ($n = 10$), control group ($n = 10$)	Virtual reality-based exercise to train balance and postural control disabilities	20 one-hour sessions, 5 sessions per week. Experimental group combined 30 min with the virtual reality-based intervention with 30 min of conventional training. The control group underwent one hour of conventional therapy.	Berg Balance Scale (BBS), Tinetti Performance-Oriented Mobility Assessment, Brunel Balance Assessment (BBA), 10-m Walking Test (10MWT)	T0 = baseline T1 = post-intervention	Virtual reality interventions can be an effective resource to enhance the improvement of balance in individuals with chronic stroke	8/10
Alwhaibi et al. (40)	30 patients allocated to: intervention group ($n = 15$), control group ($n = 15$)	Standard physical therapy plus somatosensory stimulation	Participants underwent 3 treatments/week for 8 weeks. The control group received 4 components of standard physical therapy program (25 min—15 min—10 min—10 min) while the control group received the same exercises but with a different duration (15 min—10 min—5 min—5 min). Patients also received thermal stimulation (TS) training.	Functional Independent Measure (FIM) and Quantitative Electroencephalography (QEEG)	T0 = baseline T1 = post-intervention	TS is one of the advanced approaches in rehabilitation and may improve functional performance of the affected lower extremity and neural activity of the brain.	6/10
Yang et al. (41)	25 patients allocated to: NMES-TA group (Tibialis Anterior, $n = 8$); NMES MG group (Medial Gastrocnemius, $n = 9$); control group ($n = 8$)	NMES protocol on plantar and dorsiflexors muscles	The experimental groups received 20 min-sessions of NMES. The control group received 20 min of range of motion and stretching exercises. After NMES or exercises, all participants received ambulation training for 15 min. Training sessions occurred 3 times per week for 7 weeks.	GAITRite: gait velocity, cadence, step length. Modified Ashworth Scale (MAS), EMG ankle plantar flexors during gait, handheld dynamometer, maximum position of the ankle joint during gait	T0 = 7 days before the first session T1 = after 21 sessions	Applying NMES on ankle dorsiflexors might be an effective strategy for muscle strengthening and spasticity reduction to enhance ankle control during push off and gait performance. Also, it could result in favorable effects on temporal gait symmetry in chronic stroke individuals with inadequate ankle control.	6/10

(Continued)

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Bethoux et al. (42)	399 subjects allocated to: WA group (Walk-Aid, $n = 187$), AFO group (Ankle- Foot Orthosis, $n = 212$)	Peroneal nerve functional electrical stimulation (FES) as an alternative to ankle-foot orthoses (AFO)	Patients wore WalkAide FES system (WA) or an AFO for 6 months.	10MWT, Stroke Impact Scale (SIS), 6MWT, GaitRite, Functional Ambulation Profile (FAP), Modified Emory Functional Ambulation Profile (mEFAP), BBS, TUG, Stroke-Specific Quality of Life (SSQoL), and individual SIS domain scores	T0 = baseline T1 = post-fitting, with device T2 = 1 month, T3 = 3 months T4 = 6 months	Use of FES is equivalent to the AF	5/10
Beaulieu et al. (43)	18 patients allocated to: RPMS group ($n = 9$), sham group ($n = 9$). healthy subjects ($n = 14$).	Repetitive Peripheral Magnetic Stimulation (RPMS)	The participants received the intervention (RPMS) in a single session lasting 2-3 hours.	Ankle range dorsiflexion (ROM); isometric muscle strength of dorsiflexor muscles; resistance of plantar flexors to stretch; TMS (transcranial magnetic stimulation) testing	T0 = baseline T1 = post-intervention	RPMS improved ankle impairments in chronic stroke patients	5/10
Lee et al. (44)	31 patients allocated to: local vibration stimulus training program group ($n = 16$) and sham group ($n = 15$)	Local Vibration stimulus training program	Participants underwent to training session for 30 min a day, five times a week, for 6 weeks	Balance, GAITrite	T0 = baseline T1 = post-intervention	Local vibration stimulus training program is an effective method for improvement of the postural sway and gait ability of chronic stroke patients	7/10
Park et al. (45)	30 patients allocated to: TENS Group + therapeutic exercise ($n = 15$), Placebo TENS Group + therapeutic exercise ($n = 15$)	TENS associated with therapeutic exercise	Patients underwent sessions of 30 min for 5 days/ week, lasting 6 weeks	Modified Ashworth Scale (MAS), balance system, Timed Up and Go (TUG), Gait analyzer	T0 = 1 week before treatment T1 = 1 week after treatment	A combination of therapeutic exercise and TENS may reduce spasticity and improve balance, gait, and functional activity in chronic stroke patients	6/10
Lim et al. (46)	17 patients allocated in: HBP group (home-based rehabilitative program, $n = 9$), control group ($n = 8$)	Home-based rehabilitative programs on postural balance	Participants received the treatment five times per week for 6 weeks.	10 Mt Walking Test (10MWT), Figure of 8 walk test, Four-square step test, 36 item Short-Form Survey (SF-36)	T0 = baseline T1 = post-intervention	HBP group received positive benefits with regard to the postural balance and walking abilities compared to the clinical setting exercise program	6/10
Hornby et al. (47)	90 patients allocated to: high variable protocol group ($n = 28$), high forward protocol group ($n = 30$), low variable protocol group ($n = 32$)	High-intensity stepping of variable stepping tasks (high variable), high-intensity stepping performing only forward walking (high forward), and low-intensity stepping in variable contexts at 30–40% heart rate reserve (low variable)	Participants received $\leq$ 30 one-hour training sessions over 2 months (3–5 sessions/wk), with $\leq$40 min of stepping practice each session.	6 Minutes Walking Test (6MWT), Functional Gait Assessment, 5-times sit-to-stand Test	T0 = baseline T1 = post-intervention T2 = 3-months FU	High-intensity stepping training resulted in greater improvements in walking ability and gait symmetry than low-intensity training in individuals with chronic stroke, with potential greater improvements in balance confidence	8/10

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Globas et al. (48)	38 patients allocated to: TAEX group ($n = 20$), control group ($n = 18$)	Progressive graded, high-intensity aerobic treadmill exercise (TAEX)	Treadmill training (TAEX) consisted of 39 sessions (3×/week; 3 months) vs usual care physiotherapy (control) according to the typical German prescription (1–3 sessions/week)	6-min walking test, 10-Mt Walking Test (10MWT), 5-Chair-Rise (5CR) test, Berg Balance Scale (BBS), Rivermead Mobility Index (RMI), and Medical Outcomes Study Short-Form 12 (SF-12)	T0 = baseline T1 = 3 months post-training T2 = 12 months follow up	Aerobic treadmill exercise in chronic stroke survivors improves cardiovascular fitness, gait, balance, mobility and quality of life	7/10
Chen et al. (49)	30 participants allocated to: experimental group ($n = 15$), control group ($n = 15$)	Rotational treadmill was designed to provide turning-based treadmill training	Participants underwent 12 sessions of 40 min over 4 weeks	GAITtrite, Turning Performance, LOS, Sensory Organization Test (SOT), Handheld Dynamometer, Berg Balance Scale (BBS)	T0 = baseline T1 = post-intervention T2 = 1 month follow up	Turning-based treadmill training may be a feasible and effective strategy to improve turning ability, gait symmetry, muscle strength, and balance control for individuals with chronic stroke	7/10
Choi et al. (50)	30 patients allocated to: WBV-TT group (whole body vibration—treadmill training, $n = 15$), treadmill training group (TT, $n = 15$)	Whole-body vibration combined with treadmill training	WBV-TT was performed 3 times a week (4.5 min per session) for 6 weeks. Each session included 6 exercises and each exercise was conducted for 45 seconds	Gait-rite, 6m-wt	T0 = baseline T1 = post-intervention	WBV-TT is more effective than TT for improving walking performance of patients with chronic stroke	8/10
Cho et al. (51)	30 allocated to: TRWVR group (treadmill training based real-world video recording, $n = 15$), control group ($n = 15$)	Treadmill training based real-world video recording (TBRVR)	Patients underwent training sessions of 30 min per day, three times per week, for 6 weeks	Dynamic and Static balance, Berg Balance Scale (BBS), Timed Up and Go (TUG), GAITrite	T0 = baseline T1 = post-intervention	Real-world video recording influences dynamic balance and gait in chronic stroke patients when added to treadmill walking	7/10
Hwang et al. (52)	32 participants allocated to: Treadmill training with Tilt Sensor FES (TTSF) group ($n = 16$) and Treadmill training with Placebo Tilt Sensor FES (TPTSF) group ($n = 16$).	TTSF group performed gait training on treadmill with tilt sensor FES, and TPTSF group performed gait training on treadmill with placebo tilt sensor FES.	Treadmill training combined with FES was performed for 30 min, one time per day, for 4 weeks. Conventional physical therapy was performed for 30 min, twice per day, for 4 weeks.	10-Mt Walking Test (10MWT), Berg Balance Scale (BBS), Timed Up-and Go (TUG)	T0 = baseline T1 = post-intervention	TTSF can be an effective intervention for improving balance, gait ability, and muscle architecture of tibialis anterior of stroke survivors	7/10
An et al. (53)	26 participants allocated to: MWM group (Mobilization with Movement, $n = 13$) and control group ($n = 13$)	Talocrural MWM (mobilization with movement) administered by a physiotherapist	Both groups attended conventional physiotherapy sessions 3 times a week for 5 weeks (30 min per session). Additionally, the MWM group underwent talocrural MWM 3 times a week for 5 weeks	Korean version of the Modified Barthel Index (K-MBI), Modified Ashworth Scale (MAS), Maximal concentric contraction measured with an isokinetic dynamometer	T0 = baseline T1 = post-intervention	Talocrural MWM has an augmented effect on ankle strength, mobility, and weight-bearing ability in chronic stroke patients with limited ankle motion when added to conventional therapy	6/10

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Park et al. (54)	38 patients allocated to: S-MWM group (self-mobilization with movement, $n = 19$) and CMS groups (calf muscle stretching training, $n = 19$)	The participants themselves performed the CMS. While in a lunge position (the affected side leg is forward), participants conducted S-MWM with a non-elastic strap approximately 40 cm long.	Conventional physiotherapy for 30 min per session + S-MWM and CMS techniques performed 3 times per week for 4 weeks	Ankle DF-PROM, GAITRite system, Biodex Balance System	T0 = baseline T1 = post-intervention	Both groups showed significant improvement in all outcome measures; ankle DF-PROM, gait parameters (gait speed, cadence, and stride lengths on both sides), and fall risk showed greater improvement in the S-MWM group than in the CMS group	7/10
Liao et al. (55)	56 patients allocated to: Balance Training group ($n = 19$); Lateral Wedge group ($n = 18$); Control group ($n = 19$)	The BT group received the weight shift training using the Biodex Balance System, as well as visual biofeedback balance training. The LW group used a 5° lateral wedge insole placed in the shoe of their healthy side for usual standing and walking.	BT group: the patients received 20 min of training 3 times/week for 6 consecutive weeks	CAT (balance computerized adaptive test), TUG test (Timed Up and Go)	T0 = baseline T1 = post-intervention T2 = 10 weeks follow up T3 = 18 weeks follow up	Six-week visual biofeedback training and intervention of 5° lateral wedge insoles can improve the balance ability of patients with a chronic stroke	8/10
Cho et al. (56)	38 patients allocated to: RT-AAN group (Robot-assisted reach training with assist-as-needed, $n = 19$) RT-G group (robot-assisted reach training with guidance force, $n = 19$)	Robot-assisted reach training with assist-as-needed (RT-AAN)	All participants underwent the training program 3 times a week for 6 weeks. A single training session lasted 40 min.	Fugle Meyer Assessment (FMA), Action Research Arm Test (ARAT) and Box and Block Test (BBT)	T0 = baseline T1 = 3 days after the end of intervention.	RART (robot-assisted reach training) with an active assistant protocol showed improvements of upper extremity function and kinematic performance	8/10
Cordo et al. (57)	43 patients allocated to: Torque group ($n = 22$), EMG group ($n = 21$)	Assisted movement and muscle vibration combined with either torque or EMG biofeedback	Each participant received 30 sessions (30 min duration per session) directed at the impaired hand over 10–12 weeks.	Upper Extremity-Fugl Meyer Assessment (UE-FMA), Strength Test, Box and Block Test (BBT) and Stroke Impact Scale (SIS)	T0 = baseline T1 = post-intervention	Assisted movement and muscle vibration, combined with EMG or torque biofeedback, appears to reduce upper limb impairment, improve volitional activation of the hand muscles and restore a modicum of hand function	5/10
Hung et al. (58)	44 patients allocated to: UHT group (unilateral hybrid therapy, $n = 14$), BHT group (bilateral hybrid therapy, $n = 15$), RT group (robot-assisted therapy, $n = 15$).	UHT combined unilateral RT (URT) and modified constraint-induced therapy. BHT combined bilateral RT (BRT) and bilateral arm training	The RT group received URT and BRT. The intervention frequency for the three groups was 90 min/day, 3 days/week for 6 weeks.	Fugl-Meyer Assessment (FMA), Stroke Impact Scale (SIS), Wolf Motor Function Test (WMFT) and Nottingham Extended Activities of Daily Living (NEADL) scale	T0 = baseline T1 = post-intervention T2 = 3 months follow up (FMA and SIS scores)	BHT was more effective for improving upper extremity motor function, particularly distal motor function at follow-up, and individuals in the RT group demonstrated improved functional ambulation post-intervention.	8/10

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Lin et al. (59)	33 patients allocated to: bilateral isometric handgrip force training group ($n = 16$), control group ($n = 17$)	The computer-aided interlimb force coupling training task with visual feedback included different grip force generation methods on both hands.	The bilateral isometric handgrip force training consisted of 30 min of training 3 days per week for 4 weeks, for a total of 12 sessions.	Barthel Index (BI), Upper Extremity Fugl-Meyer Assessment (FMA-UE), Motor Assessment Score (MAS) and Wolf Motor Function Test (WMFT)	T0 = baseline T1 = post-intervention	Computer-aided interlimb force coupling training improves the motor recovery of a paretic hand and facilitates motor control and enhances functional performance in the paretic upper extremity	7/10
Choi et al. (60)	36 patients allocated to: Gesture Recognition (GR) Mirror Therapy group ($n = 12$), Conventional Mirror Therapy group ($n = 12$), Control group ($n = 12$)	Gesture Recognition Mirror therapy	The patients received 15 intervention sessions of 30 min/day, 3 days/week for 5 weeks.	Manual Function Test (MFT), Neck Discomfort Score (NDS), 8-Item Short-Form Health Survey (SF-8)	T0 = baseline T1 = post-intervention	GR mirror therapy has a positive effect on upper-extremity motor function and quality of life. Traditional mirror therapy produces less neck discomfort.	7/10
Colomer et al. (61)	31 patients allocated to: experimental group ($n = 15$); control group ($n = 16$)	Mirror Therapy program included in a physical therapy program focused on balance and training	Patients underwent 24 training session of 45 min for 3 times a week	Wolf Motor Function Test (WMFT), Upper Limb motor function (FMA), Nottingham Sensory Assessment (NSA)	T0 = baseline T1 = post-intervention	MT in chronic stroke survivors with severely impaired upper limb function may provide a limited but positive effect on light touch sensitivity while providing similar motor improvement	8/10
Cho et al. (62)	27 patients allocated to: experimental group ($n = 14$) and a control group ($n = 13$)	Transcranial direct current stimulation (tDCS) matched with mirror therapy (MT)	tDCS for 20 min (2 mA intensity) followed by a 5 min rest. The experimental group received MT while the control group conducted the same exercises as the experimental group using a mirror that did not show the non-paretic upper extremity. The groups performed the same exercises for 20 min. All subjects received this intervention for 45 min three times a week for 6 weeks	Box and Block test (BBT), Grip Strength, Fugl-Meyer Assessment (FMA), Jebsen-Taylor Test	T0 = baseline T1 = post-intervention	MT with tDCS has a positive effect on the functional recovery of the upper extremity of stroke patients	5/10
Hernandez et al. (63)	51 participants allocated to: treatment group ($n = 26$) or standard care group ($n = 25$)	Use of the Jintronix system as a remotely supervised home-based program for UE rehabilitation	Each intervention consisted of a 4-week long program. Experimental group: home-based exercise program via the Jintronix system monitored offline by a therapist. Control group: home-based exercise program manual (Graded Repetitive Arm Supplementary Program).	Fugl-Meyer Assessment for UE (FMA-UE), Stroke Impact Scale (SIS), Motor Activity Log-14	T0 = baseline T1 = post-intervention T2 = 4 weeks follow up	These findings suggest that UE training for chronic stroke survivors using virtual rehabilitation in their home may be as effective as a gold standard home exercise program and that those who used the system the most achieved the greatest improvement in UE	8/10

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
De Diego et al. (64)	21 patients allocated to: experimental group (EG, $n = 12$), control group (CG, $n = 9$)	Conventional rehabilitation therapy according to the Bobath concept and sensory and motor stimulation of the upper limb	The EG received 16 sessions of the protocol of 1 hour at the center for 8 weeks, 2 sessions per week, and 1 daily session of 30 min of functional activity training at home. The CG had the usual treatment according to the Bobath concept, without prioritizing therapy of the upper limb, with 2 sessions per week.	FMA, Motor Activity Log Amount Scale (MAL—AS), Motor Activity Log How Well (MAL- HW), Stroke Impact Scale 16 (SIS-16)	T0 = baseline T1 =after 8 sessions T2 = post-intervention	The intensive sensorimotor stimulation program for the upper extremity may be an efficacious method for improving function and use of the affected limb in ADL in chronic stroke patients	6/10
Lee et al. (65)	39 patients allocated to: RT combined with NMES group (RT + ES, $n = 20$), RT with sham stimulation group (RT + Sham, $n = 19$)	Bimanual RT (robot therapy) combined with NMES (Neuromuscular Electrical Stimulation)	The participants received their respective interventions for 20 training sessions (90–100 min/day, 5 days/week for 4 weeks)	Upper Extremity Fugl-Meyer Assessment (UE-FMA), Modified Ashworth Scale (MAS), Wolf Motor Function Test (WMFT), Motor Activity Log (MAL), and Stroke Impact Scale 3.0 (SIS)	T0 = baseline T1 = post-intervention T2 = 3 months FU	RT + ES induced significant benefits in reducing wrist flexor spasticity and in hand movement quality	7/10
Knutson et al. (66)	80 patients allocated to: CCFES group ($n = 40$), NMES group neuromuscular electrical stimulation ($n = 40$).	Contralaterally controlled functional electrical stimulation (CCFES)	CCFES and NMES treatments lasted 12 weeks and consisted of: (a) 20 sessions of therapist-guided functional task practice in the lab (two per week except on weeks that included an assessment session), (b) 10 sessions per week of self-administered repetitive hand opening exercise at home. Functional task practice (FTP) was performed for 60 min per session.	Box and Blocks Test (BBT) score, Upper extremity Fugl-Meyer (UEFM) and Arm Motor Abilities Test (AMAT)	T0 = baseline, T1-T2-T3 = every 3 weeks during the treatment period, T4 = end of treatment, T5-T6-T7: 2, 4, and 6 months after end of treatment	CCFES improved hand dexterity more than NMES in chronic stroke survivors.	6/10
Tavernese et al. (67)	44 patients allocated to: experimental group ($n = 24$), control group ($n = 20$).	Segmental Muscle Vibration (SMV)	All the participants underwent a 60-min general physical therapy session, 5 times per week, over a period of 2 weeks. Participants in the EG also received 30 min of SMV therapy (120 Hz).	Normalized jerk (NJ), mean linear velocity (ms^{-1}); movement duration (s); movement length (m); HTD (hand target distance) at the end of movement (m); mean angular velocity at the shoulder ($°s^{-1}$); angle at the elbow at the end of movement (°)	T0 = baseline T1 = 2 weeks post-intervention	A combined treatment of SMV and therapeutic exercise determines a significant improvement of motor performance in the paretic upper limb during reaching movement	8/10
Costantino et al. (68)	32 patients allocated to: group A treated with vibration protocol ($n = 17$); group B with sham therapy ($n = 15$)	Local muscle vibration	Application of local muscle vibration set to a frequency of 300 Hz, for 30 min 3 times per week, for 12 sessions, applied to the skin covering the venter of triceps brachii and extensor carpi radialis longus and brevis muscles during voluntary isometric contraction	Hand Grip Strength Test, Modified Ashworth Scale (MAS), QuickDASH score, FIM scale, Fugl-Meyer Assessment (FMA), Jebsen-Taylor Hand Function Test and Verbal Numerical Rating Scale of pain	T0 = baseline T1 = post-intervention	Rehabilitation treatment with local muscle high frequency (300 Hz) vibration for 30 min, 3 times a week for 4 weeks, could significantly improve muscle strength and decrease muscle tonus, disability and pain in upper limb of hemiplegic post-stroke patients.	6/10

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TABLE 1 (Continued)

Authors	Study population	Intervention type	Dosage and frequency of intervention	Outcome measures	Assessment intervals	Conclusions	Pedro scale
Karthikbabu et al. (69)	85 patients allocated to: Plinth group ($n = 30$), Swiss ball group ($n = 28$), Control groups ($n = 27$)	Selective upper and lower trunk movements using either plinth or Swiss ball	Patients in the experimental groups received selective upper and lower trunk movements in supine and sitting positions using either stable support (plinth) or unstable support (Swiss ball). Patients underwent 1 hour exercise session, 3 sessions per week over a duration of 6 weeks.	Trunk impairment Scale, Brunel balance assessment, Tinetti scale, reintegration to normal living index, 10m-wt	T0 = baseline T1 = post-intervention T2 = 3 months follow up T3 = 12 months follow up	Plinth and Swiss ball-based trunk exercise regimes showed significant improvements in balance, mobility, physical function, and community reintegration in chronic stroke as against standard physiotherapy	7/10
Lee et al. (70)	28 patients allocated to: CCS group (Conventional Core Stabilization, $n = 14$), DNS group (Dynamic Neuromuscular Stabilization, $n = 14$)	CCS Conventional core stabilization DNS Dynamic neuromuscular stabilization	Both groups received a total of 20 sessions of CCS or DNS training for 30 min per session, 5 times a week during the 4-week period	Electromyography was used to measure the APA time for bilateral external oblique (EO), transverse abdominis/internal oblique (TrA/IO), and erector spinae (ES) activation during rapid shoulder flexion. Trunk Impairment Scale (TIS), Berg Balance Scale (BBS), Falls Efficacy Scale (FES)	T0 = baseline T1 = post-intervention T2 = 2 years follow up	Core stabilization exercises improve APA control, balance, and fear of falls in individuals with hemiparetic stroke.	5/10
Lee et al. (71)	28 patients allocated to: dual motor task training group ($n = 14$) and control group ($n = 14$)	Dual motor task exercises	Conventional exercise program for 60 min per day, 5 times a week for 6 weeks. The dual motor task training group also performed dual motor task training in the sitting position for 30 min per day, 3 times a week for 6 weeks	Trunk impairment scale (TIS), modified functional reach test (MFRT)	T0 = baseline T1 = post-intervention	Dual motor task training combined with a conventional exercise program improves trunk control ability and sitting balance	5/10
Park et al. (72)	29 patients allocated to: LATE group ($n = 14$); control Group ($n = 15$)	LATE program: land-based and aquatic exercises for trunk control and performed in the supine and sitting positions	Both groups received neurodevelopmental treatment (Bobath approach) for 30 min/day, 5 days/week, for 4 weeks. In addition, the LATE group performed the LATE program for 30 min/day, 5 days/week, for 4 weeks.	Trunk Impairment Scale (K-TIS), 5-item, 3-level Postural Assessment Scale for Stroke (PASS-3L), 3-level Berg Balance Scale (BBS -3L), Functional Reach Test (FRT), Modified Barthel Index (MBI)	T0 = 3 days before treatment T1 = post-intervention	LATE program can help improve trunk control, balance, and activities of daily living in chronic stroke patients and may be used as a practical adjunct to conventional physical therapy	7/10
Pérez-de la Cruz (73)	41 patients allocated to: control group—dry land therapy ($n = 15$), experimental group − aquatic therapy ($n = 13$), combined group − aquatic + dry land therapy ($n = 13$)	Aquatic therapy program influence on chronic stroke patients	The participants trained for a 12-week period: the sessions lasted 45 min and were conducted twice weekly.	VAS, resilience scale, 36-Item Short-Form Health Survey (SF36)	T0 = baseline T1 = post-intervention T2 = one month follow up	Physical exercise performed in water has positive effects on several factors that contribute toward improving the mood and quality of life of people with acquired brain injury	8/10
Ku et al. (74)	20 patients allocated to: experimental group ($n = 10$), control group ($n = 10$)	Ai Chi (water-based exercise emphasizing characteristics of balance training)	The training session lasted 60 min/time, 3 times/week for a total of 6 weeks	LOS, BBS; GAITRITE, FMA	T0 = baseline T1 = post-intervention	Ai Chi is feasible for balance training in stroke and is able to improve weight shifting in anteroposterior axis, functional balance, and lower extremity control as compared to conventional water-based exercise	8/10

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(28). Similar results in walking speed were seen in Kooncumchoo et al. study where they compared an innovative end effector robot (I-Walk) to overground gait training (29). Instead, Wu et al. analyzed if there were differences between a robotic resistance training and a robotic assistance training. The results were similar except for better improvements in 6 Meter Walking Test (6MWT) and Berg Balance Scale (BBS) in the assistance training (30).

3.2.1.2. Mirror neuron system

Lee et al. investigated how afferent electrical stimulation associated with mirror therapy could modify various outcomes in chronic stroke patients' life. After 4 weeks, important differences were found in Berg Balance Scale (BBS), gait velocity, step length and stride length (31). In Arya et al. work, an activity-based mirror therapy was compared to a conventional one; after 3 months of intervention, there were statistically significant improvements in Fugl Meyer Lower Extremity (FMA-LE), Rivermead Visual Gait Assessment (RVGA) and Brunnstrom recovery stages (BRS-LE). No meaningful one was found at 10MWT (32). In Son et al. study, the experimental group performed a self-observation training associated with exercise therapy with significant ameliorations in muscle activity of the rectus femoris, biceps femoris, tibialis anterior and gastrocnemius and an improvement in 10MWT and Timed Up and Go (TUG) (33). The intervention group in Bang et al. paper watched a video of treadmill walking actions taken at various speeds before the training itself with significant progress in TUG, 10MWT, 6MWT and in maximal flexed knee ankle in the swing phase during walking (34).

3.2.1.3. Motor imagery

Cho et al. investigate how motor imagery training with gait training, compared to classic gait training, could modify balance and gait abilities. After intervention there were significant improvements in FRT (Functional Reach Test), TUG (Timed Up-and-Go) and 10MWT (35). Dickstein et al. used a motor imagery technique with motor and motivational contents performed in the participants' home with a significant amelioration concerning In-home walking (36).

3.2.1.4. Virtual reality

In et al. investigated the effects of virtual reality reflection therapy (an enhanced version of the mirror therapy concept) on chronic stroke patients. After 4 weeks of program, there were significant improvements in the experimental group in BBS, Functional Reach Test (FRT), TUG, postural sway and 10MWT (37). In Kayabinar et al. study, virtual reality augmented robot-assisted gait training was compared to conventional robot-assisted gait training; after 4 weeks of intervention, there were ameliorations in motor task and cognitive task added to 10MWT in cognitive dual-task, although there was no statistically significant difference with the control group. FGA, RMI, BBS, and Functional Independence Measure (FIM) total scores improved in both groups but with no differences (38). In Llorens et al. study, a virtual reality-based stepping training was used in the intervention group to see any improvement in balance. After 20 sessions, there were significant changes in BBS, 10MWT and in Brunel Balance Assessment (BBA) (39).

3.2.1.5. Somatosensory training

Alwhaibi et al. evaluated the effects of somatosensory rehabilitation on neural and functional recovery of Lower Extremity. After treatment, there was a significant improvement in FIM but no significant changes were found in QEEG scores (40).

3.2.1.6. Electrical and repetitive peripheral magnetic stimulation

In Yang et al. study, Neuro-Muscular Electrical Stimulation (NMES) on anterior tibialis muscle or medial gastrocnemius muscle was compared to range of motion and stretching exercises in patients with inadequate ankle control. After 7 weeks of training, the NMES-TA group showed significant improvements in dynamic spasticity, spatial asymmetry, ankle plantarflexion during push off and muscle strength of ankle dorsiflexors (41). In Bethoux et al. work, the aim was to compare the effects of peroneal nerve Functional Electrical Stimulation (FES) to Ankle-Foot Orthosis (AFO). After 6 months of intervention the results were that FES stimulation is equivalent to AFO with no significant differences between groups (42). Beaulieu et al. used Repetitive Peripheral Magnetic Stimulation (RPMS) on paretic tibialis anterior muscle with a significant increase in ankle dorsiflexion mobility and maximal isometric strength and a decrease in resistance to plantar flexor stretch (43).

3.2.1.7. Local vibration stimulus program

In Lee et al. study, a local vibration stimulus training program was applied to see the effects on postural sway and gait with significant results, after 6 weeks, in postural sway distance with eyes-open and closed, in postural sway velocity with eyes-open and closed and in gait speed, cadence, step length and single limb support time (44).

3.2.1.8. Physical exercises

Park et al. associated a two-channel TENS, placed on the affected lower extremity on lateral and medial quadriceps muscle and gastrocnemius muscle, with an exercise program. After 6 weeks there were significant improvements in spasticity, static balance parameters, dynamic balance, gait speed and cadence, step and stride length on the paretic side (45). Lim et al. investigated the effects of a home- based rehabilitation program on postural balance, walking and quality of life with ameliorations in postural balance, comfortable speed, and fast speed walking but with no significant differences with the control group (46). Hornby et al., with their study, underlined how a high-intensity training can bring significant improvements in stepping amount and rate, with additional gains in spatiotemporal symmetry and balance confidence (47).

3.2.1.9. Treadmill training

Globas et al. measured how high-intensity aerobic treadmill training influenced gait performances with a significant progress of peak exercise capacity and 6MWT in the intervention group, maintained also at 1-year follow up with a little decrease of walking capacities (48). In Chen I et al. work, a turning-based treadmill was compared to a normal treadmill, and after 4 weeks of training they noticed significant improvements on turning speed, straight-walking performance, strength of hip muscles and ankle dorsiflexors and balance control, maintained also at the 1-month follow up (49). In Choi et al. study, whole-body vibration was combined with treadmill training with significant changes in walking performances, gait parameters and 6MWT compared to control group (50). Cho et al. matched treadmill training with a real-world video recording; after 6 weeks there were significant improvements in dynamic balance and

gait parameters (51). On the other hand, Hwang D. et al. used tilt sensor functional electrical stimulation on common peroneal nerve in treadmill training with significant ameliorations in TUG, BBS, 10MWT and anterior tibialis muscle architecture in the intervention group (52).

3.2.1.10. Other types of intervention

An et al. investigated how a talocrural mobilization with movements can influence ankle strength, dorsiflexion passive range of motion and weight-bearing ability on the paretic limb: they showed significant ameliorations compared to the control group after 5 weeks of intervention (53). In Park et al. work, the intervention group experienced a four-week training of self-ankle mobilization with movement, and it was compared to a calf muscle stretching group; significant changes were found in gait parameters and fall risk (54). On the other hand, Liao W. et al. put in evidence how lateral wedge soles and visual biofeedback balance training group can improve balance Computerized Adaptive Test (CAT) and TUG test (55).

3.2.2. Upper limb recovery

3.2.2.1. Robotic technology

Cho et al. used an upper limb exoskeleton machine with two different protocols: the robot-assisted as needed protocol was significantly more effective than the robot-assisted with guidance force protocol in FMA and Action Research Arm Test (ARAT) (56). Cordo et al. analyze if there are significant differences between the use of EMG biofeedback and torque biofeedback in robot-assisted movement associated with muscle vibration in severe hand impairment following stroke but the results showed no meaningful distinction between them (57). Hung et al. investigate if a hybrid approach (arm training + robot therapy) could bring changes in motor function. They divided their patients in three groups: unilateral hybrid RT, bilateral hybrid RT and robot assisted therapy. The results favored Bilateral Hybrid Therapy (BHT) over Unilateral Hybrid Therapy (UHT) on the FMA total score and distal score. RT group showed significant improvements in the mobility domain of Nottingham Extended Activities of Daily Living (NEADL) (58). Lin et al. investigated the effects of a computer-aided bilateral isometric handgrip on paretic hand and arm motor control in chronic stroke patients. After 4 weeks of interventions, there were significant improvements in the FMA-UE, BI (Barthel Index), Wolf Motor Function Test (WMFT) and Modified Ashworth Scale (MAS) (59).

3.2.2.2. Mirror neuron system

In Choi et al. work, mirror therapy was associated with a Gesture Recognition device (GR group) and compared with a second group with conventional Mirror Therapy (MR group) and a third group with sham therapy (CG). There were significant changes in upper extremity function, depression, and quality of life in the GR group and improvements in neck discomfort in MR and CG group (60). Lee et al. investigated the effects of afferent electrical stimulation associated with mirror therapy in stroke patients' life: there was an increase in muscle strength measured with a handheld dynamometer (31). In Colomer et al. study, mirror therapy was applied to chronic stroke patients with severely impaired upper limb function. After 8 weeks, the experimental group showed significant improvements in tactile sensation compared to the control group but a similar increase in FMA and ability subscales in WMFT (61). Cho et al. associated mirror therapy with transcranial Direct Current Stimulation (tDCS). This innovative technique showed significant improvements compared to control group in the Box and Block Test (BBT) and grip strength (62).

3.2.2.3. Virtual reality technique

In Hernandez et al. work, a virtual reality- based rehabilitation was compared to an evidence-based home exercise program in influencing upper extremity function; no significant differences were found between groups (63).

3.2.2.4. Somatosensory training

De Diego et al. compared a sensory stimulation and functional activity training with a control group who went under a standard rehabilitation program. After 8 weeks there were significant improvements in the experimental group especially in the sensory tests (64).

3.2.2.5. Electrical stimulation

Lee et al. decided to investigate the effects of combining robot-assisted therapy with neuromuscular electrical stimulation; after 4 weeks of intervention there were significant changes in wrist flexors MAS score, WFMT quality of movement and the hand function domain of Stroke Impact Scale (SIS) (65). Knutson et al. compared Contralaterally Controlled Functional Electrical Stimulation (CCFES) to cyclic NeuroMuscular Electrical Stimulation (cNMES) with a significant improvement at the BBT in the CCFES group (66).

3.2.2.6. Local vibration stimulus program

Tavernese et al. used segmental muscle vibration over biceps brachii and flexor carpi ulnaris muscles of the paretic side with a significant improvement in the normalized jerk, an indicator of smoothness of the movement, in mean linear velocity, in mean angular velocity at shoulder, in distance to target at the end of movement and movement duration (67). On the other hand, Costantino C. et al. analyzed the short-term effect of local muscle vibration treatment on upper limb obtaining significant results, after 4 weeks, in grip muscle strength, pain and quality of life and decrease of spasticity (68).

3.2.3. Other outcomes

3.2.3.1. Different approaches of trunk exercises regimes

Karthikbabu et al. compared plinth and Swiss ball-based trunk exercise regimes with a standard physiotherapy; after 6 weeks there were significant changes in Trunk Impairment Scale (TIS), BBA, Tinetti scale, gait speed, SIS and community reintegration but they were retained during the 3–12 months follow up (69). In Lee et al. work, there was a comparison of the effects of a Conventional Core Stabilization (CCS) and a Dynamic Neuromuscular Stabilization (DNS) on Anticipatory Postural Adjustment (APA), time, balance performance and fear of falls in chronic stroke patients. After the intervention the APA times changed significantly in the DNS group; the BBS, TIS and Falls Efficacy Scale (FES) scores improved in both groups but with a time stability only in the DNS group (70). Lee et al. investigated the effect on trunk control and dynamic balance ability in the sitting position of a dual motor task training program. After 6 weeks, the experimental group showed significant improvements in trunk control ability and dynamic balance in sitting position (71).

3.2.3.2. Aquatic programs

Park et al. investigated the effects of a Land-based and Aquatic Trunk Exercise program (LATE) in chronic stroke patients; after 4 weeks of intervention there were clinically significant improvements in Korean-TIS, 3-level Postural Assessment Scale for Stroke (PASS 3-L), BBS 3-Level and Modified-BI scores and Functional Reach Test (FRT) distance (72). In Perez-de la Cruz work, the program of Ai Chi aquatic therapy showed that there were significant ameliorations in post treatment pain and resilience; also, they found changes in the SF-36 test except for general health, vitality, and social functions (73). Also, Ku et al. studied the effects of Ai Chi therapy but under a different point of view, focusing on the significant changes seen in Limits of Stability (LOS) test (anteroposterior axis), BBS and FMA (74).

4. Discussion

In this systematic review, we conducted the research including randomized controlled trials (RCT) published over the last 10 years with the purpose of identifying all the effective rehabilitation treatments and setting in chronic stroke patients. We also wondered about the possibilities of improvements and the future perspectives for both patients and research. In fact, the mechanism on which recovery can occur even more than 6 months after the acute event has not been fully clarified yet, therefore it cannot be assumed that any therapeutic option will be successful. Insights of this kind could make a significant contribution to the knowledge of this chronic neurological issue and above all to what a patient can probably expect from the course of his disease.

Several authors decided to explore the rehabilitative perspective of robotic technology, obtaining most of the results. In Calabrò et al. and Kooncumchoo et al. studies, two types of gait training machines (Ekso in the first one and I-Walk in the second one) were tested: in both studies there was a significant improvement in 10MWT/speed but only in the first one there were positive changes in gait quality. Even if the I-Walk machine did not show massive advantages compared to conventional therapy, it sufficiently facilitates locomotor function with the setting of task-specific training and an adequate number of repetitions with an appropriate gait pattern (50 step/min). In this way, the patient learns to control new movements with normal biomechanics and to use less energy when performing tasks. In contrast, the repetitions in the conventional PT group were possibly inadequate to control precise movement but the sensory stimulation by the physical therapist provided a more effective patient response and range of motion (28, 29).

Both in Wu et al. and Cho et al. studies, the robotic assistance protocol showed to be superior or not inferior to other protocols. In Wu et al. work, the resistance protocol did not overcome the assistance training protocol in improving endurance, balance, and balance confidence in individuals poststroke. A possible reason is that the motor memory and the acquired cognitive strategies, resulted from the resistance force applied to lower limbs, may be less retained and transferred to overground walking. Certainly, a force perturbation and a controlled assistance load to the paretic leg during treadmill training may be used as an adjuvant tool to improve locomotor functions in poststroke patients, even for subjects of a high functional level (30, 56).

Hung et al. decided to investigate if robot-assisted therapy could bring more improvements either if associated with unilateral or bilateral arm training. In the end. BHT was more effective for improving upper extremity motor function probably because the patients were more likely to use their affected Upper Extremity (UE) with the assistance of the unaffected UE and practiced more in dexterity tasks compared with those in the UHT group. At the same time, UHT is useful in term of enhancing UE motor abilities and physical- related Quality of Life but the results were not maintained at long term. Instead, the robot training group showed higher improvements in functional ambulation (58). On the other hand, Cordò et al. studied an existing protocol using robot-assisted movement combined with local vibration therapy; they wanted to assess if EMG biofeedback or torque biofeedback could improve the recovery of the severe hand impairment. The results were overlapping in both cases (57). Upper Limb function was also used as an outcome in Lin et al. article: the intervention group reached optimal changes in FMA, BI, WMFT and MAS by using a computer-aided bilateral isometric handgrip (59).

A hybrid approach was used by Lee et al. combining robot-assisted therapy with Neuromuscular Electrical Stimulation to implement the functions of the upper limb, in particular of the hand (65). They achieved good results as well as Yang et al. that used NMES on anterior tibialis muscle and medial gastrocnemius muscle (41). Knutson et al. demonstrated the predominant effects of CCFES on cNMES in achieving a finer hand dexterity (66). On the contrary, intervention superiority was not obtained in the study conducted by Bethoux et al. as they used FES on common peroneal nerve com-pared to Ankle Foot Orthosis (42). Beaulieu et al. showed how also RPSM is an effective tool for ameliorations in stroke patients with a paretic tibialis anterior muscle and with spastic plantar flexor muscles (43).

A great technologic resource for recovery in chronic stroke patients is the use of virtual reality of different types (immersive or exergames) in lower limb and balance function. The protocols used by the authors are different, some using Exergame with physical exercise that integrates motion-tracking technology that enables interaction with the game and real-time feedback of user's performance or immersive VR with deep mental involvement in something action. In the context of virtual reality, and in a technical acceptance of the term, immersion is achieved by removing as many real-world sensations as possible and substituting these with the sensations corresponding to the virtual reality experience, but the patient must have good confidence with the technology and bring back an adequate cognitive reserve, that's why an adequate MMSE is always required.

Supporting evidence can be found in Kayabinar et al. and in Llorens et al. studies where they both used Virtual Reality combined with robotic technology or with stepping training.

In Kayabinar et al. work, VR was added as support in robot-assisted gait training under the form of an exergame: the experimental group was tasked to walk in a forest environment with many trees, without hitting them and trying to collect the coins that appeared on the screen. The patients determined their direction during the game by transferring weight to their extremities on the device. The protocol lasted 6 weeks, two session/week, for a total of 12 sessions (38).

On the other hand, Llorens et al. associated immersive VR with stepping training to create a protocol of 20 one-hour rehabilitation sessions, 5 days a week for 4 weeks. The experimental group underwent 30 min of conventional therapy and 30 min of training with the virtual

rehabilitation system in that order. In this group, the exercises of conventional therapy were administered consecutively in single 5-min repetitions and the training with the virtual rehabilitation system consisted of three 6-min repetitions with one and a half minute breaks between them. The exercise immersed the participants in a 3D virtual environment with their feet represented by two shoes that mimicked their movement in the real world (39).

Also, the combination of immersive VR with MT showed to be an excellent therapeutic choice as confirmed by In et al. where visual illusion was used to help the patient in the recovery of the Lower Limb Function (37).

Instead, as regards the Upper Limb Function (ULF), VR has not proved to be superior compared to home exercises programs as seen in Hernandez et al. (63).

Following the discovery of the mirror neuron system, it has been years since mirror therapy has been used as a fundamental tool for recovery in stroke patients. Therefore, in our research it is not surprising the great number of articles regarding new upgrades of this technique: for example, Arya et al. showed how an activity-based mirror therapy was more effective than the conventional one (32).

Assuming the positive effects of MT, some authors have combined it with other rehabilitation technologies such as afferent electrical stimulation (31) and TDCS (Transcranial Direct Current Stimulation). Minimum collateral effects were found in the second work: a patient dropped out the study for the appearance of a headache (62). The pairing of tDCS with MT may influence restoration of daily function and movement efficiency of the paretic hand in chronic stroke patients. Sequentially applying tDCS prior to MT seems to be advantageous for enhancing daily function and hand movement control and may be considered as a potentially useful strategy in future clinical application. Both these hybrid techniques have reported good results especially regarding muscle strength.

Choi et al. have implemented mirror therapy with a gesture recognition device obtaining significant changes in motor function but also in quality of life and depression (60). A limit of this technique was found by Colomer et al. and relates to the severity of the upper limb impairment: patients with severely impaired UE function, treated with MT, showed some improvements in tactile sensation similarly to the control group in FMA and ability subscales (61).

However, authors agree in suggesting MT even in completely plegic stroke survivors, as it uses visual stimuli for producing a desired response in the affected limb to have effects not just on motor impairments but also on sensations, visuospatial neglect, and pain after stroke. Also, MT is an easy and low-cost method.

Son et al. demonstrated how self-observation training (a specific protocol based on eliciting mirror neuron system) associated with exercise therapy can improve muscle activity of the most important muscles involved in gait (33). Also, a video of treadmill walking action taken at various speeds can be an optimal instrument for the recovery of gait functions as demonstrated by Bang et al. (34). Cho et al. used an innovative program based on motor imagery training where patients were asked to conceive motor patterns associated with gait; there were improvements in many outcomes such as gait abilities and balance (35). The same technique was used by Dickstein et al. but it was performed in a household setting with optimal results (36). Somatosensory training was treated by Alwhaibi et al. and De Diego et al. with the purpose of acquiring some latent function, as actually noticed in the results obtained in the FIM score and in the sensory tests (40, 64). In our research, a technique that obtained excel-lent achievements both in postural sway and in upper limb function was the local vibration stimulus training program (44, 68).

More in detail, Tavernese et al. demonstrated how the segmental muscle vibration can improve, at least in a short-term period, upper limb motor performances of reaching movement (67).

Physical exercise is the basis of rehabilitation treatment after a stroke episode, we therefore tried to define what features it should have to be effective in the chronic stroke patient. For example, high-intensity exercise appears to be effective in gaining gait abilities (stepping amount and rate) and spatiotemporal symmetry as showed by Hornby et al. (47). Its positive influence can also be enhanced by the combination with TENS, placed on the affected lower extremity, as seen in Park et al. work with a reduction of spasticity and an improvement in balance and gait (45).

As a matter of fact, lack of trunk control is usually a critical problem in chronic stroke patient, for this reason plenty of studies are introducing specific new protocols about it.

Karthikbabu et al. tried to demonstrate the efficacy of a plinth and Swiss ball-based trunk exercise regime, but the initial good results were not maintained over the time (12 months follow up) (69). Instead, in the research of Lee et al. the beneficial effects reached with a dual motor task training program were sustained (71). Lee et al. decided to focus on anticipatory postural adjustments (APA) with two different strategies. The one with better results was dynamic neuromuscular stabilization (DNS) with achievements maintained over the time (70). Treadmill Training is another classic fundamental tool that can be used in chronic stroke patient for recovery in gait performance and balance skills as seen in Globas et al. paper where patients improved their walking capacities after a treadmill training (48). In our research we found four studies that tried to ameliorate this technique. Chen I. et al. demonstrated that turning-based treadmill is more effective than the normal one in walking performance (49). This outcome was also studied and improved in Choi et al. work and in Cho et al. work where the treadmill training was associated with a whole-body vibration in the first one and with real-world video recording in the second one (50, 51). Treadmill training was also matched with tilt sensor functional electrical stimulation on common peroneal nerve demonstrating to be a valid instrument in balance, gait and muscle architecture (42).

Aquatic programs in chronic stroke patients seem to be well accepted and performed, presuming an adequate cardiovascular and cognitive condition. Park et al. supplemented a land-based trunk exercise program with an aquatic one in patients with significant improvements in balance, independence, and quality of life (72).

A well specified protocol is Ai Chi which consists of Tai Chi principles applied in water. This form of aquatic exercise involves a total of 19 standardized movement patterns that focus on coordination of body movements with breathing and specific patterns. This practice is safe, standardized, does not require specific equipment, it can be taught in a group setting and allows participants to continue their own. It has been proven to be a valid therapeutic option in improving balance, motor function and in reducing post treatment pain (73, 74).

In our research we found out that other different approaches have been applied to these patients, such as different types of mobilizations (talocrural and self-ankle) as used in An et al. and Park et al. works, which demonstrated how balance and gait parameters can be restored by using them (52, 53).

Instead, Liao et al. established how both lateral wedge soles and visual biofeedback balance training can reinforce balance abilities (55).

Some of the selected studies have shown that chronic stroke patients' rehabilitation can also be performed in a home environment, with or without the presence of the physical therapist, taking for granted an adequate cognitive condition and ability to understand the instructions: in this way the management of the patient after discharging gets simpler (36, 46, 54, 63, 64).

Moreover, a home-based setting allows greater patient compliance. Home rehabilitation makes it possible to contain the high costs of inpatient rehabilitation programs and improve the continuity of care while patients are transferred to home. Moreover, the possibility of treatment at home allows to reduce the economic costs and makes life easier for the patient and the caregiver and is a valid tool during periods of pandemic such as covid.

After discharge from in-hospital rehabilitation, chronic post-stroke patients should have the opportunity to continue the rehabilitation through structured programs to maintain the benefits acquired during intensive rehabilitation treatment.

5. Limitations

The present study represents an overview, through scoping review, of the main rehabilitation techniques commonly used in patients with disabilities secondary to chronic stroke. No comparisons were made between the different neurorehabilitation techniques or the waiting list or with placebo. This comparison will be the subject of future studies.

6. Conclusion

Our study provides an overview of the main rehabilitation techniques used in patients with chronic stroke sequelae with different levels of efficacy. For a long time, it was believed that the window of opportunity within which to provide stroke rehabilitation was limited to the first 3–6 months after the acute event. As a result, too often, rehabilitation resources for managing chronic stroke have not been adequate. But when does one reach a phase of stabilized outcomes and is it therefore correct to speak of chronicity? Although the definition of acute phase and chronic phase in terms of recovery is still debated, there are different evidence in support of a rehabilitation continuity in the chronic hemiplegic patient aimed at guaranteeing further results also in the long term. Considering these considerations, our data suggest that a prosecution of the rehabilitation is possible even after the first 6 months, not only as a maintenance treatment but also aimed to acquire or recover some loss functions. Furthermore, we have noticed how a rehabilitation protocol can be ap-plied in an outpatient setting but also at home, and this could increase patient compliance including caregiver support. The reading of this evidence is intricate by methodological factors such as the variety of used scales and outcomes, follow up timing, range and characteristics of the population studied. Nonetheless other studies are needed to establish shared neuro- rehabilitative protocols with respect to the different characteristics of the patients in the chronic post-stroke phase.

Author contributions

TP, EM, SC, and FS: conceptualization. TP, EM, and SC: methodology. EM and SC: investigation and formal analysis. EM, SC, and MM: data curation. TP, FS, EM, and SC: writing—original draft and preparation. TP, EM, SC, MC, MM, and MP: writing—review and editing. TP, MM, MP, FA, and AB: visualization. TP, MM, and MP: supervision. All authors read and approved the final version of the Manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2016) 47:e98–e169. doi: 10.1161/STR.0000000000000098

2. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, et al. World stroke organization (WSO): global stroke fact sheet 2022. *Int J Stroke*. (2022) 17:18–29. doi: 10.1177/17474930211065917

3. Thrift AG, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, Feigin VL, et al. Global stroke statistics. *Int J Stroke*. (2017) 12:13–32. doi: 10.1177/1747493016676285

4. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol*. (2009) 8:741–54. doi: 10.1016/S1474-4422(09)70150-4

5. Gittler M, Davis AM. Guidelines for adult stroke rehabilitation and recovery. *JAMA*. (2018) 319:820–1. doi: 10.1001/jama.2017.22036

6. Yagura H, Miyai I, Seike Y, Suzuki T, Yanagihara T. Benefit of inpatient multidisciplinary rehabilitation up to 1 year after stroke. *Arch Phys Med Rehabil*. (2003) 84:1687–91. doi: 10.1053/S0003-9993(03)00286-7

7. Miyai I, Suzuki T, Kii K, Kang J, Kajiura I. Functional outcome of multidisciplinary rehabilitation in chronic stroke. *Neurorehabil Neural Repair*. (1998) 12:95–9.

8. Coscia M, Wessel MJ, Chaudary U, Millán J, Micera S, Guggisberg A, et al. Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain*. (2019) 142:2182–97. doi: 10.1093/brain/awz181

9. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke*. (2001) 32:1279–84. doi: 10.1161/01.STR.32.6.1279

10. Page SJ, Gater DR, Bach-Y-Rita P. Reconsidering the motor recovery plateau in stroke rehabilitation. *Arch Phys Med Rehabil*. (2004) 85:1377–81. doi: 10.1016/j.apmr.2003.12.031

11. Smith G V, Silver KHC, Goldberg AP, Macko RF. *Task-oriented exercise improves hamstring strength and spastic reflexes in chronic stroke patients*. (1999). Available at: http://www.strokeaha.org

12. Whitall J, Waller SMC, Silver KHC, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke*. (2000) 31:2390–5. doi: 10.1161/01.STR.31.10.2390

13. Cakar E, Durmus O, Tekin L, Dincer U, Kiralp MZ. The ankle-foot orthosis improves balance and reduces fall risk of chronic spastic hemiparetic patients. *Eur J Phys Rehabil Med*. (2010) 46:363–8.

14. Januário F, Campos I, Amaral C. Rehabilitation of postural stability in ataxic/hemiplegic patients after stroke. *Disabil Rehabil*. (2010) 32:1775–9. doi: 10.3109/09638281003734433

15. Michielsen ME, Selles RW, Van Der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabil Neural Repair*. (2011) 25:223–33. doi: 10.1177/1545968310385127

16. Ehrensberger M, Simpson D, Broderick P, Blake C, Horgan F, Hickey P, et al. Unilateral strength training and Mirror therapy in patients with chronic stroke: a pilot randomized trial. *Am J Phys Med Rehabil*. (2019) 98:657–65. doi: 10.1097/PHM.0000000000001162

17. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev*. (2014) 2014:CD010820. doi: 10.1002/14651858.CD010820.pub2

18. Pekna M, Pekny M, Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke*. (2012) 43:2819–28. doi: 10.1161/STROKEAHA.112.654228

19. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke* (1988);19:1497–1500. doi: 10.1161/01.STR.19.12.1497

1524-4628.

20. Barnes M, Dobkin B, Bogousslavsky J. *Recovery after stroke* Cambridge University Press (2005).

21. Levin MF, Kleim JA, Wolf SL. What do motor recovery and compensationg mean in patients following stroke? *Neurorehabil Neural Repair*. (2009) 23:313–9. doi: 10.1177/1545968308328727

22. Stroke Prevention and Educational Awareness Diffusion. *Ictus cerebrale: Linee guida italiane di prevenzione e trattamento* (2016).

23. Management Stroke Rehabilitation Working Group. *VA/Dod clinical practice guideline for the management of stroke rehabilitation* The Management of Stroke Rehabilitation Working Group. Available at: http://www.healthquality.va.govor http://www.qmo.amedd.army.mil.

24. Teasell R, Foley Msc N, Mbbs NH, Salter Msc K, Cotoi Msc A, Richardson M. *Evidence-based review of stroke rehabilitation*. 17th ed Available at: www.ebrsr.com.

25. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth*. (2020) 18:2119–26. doi: 10.11124/JBIES-20-00167

26. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. (2018) 169:467–73. doi: 10.7326/M18-0850

27. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother*. (2009) 55:129–33. doi: 10.1016/S0004-9514(09)70043-1

28. Calabrò RS, Naro A, Russo M, Bramanti P, Carioti L, Balletta T, et al. Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial. *J Neuroeng Rehabil*. (2018) 15:35. doi: 10.1186/s12984-018-0377-8

29. Kooncumchoo P, Namdaeng P, Hanmanop S, Rungroungdouyboon B, Klarod K, Kiatkulanusorn S, et al. Gait improvement in chronic stroke survivors by using an innovative gait training machine: a randomized controlled trial. *Int J Environ Res Public Health*. (2022) 19:224. doi: 10.3390/ijerph19010224

30. Wu M, Landry JM, Kim J, Schmit BD, Yen SC, Macdonald J. Robotic resistance/assistance training improves locomotor function in individuals poststroke: a randomized controlled study. *Arch Phys Med Rehabil*. (2014) 95:799–806. doi: 10.1016/j.apmr.2013.12.021

31. Lee D, Lee G. Effect of afferent electrical stimulation with mirror therapy on motor function, balance, and gait in chronic stroke survivors: a randomized controlled trial. *Eur J Phys Rehabil Med*. (2019) 55:442–9. doi: 10.23736/S1973-9087.19.05334-6

32. Arya KN, Pandian S, Kumar V. Effect of activity-based mirror therapy on lower limb motor-recovery and gait in stroke: a randomised controlled trial. *Neuropsychol Rehabil*. (2019) 29:1193–210. doi: 10.1080/09602011.2017.1377087

33. Son YL, Kim JW. The effects of mirror neuron system-based self-observation training on lower limb muscle activity and dynamic balance in patients with chronic stroke. *J Phys Ther Sci*. (2018) 30:1241–4. doi: 10.1589/jpts.30.1241

34. Bang DH, Shin WS, Kim SY, Choi JD. The effects of action observational training on walking ability in chronic stroke patients: a double-blind randomized controlled trial. *Clin Rehabil*. (2013) 27:1118–25. doi: 10.1177/0269215513501528

35. Cho HY, Kim JS, Lee GC. Effects of motor imagery training on balance and gait abilities in post-stroke patients: a randomized controlled trial. *Clin Rehabil*. (2013) 27:675–80. doi: 10.1177/0269215512464702

36. Dickstein R, Deutsch JE, Yoeli Y, Kafri M, Falash F, Dunsky A, et al. Effects of integrated motor imagery practice on gait of individuals with chronic stroke: a half-crossover randomized study. *Arch Phys Med Rehabil*. (2013) 94:2119–25. doi: 10.1016/j.apmr.2013.06.031

37. In T, Lee K, Song C. Virtual reality reflection therapy improves balance and gait in patients with chronic stroke: randomized controlled trials. *Med Sci Monit*. (2016) 22:4046–53. doi: 10.12659/MSM.898157

38. Kayabinar B, Alemdaroğlu-Gürbüz İ, Yilmaz Ö. The effects of virtual reality augmented robot-assisted gait training on dual-task performance and functional measures in chronic stroke: a randomized controlled single-blind trial. *Eur J Phys Rehabil Med*. (2021) 57:227–37. doi: 10.23736/S1973-9087.21.06441-8

39. Lloréns R, Gil-Gómez JA, Alcañiz M, Colomer C, Noé E. Improvement in balance using a virtual reality-based stepping exercise: a randomized controlled trial involving individuals with chronic stroke. *Clin Rehabil*. (2015) 29:261–8. doi: 10.1177/0269215514543333

40. Alwhaibi RM, Mahmoud NF, Basheer MA, Zakaria HM, Elzanaty MY, Ragab WM, et al. Impact of somatosensory training on neural and functional recovery of lower extremity in patients with chronic stroke: a single blind controlled randomized trial. *Int J Environ Res Public Health*. (2021) 18:583:1–10. doi: 10.3390/ijerph18020583

41. Yang YR, Mi PL, Huang SF, Chiu SL, Liu YC, Wang RY. Effects of neuromuscular electrical stimulation on gait performance in chronic stroke with inadequate ankle control - a randomized controlled trial. *PLoS One*. (2018) 13:e0208609. doi: 10.1371/journal.pone.0208609

42. Bethoux F, Rogers HL, Nolan KJ, Abrams GM, Annaswamy TM, Brandstater M, et al. The effects of peroneal nerve functional electrical stimulation versus ankle-foot orthosis in patients with chronic stroke: a randomized controlled trial. *Neurorehabil Neural Repair*. (2014) 28:688–97. doi: 10.1177/1545968314521007

43. Beaulieu LD, Massé-Alarie H, Brouwer B, Schneider C. Noninvasive neurostimulation in chronic stroke: a double-blind randomized sham-controlled testing of clinical and corticomotor effects. *Top Stroke Rehabil*. (2015) 22:8–17. doi: 10.1179/1074935714Z.0000000032

44. Lee SW, Cho KH, Lee WH. Effect of a local vibration stimulus training programme on postural sway and gait in chronic stroke patients: a randomized controlled trial. *Clin Rehabil*. (2013) 27:921–31. doi: 10.1177/0269215513485100

45. Park J, Seo D, Choi W, Lee S. The effects of exercise with TENS on spasticity, balance, and gait in patients with chronic stroke: a randomized controlled trial. *Med Sci Monit*. (2014) 20:1890–6. doi: 10.12659/MSM.890926

46. Lim JH, Lee HS, Song CS. Home-based rehabilitation programs on postural balance, walking, and quality of life in patients with stroke: a single-blind, randomized controlled trial. *Medicine*. (2021) 100:E27154. doi: 10.1097/MD.0000000000027154

47. Hornby TG, Henderson CE, Plawecki A, Lucas E, Lotter J, Holthus M, et al. Contributions of stepping intensity and variability to mobility in individuals poststroke. *Stroke*. (2019) 50:2492–9. doi: 10.1161/STROKEAHA.119.026254

48. Globas C, Becker C, Cerny J, Lam JM, Lindemann U, Forrester LW, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabil Neural Repair*. (2012) 26:85–95. doi: 10.1177/1545968311418675

49. Chen IH, Yang YR, Chan RC, Wang RY. Turning-based treadmill training improves turning performance and gait symmetry after stroke. *Neurorehabil Neural Repair*. (2014) 28:45–55. doi: 10.1177/1545968313497102

50. Choi W, Han D, Kim J, Lee S. Whole-body vibration combined with treadmill training improves walking performance in post-stroke patients: a randomized controlled trial. *Med Sci Monit*. (2017) 23:4918–25. doi: 10.12659/MSM.904474

51. Cho KH, Lee WH. Effect of treadmill training based real-world video recording on balance and gait in chronic stroke patients: a randomized controlled trial. *Gait Posture*. (2014) 39:523–8. doi: 10.1016/j.gaitpost.2013.09.003

52. Hwang DY, Lee HJ, Lee GC, Lee SM. Treadmill training with tilt sensor functional electrical stimulation for improving balance, gait, and muscle architecture of tibialis anterior of survivors with chronic stroke: a randomized controlled trial. *Technol Health Care*. (2015) 23:443–52. doi: 10.3233/THC-150903

53. An CM, Jo SO. Effects of talocrural mobilization with movement on ankle strength, mobility, and weight-bearing ability in hemiplegic patients with chronic stroke: a randomized controlled trial. *J Stroke Cerebrovasc Dis*. (2017) 26:169–76. doi: 10.1016/j.jstrokecerebrovasdis.2016.09.005

54. Park D, Cynn HS, Yi C, Choi WJ, Shim JH, Oh DW. Four-week training involving self-ankle mobilization with movement versus calf muscle stretching in patients with chronic stroke: a randomized controlled study. *Top Stroke Rehabil*. (2020) 27:296–304. doi: 10.1080/10749357.2019.1690831

55. Liao WC, Lai CL, Hsu PS, Chen KC, Wang CH. Different weight shift trainings can improve the balance performance of patients with a chronic stroke: a randomized controlled trial. *Medicine*. (2018) 97:e13207. doi: 10.1097/MD.0000000000013207

56. Cho KH, Song WK. Robot-assisted reach training with an active assistant protocol for long-term upper extremity impairment poststroke: a randomized controlled trial. *Arch Phys Med Rehabil*. (2019) 100:213–9. doi: 10.1016/j.apmr.2018.10.002

57. Cordo P, Wolf S, Lou JS, Bogey R, Stevenson M, Hayes J, et al. Treatment of severe hand impairment following stroke by combining assisted movement, muscle vibration, and biofeedback. *J Neurol Phys Ther*. (2013) 37:194–203. doi: 10.1097/NPT.0000000000000023

58. Hung C-s, Lin K-c, Chang W-y, Huang W-c, Chang YJ, Chen CL, et al. Unilateral vs bilateral hybrid approaches for upper limb rehabilitation in chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. (2019) 100:2225–32. doi: 10.1016/j.apmr.2019.06.021

59. Lin CH, Chou LW, Luo HJ, Tsai PY, Lieu FK, Chiang SL, et al. Effects of computer-aided interlimb force coupling training on paretic hand and arm motor control following chronic stroke: a randomized controlled trial. *PLoS One*. (2015) 10:e0131048. doi: 10.1371/journal.pone.0131048

60. Choi HS, Shin WS, Bang DH. Mirror therapy using gesture recognition for upper limb function, neck discomfort, and quality of life after chronic stroke: a single-blind randomized controlled trial. *Med Sci Monit*. (2019) 25:3271–8. doi: 10.12659/MSM.914095

61. Colomer C, Noè E, Llorens R. Mirror therapy in chronic stroke survivors with severely impaired upper limb function: a randomized controlled trial. *Eur J Phys Rehabil Med*. (2016) 52:271–8.

62. Cho HS, Cha HG. Effect of mirror therapy with tDCS on functional recovery of the upper extremity of stroke patients. *J Phys Ther Sci*. (2015) 27:1045–7. doi: 10.1589/jpts.27.1045

63. Hernandez A, Bubyr L. Virtual reality-based rehabilitation as a feasible and engaging tool for the management of chronic poststroke upper-extremity function recovery: randomized controlled trial. *JMIR Serious Games*. (2022) 1:e37506. doi: 10.2196/preprints.37506

64. De Diego C, Puig S, Navarro X. A sensorimotor stimulation program for rehabilitation of chronic stroke patients. *Restor Neurol Neurosci*. (2013) 31:361–71. doi: 10.3233/RNN-120250

65. Lee YY, Lin KC, Cheng HJ, Wu CY, Hsieh YW, Chen CK. Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial. *J Neuroeng Rehabil*. (2015) 12:96. doi: 10.1186/s12984-015-0088-3

66. Knutson JS, Gunzler DD, Wilson RD, Chae J. Contralaterally controlled functional electrical stimulation improves hand dexterity in chronic hemiparesis: a randomized trial. *Stroke*. (2016) 47:2596–602. doi: 10.1161/STROKEAHA.116.013791

67. Tavernese E, Paoloni M, Mangone M, Mandic V, Sale P, Franceschini M, et al. Segmental muscle vibration improves reaching movement in patients with chronic stroke. A randomized controlled trial. *Neurorehabilitation*. (2013) 32:591–9. doi: 10.3233/NRE-130881

68. Costantino C, Galuppo L, Romiti D. Short-term effect of local muscle vibration treatment versus sham therapy on upper limb in chronic post-stroke patients: a randomized controlled trial. *Eur J Phys Rehabil Med*. (2017) 53:32–40. doi: 10.23736/S1973-9087.16.04211-8

69. Karthikbabu S, Chakrapani M, Ganesan S, Ellajosyula R, Solomon JM. Efficacy of trunk regimes on balance, mobility, physical function, and community reintegration in chronic stroke: a parallel-group randomized trial. *J Stroke Cerebrovasc Dis*. (2018) 27:1003–11. doi: 10.1016/j.jstrokecerebrovasdis.2017.11.003

70. Lee NG, You J, Yi CH, Jeon HS, Choi BS, Lee DR, et al. Best Core stabilization for anticipatory postural adjustment and falls in hemiparetic stroke. *Arch Phys Med Rehabil*. (2018) 99:2168–74. doi: 10.1016/j.apmr.2018.01.027

71. Lee Y, Lee J, Shin S, Lee S. The effect of dual motor task training while sitting on trunk control ability and balance of patients with chronic stroke. *J Phys Ther Sci*. (2012) 24:345–9. doi: 10.1589/jpts.24.345

72. Park HK, Lee HJ, Lee SJ, Lee WH. Land-based and aquatic trunk exercise program improve trunk control, balance and activities of daily living ability in stroke: a randomized CLINICAL trial. *Eur J Phys Rehabil Med*. (2019) 55:687–94. doi: 10.23736/S1973-9087.18.05369-8

73. Pérez-De la Cruz S. Influence of an aquatic therapy program on perceived pain, stress, and quality of life in chronic stroke patients: a randomized trial. *Int J Environ Res Public Health*. (2020) 17:1–12. doi: 10.3390/ijerph17134796

74. Ku PH, Chen SF, Yang YR, Lai TC, Wang RY. The effects of ai chi for balance in individuals with chronic stroke: a randomized controlled trial. *Sci Rep*. (2020) 10:1201. doi: 10.1038/s41598-020-58098-0

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Gait analysis patterns and rehabilitative interventions to improve gait in persons with hereditary spastic paraplegia: a systematic review and meta-analysis

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Background: Hereditary spastic paraplegias (HSPs) are a group of inheritance diseases resulting in gait abnormalities, which may be detected using instrumented gait analysis. The aim of this systematic review was 2-fold: to identify specific gait analysis patterns and interventions improving gait in HSP subjects.

Methods: A systematic review was conducted in PubMed, Cochrane Library, REHABDATA, and PEDro databases, in accordance with reporting guidelines of PRISMA statement and Cochrane's recommendation. The review protocol was recorded on the PROSPERO register. Patients with pure and complicated HSP of any age were included. All types of studies were included. Risk of bias, quality assessment, and meta-analysis were performed.

Results: Forty-two studies were included: 19 were related to gait analysis patterns, and 24 were intervention studies. The latter ones were limited to adults. HSP gait patterns were similar to cerebral palsy in younger subjects and stroke in adults. Knee hyperextension, reduced range of motion at knee, ankle, and hip, reduced foot lift, and increased rapid trunk and arm movements were reported. Botulinum injections reduced spasticity but uncovered weakness and improved gait velocity at follow-up. Weak evidence supported intrathecal baclofen, active intensive physical therapy (i.e., robot-assisted gait training, functional exercises, and hydrotherapy), and functional electrical stimulation. Some improvements but adverse events were reported after transcranial magnetic stimulation, transcutaneous spinal direct current stimulation, and spinal cord stimulation implant.

Conclusion: Knee hyperextension, non-sagittal pelvic movements, and reduced ROM at the knee, ankle, and hip represent the most peculiar patterns in HSP, compared to diplegic cerebral palsy and stroke. Botulinum improved comfortable gait velocity after 2 months. Nonetheless, interventions reducing spasticity might result in ineffective functional outcomes unveiling weakness. Intensive active physical therapy and FES might improve gait velocity in the very short term.

KEYWORDS

gait analysis, walking, physical therapy modalities, rehabilitation, spasticity, botulinum toxins, spastic paraparesis, gait disorders

1. Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous and large group of neurodegenerative diseases of which the main common feature is lower limb spasticity and weakness, based on the retrograde distal degeneration of the corticospinal and posterior column pathways (1). The key diagnostic clinical finding, characterizing the pure forms, is progressive upper motor neuron (UMN) syndrome of the lower limb which includes spasticity (1), hyperreflexia, extensor plantar responses, weakness, and loss of selective control (2, 3). In complicated forms (4), additional neurologic deficits are present, such as ataxia, amyotrophy, optic atrophy, pigmentary retinopathy, intellectual disability, extrapyramidal signs, dementia, deafness, ichthyosis, peripheral neuropathy, and epilepsy, with neuroimaging abnormalities such as cerebellar atrophy (2). Prevalence is estimated at 3–10 cases per 100.000 in the European population (2) and incidence at 1.27–9.6/100.000 (5). Depending on the presence or absence of a family history of spastic paraparesis and the results of genetic testing, the disease is named HSP or SSP, as sporadic (6). The genetic basis of HSP is complex, with more than 70 known subtypes involving autosomal, dominant or recessive, and X-linked inheritance patterns (1, 7), causing dysfunction of protein involved in intracellular trafficking or mitochondrial function (7, 8). The age of symptom onset, rate of progression, and degree of disability are often variable among different genetic types of HSP, as well as within individual families having the same gene mutation (6, 9, 10). Early childhood onset forms tend to be relatively non-progressive over many years, resembling spastic diplegia forms of cerebral palsy (11). On the contrary, late onset is associated with more progressive disease and gait decline (9, 12).

The gait impairment is the most frequent clinical sign in HSP patients, and it is often recognized as the onset symptom (10, 13). It results from the combination of several factors such as spasticity, weakness, loss of selective control, impaired proprioception, and vibratory sensitivity (3). Identifying the gait characteristics and evolution of HSP subjects is the key to develop a gait functional prognosis for this population and formulate appropriate interventions. In addition, differentiating the HSP gait pattern from similar ones, observed in other pathologies, is desirable to support differential diagnosis. Moreover, gait capacity and balance are mutually influenced; then, analyzing the gait pattern is also useful for identifying specific issues that increase the risk of falls (14). Computerized gait analysis (GA) is the best way to provide a reliable and repeatable measurement of specific gait parameters and impairments (6, 15). Some authors have investigated the deficits in gait in HSP using GA, compared to their healthy peers or other patients, mostly to stroke or spastic diplegic cerebral palsy (DCP) subjects. Nonetheless, no review has systematically summarized the evidence from these studies to comprehensively describe the different observed gait patterns. Some review studies have been published (16, 17) regarding treatment in HSP patients, but none focused on the effect of the rehabilitative treatment on gait function. The aim of the present systematic review was 2-fold: to identify which gait patterns characterize HSP patients using computed gait analysis and to identify which rehabilitative treatment (orthotic devices, botulinum toxin, physiotherapy, physical therapy, and other approaches) leads to improvement in any type of gait parameters in hereditary spastic paraplegia patients.

Abbreviations: 10MWT, 10-m walking test; 2MWT, 2-min walking test; APAs, anticipatory postural adjustments; BoNT-A, Botulinum Neurotoxin-A; COM, center of mass; COP, center of pressure; DCP, diplegic cerebral palsy; FES, functional electric stimulation; FRT, Functional Reach Test; GA, gait analysis; HSP, hereditary spastic paraplegia; ITB, intrathecal baclofen; MAS, modified Ashworth scale; MOS, margin of stability; MRC, Medical Research Council; NRS, numeric rating scale; RF, rectus femoris; RoB, risk of bias; ROM, range of motion; rTMS, transcranial magnetic stimulation; SAS, starling acoustic stimulus; SCS, spinal cord stimulation; SO, soleus; SPRS, Spastic Paraplegia Rating Scale; SSP, sporadic spastic paraplegia; TA, tibialis anterior; TUG, Timed UP and Go test; UMN, upper motor neuron; VAS, visual analogical scale; VEP, visual evoked potential; WHS, Walking Handicap Scale.

2. Methods

2.1. Search and selection

The present study consists of a systematic review of primary studies and was performed and reported in accordance with the reporting guidelines of the PRISMA statement (18) and Cochrane's methodological recommendation (19). The review protocol was registered on the PROSPERO public online register for systematic review, with registration number CRD42021290141. The study was conducted according to the pre-specified protocol, except for quality and risk-of-bias assessment, which was performed with more specific and adequate tools; in addition, a meta-analysis was performed.

The scope of the systematic review was structured according to the Patients, Intervention, Control, and Outcome (PICO) framework for intervention:

- P: patients of all ages with a diagnosis of pure or complicated form of HSP
- I: gait pattern description (3D gait analysis) or intervention to improve gait pattern (orthotic devices/botulinum toxin/physiotherapy/physical therapy, and other rehabilitative approaches).
- C: gait analysis pattern of healthy controls or of patients affected by other diseases and/or no intervention or different interventions to improve gait function in HSP
- O: variables of 3-dimensional gait analysis (kinematics and/or kinetics and/or surface electromyography and/or spatiotemporal parameters) for gait pattern description. Any gait parameter or outcome measure to assess gait improvement after intervention (gait analysis and/or walk/gait speed and/or mobility test and/or spatiotemporal parameters and/or any type of walking test).

A unique search strategy was considered including both aims of the present review, based on an overlap of keywords and terms. Search procedures are described in Supplementary Table 1. A literature search was performed on 10 May 2021 in four international databases (PubMed, Cochrane Library, REHABDATA, and PEDro). Articles published from the inception of databases to 10 May 2021 were searched, with no limit relative

to the year of publication, language, age, and type of primary study design. Other articles were also obtained from the reference lists of articles identified by the primary search in the databases. Pharmacological treatments were excluded from the search because they were the object of a recent review study (16).

The population of interest included ambulatory HSP patients, able to perform gait analysis, with a definite diagnosis of HSP or HSP/SSP according to Harding or McDermott criteria (13, 20), with both pure and complicated forms, of all ages. Studies were included if they presented a gait analysis evaluation in HSP patients, with or without comparison with healthy or pathological controls. Studies assessing gait function, by means of any type of gait outcome measure, following an intervention, were also included. Outcomes of interest were the variables of computerized gait analysis (including spatiotemporal parameters and kinetic and kinematic variables) and any type of gait assessment only following gait-focused treatment. Exclusion criteria were as follows: animal study, languages different from English and Italian with no possibility to achieve an official translated version, ongoing study or lacking publication of results, and mixed samples without reporting specific results in HSP patients. According to these inclusion and exclusion criteria, all studies were screened first by title/abstract and then by full text by two independent groups of two authors each (SF, AC, GM, and IS). Each group was blind to each other's decisions. Any disagreement was resolved through discussion among authors. Not retrieved articles and ongoing studies were just recorded as not retrieved.

2.2. Data extraction

Two authors independently completed the data extraction (SF and AC), sorting the information into two different content areas, one focused on HSP gait-analysis-pattern description and the other focused on rehabilitative interventions to improve gait (intervention). The authors extracted data about study design and methodology, participant characteristics, protocol details, outcome measures, and results of the studies. Any disagreement among the authors was discussed and resolved by consensus.

2.3. Quality and risk-of-bias assessment

The quality of studies was assessed by means of a checklist approach using the Joanna Briggs Institute (JBI) critical appraisal tool (21) for case–control studies, case series, and case report studies. These scales enquired 8 to 10 items, questioning information regarding study design, population, intervention, and outcome details, and whenever appropriate, statistical analysis quality. According to the study by George et al. (22), a cutoff score >70% was considered a sufficient level of quality, while a quality score equal or lower suggested some methodological limitations. The National Institutes of Health (NHI) quality assessment tool (23, 24) was used for quality assessment in before-after (pre-post) studies without a control group, assigning a quality rating as "Good", "Fair", or "Poor" according to NIH guidance (23). This scale consists of 12 items questioning the studies' internal validity and risk of bias. The Physiotherapy Evidence Database (PEDro) scale (25) was used for randomized controlled studies (RCTs). It consists of 11 items enquiring information about inclusion criteria, randomization and assignation process, population features, blinding of patients and operators, dropout and missing data, results, and statistical analysis report. Total PEDro scores of 0–3 were considered "Poor", 4–5 "Fair", 6–8 "Good", and 9–10 "Excellent". The risk of bias (RoB) was assessed also with a domain-based approach using the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) (26, 27) tool in controlled studies and using version 2 of the Cochrane risk-of-bias (ROB2) tool for RCTs (specific for crossover design) (28, 29). The ROBINS tool enquired about the following dimensions: bias due to confounding (D1), in the selection of participants (D2) and the classification of interventions (D3), deviation from intended interventions (D4), missing outcome data (D5), bias in the measurement of the outcome (D6), and in the selection of the reported results (D7). The ROB2 tool enquired about the following dimensions: bias arising from the randomization process (D1) and from period and carryover effects (D1b), bias due to deviation from the intended intervention (D2), and to missing outcome data (D3), and bias in the measurement of the outcome (D4) and in the selection of the reported results (D5). The same two independent groups of reviewers (SF, AC, GM, and IS) assessed the methodological quality and the risk of bias of all the included studies. Any disagreement between the two groups was resolved through discussion among the authors. The assessment of quality and RoB did not provide criteria for excluding articles but for stratifying them.

2.4. Meta-analysis

Studies performing the same type of treatment, sharing almost one outcome measure, and having a sample >1 participant were selected for the meta-analysis.

The meta-analyses were carried out using R software (30) and the package "Metafor" (31) on the main results of the selected studies that include the number of observations (n), the means, and the standard deviations (sd). Heterogeneity among the studies was tested with Cochran's Q-test (32), which tests whether the variability in the observed effect sizes or outcomes is larger than would be expected based on sampling variability alone. The estimation of the weighted means was carried out via a fixed effect model when no significant heterogeneity was detected among studies, or a random effect model otherwise.

To evaluate the significance of the effect of the treatment at the different time points, a random effect model was used, estimating the standardized mean difference and reporting the 95% confidence interval as summary statistics. The standard deviation of the change was performed with the method suggested by Morris et al. (33), taking the correlation coefficient $r = 0.40$ as a conservative estimate.

Since studies might have differences in such aspects as quality, which might influence the result of meta-analysis, a sensitivity analysis was conducted changing the effect model and removing the studies with a higher risk of bias to confirm the robustness of our findings.

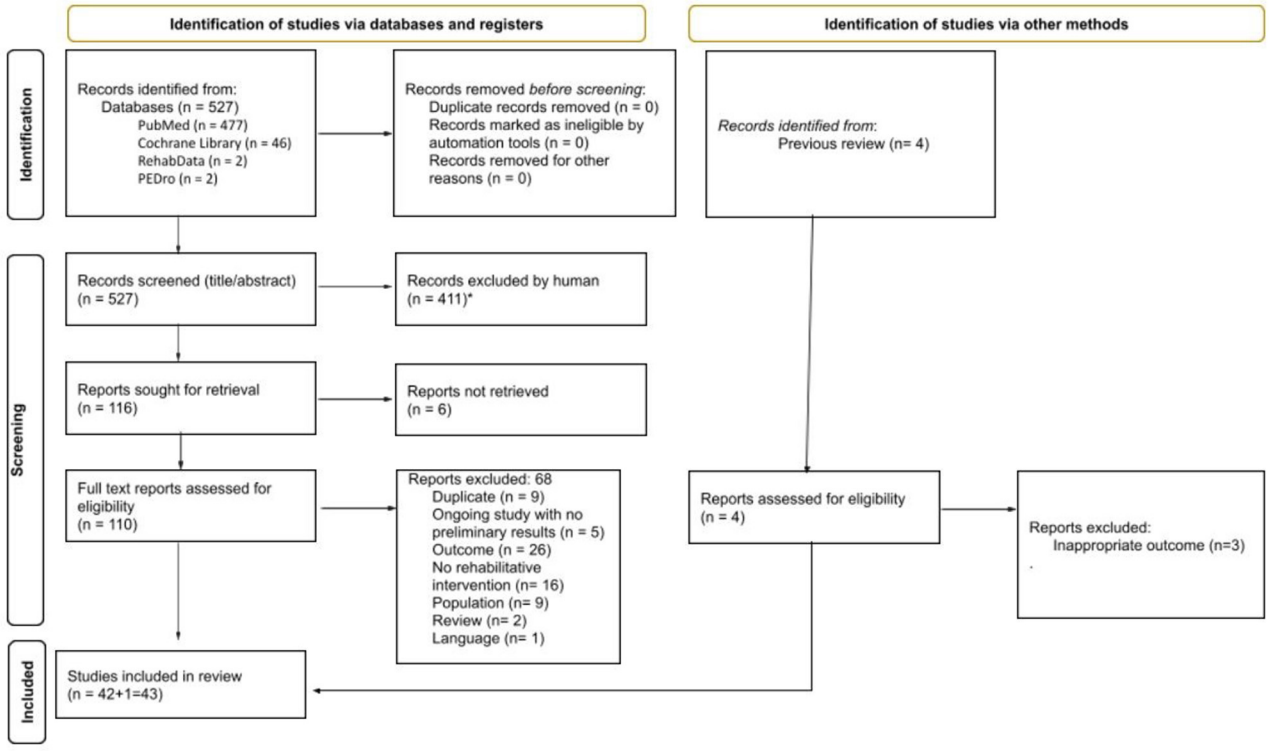

FIGURE 1
PRISMA flow diagram.

3. Results

Figure 1 provides details about study identification and selection (PRISMA flow diagram). A total of 527 records were found through database searches. Exclusion based on title/abstract screening resulted in 116 full texts being examined for eligibility, whereas 411 articles did not meet the inclusion criteria. After full-text analysis, 43 studies were finally included in the review and were divided as follows: 19 in the gait analysis pattern (GA pattern) database and 24 in the intervention database.

3.1. Quality and risk-of-bias assessment

The results of the quality assessment are represented in Tables 1, 2. An overall synthesis of RoB of included studies is represented in Figures 2, 3. Concerning the confounding factors, age, weight, time from onset, gender, walking abilities and/or aids, and gait analysis protocol were considered relevant to identify and compare gait analysis between groups. For intervention studies, examples of confounding include differences at baseline in patients' characteristics and co-interventions such as drug intake.

3.1.1. Quality and rob of gait pattern studies

The quality assessment of GA pattern studies is represented in Table 1. Among the case–control studies, only two studies, namely Adair et al. (40) and Cimolin et al. (34), did not reach a sufficient quality score because of a lack of adequate matching groups and identifying confounding factors. In addition, some concerns were resolved about statistical analysis methods in one of these studies (40), such as the use of discrete variable analysis for continuous variables and the lack of any correction method. The other studies achieved a Good (5, 34, 37–39, 41, 42, 44–47) or Fair (6, 7, 9, 35, 43, 70) quality judgment, associated with a low risk of bias, but presented some limitations. Bonnefoy et al. (39) presented groups different in age, Klebe et al. (6) had some incomplete data (no SIAS marker in 6 patients-50% of the sample, for safety device use), and Wolf et al. (37) declared that comparison of more homogeneous subgroups might be possible but with limited statistical power and the risk of additional bias effects. Some authors (6, 35, 39, 43, 46) did not provide a clear description of the subject characteristics, comparability, matching, or recruitment. Regarding the identification and the management of confounding factors, the authors mostly instructed the control subject to walk at a low comfortable speed (38, 42, 44, 46), to avoid any potential bias due to speed differences between groups and to ensure that the general characteristics of gait could be compared. The subject match was also often done based on age. Some authors (40, 41, 44) did not allow the use of aids to perform gait, resulting in a restriction of the sample size.

The RoB of GA studies was assessed by means of the ROBINS-I tool, as represented in Figure 2. A RoB in D1 resulted whenever the authors did not make appropriate matching between patients and control groups, in particular, considering confounding factors such as age, anthropometric data, or walking speed. For example,

TABLE 1 Quality of gait analysis pattern studies assessed by means of the Joanna Briggs Institute (JBI) tools for methodological appraisal of studies.

Case–control Study/JBI Item	Comparability and match		Selection and exposure			Confounding factors identify and deal with		Assessing outcome and exposure length		Statistical analysis	Overall score	Judgment
	1	2	3	4	5	6	7	8	9	10		
Klebe et al. (6)	Y	UN	Y	Y	Y	N	N	Y	Y	Y	7	Fair
Cimolin et al. (34)	Y	UN	UN	Y	Y	N	UN	Y	Y	Y	6	Poor
de Niet et al. (35)	UN	Y	UN	Y	Y	Y	N	Y	Y	Y	7	Fair
Piccinini et al. (36)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8	Good
Wolf et al. (37)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	Good
Marsden et al. (38)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8	Good
Bonnefoy et al. (39)	UN	UN	Y	Y	Y	Y	Y	Y	Y	Y	8	Good
Adair et al. (40)	UN	N	UN	Y	Y	UN	N	Y	Y	UN	4	Poor
Serrao et al. (41)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	Good
Rinaldi et al. (42)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	Good
Martino et al. (43)	Y	UN	Y	Y	Y	N	N	Y	Y	Y	7	Fair
Pulido et al. (5)	Y	Y	UN	Y	Y	Y	UN	Y	Y	Y	8	Good
Serrao et al. (44)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	Good
Van Lith et al. (45)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8	Good
Martino et al. (46)	UN	Y	UN	Y	Y	Y	Y	Y	Y	Y	8	Good
Van Vugt (70)	Y	Y	UN	Y	Y	N	N	Y	Y	Y	7	Fair
Case series Study/JBI Item	**Selection, inclusion and condition measure**					**Information about patients and outcome**				**Statistical analysis**	**Overall score**	
	1	2	3	4	5	6	7	8	9	10		
Armand et al. (9)	Y	Y	Y	UN	UN	Y	Y	Y	UN	Y	7	Fair
Van Beusichem et al. (7)	Y	Y	Y	N	N	Y	Y	UN	Y	NA	7	Fair
Case report study/JBI item*	**Case reporting and description**							**Takeaway lessons**	**/**	**/**	**Overall score**	
	1	2	3	4	5	6	7	8	/	/		
Malone et al. (47)	Y	Y	Y	Y	Y	Y	N	Y	/	/	7	Good

*Case report JBI items: 1. demographic characteristics; 2. patient's history; 3. current clinical condition, 4. diagnostic tests or assessment methods and results; 5. intervention(s) or treatment procedure(s); 6. post-intervention clinical condition; 7. adverse events identifications; 8. takeaway lessons.

Y, Yes; N, No; UN, Unknown; NA, Not Appropriate (counted as Y). Studies are listed by year and in the same year by alphabetic order.

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TABLE 2 Quality of intervention studies assessed by means of the National Health Institutes (NHI) scale for pre-post non-controlled studies, the Joanna Briggs Institute tools for methodological appraisal of studies (JBI) for case reports and case–control studies, and the Physiotherapy Evidence Database (PEDro) scale for RCTs.

Pre-post non-controlled	1	2	3	4	5	6	7	8	9	10	11	12	TOT	Note	Judgment
Klebe et al. (48)	Y	Y	Y	Y	UN	Y	Y	N	Y	Y	Y	NA	9	$n = 22$ pts was judged unclearly in point 5	Good
Rousseaux et al. (49)	Y	Y	N	Y	UN	Y	Y	N	Y	Y	Y	NA	8	Only pure HSP. $n = 15$ pts was judged unclearly in point 5	Fair
Zhang et al. (50)	Y	N	UN	UN	UN	Y	Y	N	Y	Y	N	NA	5	No inclusion criteria and sample description, no multiple time point, and $n = 11$ pts was judged unclearly in point 5	Poor
Bertolucci et al. (51)	Y	Y	N	Y	UN	Y	Y	N	Y	Y	N	NA	7	Only pure genetic HSP. $n = 13$ pts was judged unclearly in point 5. No data in the T2 time point	Fair
de Niet (52)	Y	Y	N	Y	UN	Y	Y	N	Y	Y	Y	NA	8	Only pure HSP. $n = 16$ pts was judged unclearly in point 5	Fair
Denton et al. (53)*	Y	Y	Y	Y	UN	Y	Y	N	Y	Y	N	NA	8	For pre-post features; No multiple time point evaluation	Fair
Marvulli et al. (54)	Y	Y	Y	UN	UN	Y	Y	N	Y	UN	Y	NA	7	$n = 10$ pts was judged unclearly in point 5. No clear statistical analysis	Fair
Servelhere et al. (55)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	10	No multiple time point evaluation, $n = 33$ pts was judged sufficient based on the study by Van Lith 2019	Good
van Lith et al. (56)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	NA	10	Only pure HSP.	Good
Paparella et al. (57)	Y	Y	Y	Y	UN	Y	Y	N	N	UN	Y	NA	7	Retrospective design. $n = 18$, Missed data > 20% at T3. No clear statistical analysis	Fair

NIH Scale for Pre-post not controlled study: 1. Study question; 2. Eligibility criteria and study pop. clear description; 3. If study participants are representative of populations of interest; 4. All eligible participants were enrolled; 5. Sample size for confidence finding; 6. Intervention is clearly described; 7. Outcome measures are clearly described, valid, and reliable; 8. Blinding of outcome assessors; 9. F-up rate (drop out less than 20% and accounted for in analysis - ITT); 10. Appropriate statistical analysis and p-value report; 11. Multiple time points for outcome measures; 12. Statistical analysis at the group level.

(Continued)

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TABLE 2 (Continued)

Case reports	1	2	3	4	5	6	7	8	TOT	Note	Judgment
Pease (58)	Y	Y	Y	Y	Y	Y	N	Y	**7**	No account for adverse events or unanticipated events	Good
Dan et al. (59)	N	N	Y	Y	Y	Y	N	Y	**5**	No account for adverse events or unanticipated events, no description of cases	Fair
Klebe et al. (60)	N	N	N	Y	Y	Y	Y	Y	**5**	No description of the cases	Fair
Molteni et al. (61)	Y	Y	Y	Y	Y	Y	N	Y	**7**	No account for adverse events or unanticipated events	Good
Samuel et al. (62)	Y	Y	Y	Y	Y	Y	N	Y	**7**	No account for adverse events or unanticipated events	Good
Heetla et al. (63)	Y	Y	Y	Y	Y	Y	Y	Y	**8**		Good
Seo et al. (64)	Y	Y	Y	Y	Y	Y	N	Y	**7**	No account for adverse events or unanticipated events	Good
Shin et al. (65)	Y	Y	Y	Y	Y	Y	Y	Y	**8**		Good
Pinto de Souza et al. (8)	Y	Y	Y	Y	Y	Y	Y	Y	**8**		Good
JBI scale for case report: clearly describe 1. Demographic characteristics; 2. Patient's history/timeline; 3. Current clinical condition; 4. Diagnostic tests or assessment methods and results; 5. Intervention(s) or treatment procedure(s); 6. Post-intervention clinical condition; 7. Adverse events identifications; 8. Takeaway lessons											
Case–control	1	2	3	4	5	6	7	8	9	10	TOT	Note	Judgment
Marsden et al. (38)	Y	Y	Y	UN	NA	N	N	Y	Y	Y	**6**	No identification of confounding factors	Fair
JBI scale for case–control: 1. Groups comparability; 2. Appropriate matching; 3. Same criteria for case and control; 4. Validity of exposure measurement; 5. Equal exposure measurement for both groups; 6. Confounding factors identifying; 7. Confounding factors dealing strategy; 8. Validity of outcome assessment; 9. Length of period of exposure; 10. Appropriate statistical analysis.													

(Continued)

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TABLE 2 (Continued)

RCT	1	2	3	4	5	6	7	8	9	10	11	TOT	Note	Judgment
Denton et al. (53)*	*1*	*1*	*0*	*1*	*0*	*0*	*0*	*1*	*0*	*1*	*1*	***6***	For the randomization part. No blinded study.	Good
Denton et al. (66)	1	1	0	1	0	0	0	1	1	1	1	**7**	No blinded study.	Good
Antczak et al. (67)	1	1	1	0	1	0	1	1	0	0	1	**7**	No baseline comparison, no between-group results	Good
Ardolino et al. (68)	1	0	1	0	1	0	1	1	0	1	1	**7**	Alternating allocation is not a randomization process and no baseline comparison	Good
Diniz de Lima et al. (69)	1	1	1	0	1	1	1	1	1	1	1	**10**	No baseline comparison	Excellent
PEDro Scale for RCT: 1. Specific inclusion criteria; 2. Randomization; 3. Concealed assignation; 4. Baseline comparability; 5. Blinding of patients; 6. Blinding of therapists; 7. Blinding of assessors; 8. Drop out < 15% for at least one outcome; 9. Strategy to deal with missing data - Intention to treat; 10. Reported results statistical comparison of at least one outcome; 11. Report of variability data (interval, dev. St.).														

Y: Yes, N: No, UN: Unknown, NA: Not Appropriate (counted as Y), TOT: Total Score. * Analyzed with both assessment tools (see text). Studies are listed by year and in the same year by alphabetic order.

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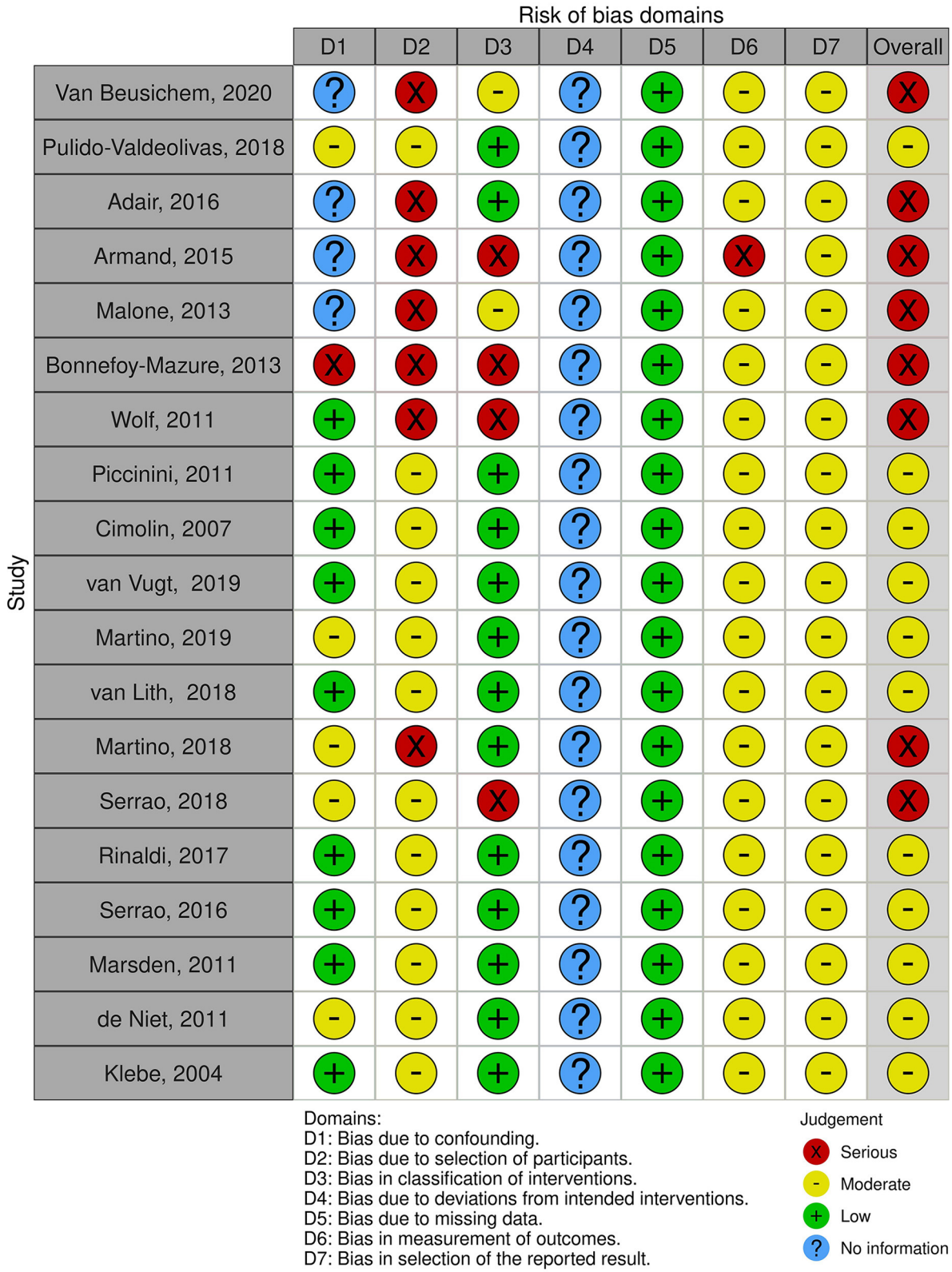

FIGURE 2
Risk of bias of gait analysis pattern studies: ROBINS-I plot.

Bonnefoy et al. (39) presented the patient's group data including the results of different gait analyses performed by the same group of patients over the years. In the study by Adair et al. (40), the healthy control group's data were derived from another study and the information about comparability was not reported. In case reports and case series studies, no information was provided regarding

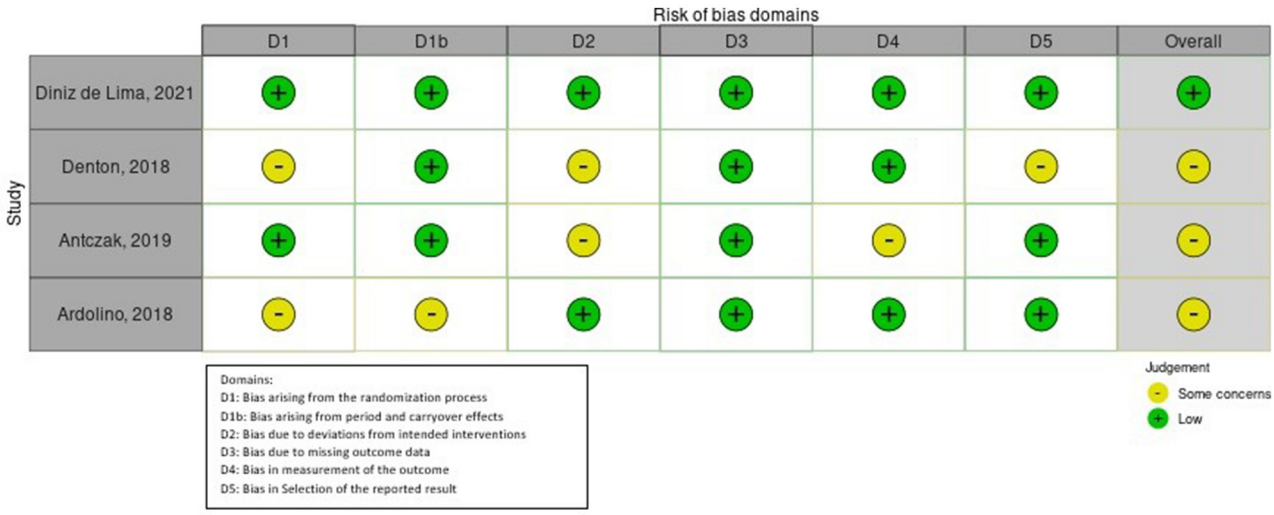

FIGURE 3
Risk of bias of RCT intervention studies: ROB2 plot.

D1. Only one author performed a blind matching among groups (37). A serious risk in D2 was identified in case reports (47) and case series (6, 9): because of the nature of the studies, the results might affect the recruitment. The risk in D2 was also serious if the patients were retrospectively recruited or excluded (37, 39) or recruited depending on the ability to perform gait analysis (40, 43). Studies based on a retrospective design presented a serious risk in D3. D4 was considered inappropriate in GA pattern studies, because no therapeutic intervention was considered, except gait analysis. All the studies achieved low risk in D5 because they did not report a high relevant percentage of missing data. An overall moderate risk in D6 was evidenced because the methods of gait data analysis were comparable across groups and the outcome measure was probably not influenced by the knowledge of the investigators, nonetheless, no one used any type of blinding method for the analysis. Only the study by Armand et al. (9) presented a serious risk in this domain because the authors compared GA performed with different instruments over the years. An overall moderate RoB was evidenced also in D7 because, in all studies, the outcome measurements and analyses were consistent with the a priori plan, though a pre-registered protocol was never reported. Overall, according to the ROBINS guide flowchart, eight studies presented a serious risk and 11 a moderate risk of bias.

3.1.2. Quality and RoB of intervention studies

The quality of intervention studies is represented in Table 2. NHI scale for pre-post non-controlled studies was used for retrospective observational cohort studies (54, 57) and a randomized pre-post-intervention study (53). JBI case–control scale was used to assess the study by Marsden et al. (71) in which the authors compared the effect of different Functional Electric Stimulation (FES) stimulating patterns between HSP patients and controls providing an inter- and intragroup analysis. Denton et al. (53) randomized the order of presentation of two types of intervention (cooling or warming) in a crossover design and analyzed the pre-post effect, including comparison with controls. Therefore, to avoid bias in reporting results, this study was assessed either with pre-post or with RCT tools for quality assessment.

In the NHI scale, the study questions were clearly stated in the title, abstract, or text. Among pre-post studies, the main limitations were inadequate representation of the population of interest, whenever only pure HSP phenotype was included, small sample size with the lack of power calculation, and no-blind design. Item 12 was considered non-applicable for this type of study population. In the final quality judgment, three studies were Good, six were Fair, and one was Poor.

Among case reports, only two did not reach a sufficient score (59, 60). The most frequent limitation was the lack of declaring the presence or the absence of collateral effects (58, 59, 61, 62, 64); Dan et al. (59) and Klebe et al. (60) did not provide a clear description of the patient's characteristics.

Among RCT (crossover design), one study reached an Excellent rating (10/11) (69) and four studies had a Good quality rating (7/11). Only one study (66) presented a baseline comparison between the crossover groups but did not implement any type of blind procedure. In most of these studies, the operator who administered the treatment was not blinded, whereas the patients and the outcome assessors were blind. In 50% of the studies, the management of missing data was addressed.

Limited to crossover RCTs, the RoB was assessed by means of the ROB2 tool (see Figure 3).

Relative to D1, Denton et al. (66) gave no information about concealed allocation, Ardolino et al. (68) used an alternate allocation design which is considered an incorrect randomization process (72). Some concerns were attributed to the study by Ardolino et al. (68) relative to the D1b domain because the authors did not specify whether the number of participants allocated to each of the two groups corresponded or not, even if they took into account sufficient time to carryover the effects. Denton et al. (66) and Antczak et al. (67) presented RoB in D2 because no information was given regarding the possible influence of unblinding treatment

providers on the outcome, even though patients and evaluators were blind. Some concerns in D4 emerged in the study by Antczak et al. (67) because the evaluation of the datasets was not blindly executed. Regarding D5, all the authors referred the study to a pre-specified trial protocol, except for Denton et al. (66). Finally, only Diniz de Lima et al. (69) presented a low RoB.

3.2. Evidence synthesis

3.2.1. Gait analysis pattern studies

All patients fulfilled the diagnostic clinical criteria for HSP according to defined criteria (2, 13, 20). The number of included HSP patients ranged across studies from 6 to 50 for the case–control studies and from 1 to 6 for the case series studies. A total of 341 HSP patients were included across all the 19 studies. No explicit differentiation was done among HSP patients with early or late onset—with onset predominantly above or below 35 years according to Harding (13). Nonetheless, nine studies focused on children and young subjects (named median age <18 years old). Most studies considered pure forms of HSP. Very few patients presented complicated forms, including urinary disturbances (6), intellectual deficit, ataxia, and peripheral neuropathy (7).

Characteristics of included studies are represented in Supplementary Table 2.

Since the included studies considered either minors (mostly compared to spastic diplegic subjects) or adults (compared to stroke patients) as samples, the results are presented separately.

3.2.2. Gait analysis pattern studies in children and adolescents

The results of the included studies are represented in Table 3. With sample sizes ranging from 1 to 29, a total population of 111 patients was included in these studies.

The oldest study by Klebe et al. (6) found a typical gait pattern of patients with sporadic or HSP, compared to healthy subjects, consisting of reduced speed, cadence, and step length; increased step width and increased variation of stride length; reduced sagittal knee range of motion (ROM), with increased minimal knee angle; reduced step height with reduced maximum hip angle; increased maximum ankle angle due to equinovarus feet; and circumduction but no significant variation of foot progression angle.

Van Beusichem et al. (7) applied the Rodda (73) gait classification system for cerebral palsy, to describe the pattern of four subjects affected by a complicated form of HSP due to *de novo* KIF1A mutations. All four gait classes were represented with a progression from classes I and II to III and IV at the last evaluation at 10–18 years.

Pulido-Valdeolivas et al. (5) identified six gait patterns in a group of 26 HSP subjects, aged 4–17 years; the authors compared gait analysis data among patients and healthy subjects, by means of Dynamic Time Warping (5). Pattern I, in the early phase of HSP, was "close to normal" with slightly increased stance time and double support, hip and knee flexion at initial contact (IC), and delayed peak knee flexion in the swing phase. Pattern II presented overall increased anterior pelvic tilt and hip flexion, and increased knee flexion at IC. Pattern III was characterized by knee recurvatum, with reduced and delayed peak knee flexion in the swing phase. Crouch gait corresponded to pattern IV, while constant and severe anterior pelvic tilt, with recurvatum and equinus, distinguished pattern V. Pattern VI was similar to "jump knee" pattern in CP patients (74). Spatiotemporal parameters were relatively spared for patterns I, II, and VI; while they were impaired in patterns III, IV, and V. Asymmetry was described in 27% of HSP subjects, with different patterns in right and left limbs. The authors also found a correlation between GMFCS stages and increased knee flexion at IC, pelvic rotation, and obliquity. They concluded that knee flexion and non-sagittal pelvic movements were relevant indicators of HSP progression. Overlapped polyneuropathy determined an increased range of pelvic rotation in terminal swing and increased time to peak knee flexion, and was most reported in patterns I, II, and III. Abnormal visual evoked potentials (VEPs) were more frequent in subjects classified in pattern III (knee recurvatum).

Armand et al. (9) examined the gait evolution in several subjects affected by HSP (mutations in SPG3A) from the same family. The Gait Deviation Index (75) differed among subjects, but it showed an overall tendency to amelioration from childhood to adolescence and deterioration from adolescence to adulthood.

Adair et al. (40) interestingly analyzed trunk and pelvis kinematics and found increased ROM of the trunk and pelvis in the sagittal plane, with increased posterior trunk lean and anterior pelvic tilt and increased trunk obliquity during the swing phase.

The other four studies included spastic DCP subjects in comparison with HSP and healthy controls (34, 36, 37, 39). HSP and DCP showed similar patterns, and, in both groups, sagittal kinematics could be categorized according to the classification by Sutherland and Davids (74). The principle noticeable difference was that HSP subjects presented more often and longer knee hyperextension during midstance compared to DCP (34, 36, 37). Based on findings by Bonnefoy-Mazure et al. (39), HSP presented significantly reduced gait speed compared to both controls and DCP. Another peculiar characteristic of HSP subjects was increased trunk ROM and peak angular velocity in the sagittal plane during the swing phase (37, 39). HSP presented upper limb patterns similar to healthy subjects, while DCP kept their arms symmetrically elevated, with shoulders abducted and elbows flexed (39).

3.2.3. Gait analysis pattern studies in adults

The results of the included studies are represented in Table 4. The sample size ranged from 6 to 50 subjects. A total of 230 subjects were included in 10 studies; the mean age at the time of GA was 47 years (SD 2.8 years). The mean disease duration among six of these studies (6, 41–44, 46) (in the others no data were available) was 19.7 years, with a prevalence of early-onset forms compared to late-onset forms.

Serrao et al. (41) and Martino et al. (43) identified three kinematic patterns as distinctive of HSP, compared to healthy subjects: increased ROM at the hip, with normal values at knee and ankle; reduced knee and ankle ROM, with normal hip ROM; and reduced ROM at hip, knee, and ankle. A reduced ROM at the knee and ankle was described also in other studies (38, 42, 44, 46), with a

TABLE 3 Results in child GA studies.

Author /design	HSP ST results	HSP Kinematic results	HSP Kinetic results	HSP sEMG or other functional results
Cimolin et al. (34) case–control	HSP showed lower* gait speed, higher* step width, and reduced* anterior step length vs. TD group. Stance time is close to normal and Nsign difference between HSP and SD.	Nsign differences between HSP and SD in pelvis kinematics in all planes. In the sagittal plane: higher ROM of pelvic tilt* and mean pelvic tilt*, higher* hip flexion in Gc (angle at iC, min angle in St and max angle in Sw), than TD. Higher knee angle at initial contact than SD* and TD*. Higher Knee hyperextension in midstance than TD, similar but longer in the HSP compared to the SD. Higher max ankle angle in stance* and in swing*, lower* ankle angle at iC, Lower mean foot progression* than SD. In the transversal plane: normal foot angle, closer to TD.	Nsign statistical difference between HSP and SD. minAP (absorbed power values in early and midstance) close to HC. Lower maxAP* (push-off at terminal stance) than HC.	/
Piccinini et al. (36) case–control	Normal duration of stance phase, shorter* anterior step length, lower* gait speed, and higher* step width when compared to TD group. Nsign differences between HSP and SD.	Frontal and Transversal planes: higher pelvic tilt*, pelvic rotation*, and pelvic obliquity* than TD. Sagittal plane: Higher* hip flexion during the whole Gc than TD (higher* flex at iC, min hip angle in St and max in Sw). Lower mean hip rotation* than SD. Transversal plane: normal hip, normal foot angle progression. Sagittal plane: higher* knee flexion at iC, quite normal during midstance, and lower* flexion in the swing phase than TD. In addition, 70% of knee hyperextension is in midstance than SD. Than SD: Longer* phase of knee hyperextension during midstance and quite normal position of the ankle during the whole gait cycle. Higher* dorsiflexion of the ankle at iC, St, and Sw than SD	Knee: higher knee flexor moment in midstance than SD and HC. Lower max knee power than SD, close to HC; higher values of minimum knee power. Hip: higher hip moment (max extension moment) and power at iS than HC, Nsign with SD. Ankle joint: lower values of the peak in the plantar flexor moment during tS, quite normal values of minimum absorbed power in iS and midS, and more limited values of maximum ankle power generation at push-off than HC, Nsign with SD.	Low activation of rectus femoris during all gait cycle
Wolf et al. (37) retrospective case–control	HSP group presents Nsign with higher double support and Nsign with lower speed than TD and CP, Nsign difference between HSP and CP	Sagittal plane trunk: HSP had increased* peak trunk tilt velocities vs. CP, quick forward and backward movement of the trunk at the end of loading response and stance–swing transition.	/	/
Bonnefoy-Mazure et al. (39) retrospective case–control	HSP normalized speed is slower* vs. TD and SD groups. Arm swing length is greater* in the top-to-bottom direction vs. SD; significantly greater in the medio-lateral direction compared to the TD group.	Lower Limbs sagittal plane: Nsign differences between the SD and HSP. Differences* between the HSP and HC for HIP, knee, and ankle: Higher hip angle at initial contact*, higher minimum hip angle in stance*, higher peak of hip angle in swing*, and higher mean hip angle in the gait cycle*. Higher knee angle at initial contact*, higher minimum knee angle in swing*, higher mean knee angle in the gait cycle*. Lower peak of knee angle in swing* and range of knee angle in the Gc*. Higher mean foot progression*, Lower peak of ankle angle in swing*. Thorax, pelvis, and spine kinematics in the sagittal plane: Higher spine ROM and peak angular velocity than SD. Respect to HC: Higher peak of pelvis angle in stance* and in swing*, higher minimum pelvis angle in stance* and in swing*, higher pelvis ROM in the Gc*, higher mean pelvis angle in the Gc*. Respect HC: Lower minimum thorax angle in stance* and in swing*, higher thorax ROM in Gc*. Respect HC: Higher spine ROM during Gc*, Lower mean spine angle in the gait cycle*. Elbow and shoulder kinematics: Differences* between HSP and SD groups: lower* peak of shoulder angle, lower* mean elbow angle of flexion, lower* peak of elbow and shoulder angles, lower* minimum elbow and shoulder angles during stance, higher* ratio of the mean angle in the Gc between the left and right sides. Nsign differences between the HSP and HC for the shoulder and the elbow ROM.	/	/

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TABLE 3 (Continued)

Author /design	HSP ST results	HSP Kinematic results	HSP Kinetic results	HSP sEMG or other functional results
Malone et al. (47) case report	After patella fracture gait speed was slower* compared with the previous analysis	Mild midstance crouch of 20° with reduced knee flexion in swing and dynamic ankle equinus.	Abnormal knee extensor moment in terminal stance	/
Armand et al. (9) retrospective case series	Nsign decreased normalized walking speed in 5 patients (time effect).	/	/	/
Adair et al. (40) case–control	/	The 8/30 parameter distinguishes HSP from HC. In the sagittal plane: HSP had increased excursion of trunk and pelvis ROM; increased posterior trunk lean and increased anterior pelvic tilt. In the coronal plane: HSP had increased trunk ROM obliquity, large peaks of trunk obliquity during the swing phase of the left leg, and delayed maximal pelvic rise. In the transverse plane: HSP had a delay in the timing (later peaks) of maximal posterior pelvic rotation.	/	/
Pulido-Valdeolivas et al. (5) case–control	Six patterns vs. HC: Patterns I, II, and VI: Nsign increased stance times and Nsign decreased single support. Pattern IV, V, and part of Pattern III: reduction of normalized walking speed (Nsign), cadence (*), % of cycle in single support (*), stance (Nsign), in first double support and second double support (*). Normalized walking speed and cadence decrease* with increasing age.	Correlation with age: increased* range of pelvic rotation in tSw, decreased maximum knee flexion vs. HC. Correlation with polyneuropathy: Nsign increased range of pelvic rotation in tSw, increased time to peak of knee flexion, mean hip abduction in first double support and single support, and minimum ankle dorsiflexion in stance. Correlation with GMFCS: GMFCS II and III: delay of peak knee flexion with increased knee flexion at initial contact, increased pelvic rotation, and pelvic obliquity in St. Correlation with thin corpus callosum: Nsign increased ranges of pelvic rotation in second double support and in terminal swing, increased mean pelvic tilt, lower range of ankle dorsiflexion in stance.	/	/
Van Beusichem et al. (7) case series	/	Different parameters on different patterns: Rodda's type III: apparent equinus, and II: jump knee. Rodda's type IV: crouch gait, with increased knee and hip flexion in midstance, with complete foot contact. Type I true equinus; during midstance hyperextension of the knee and complete foot contact.	/	/

ST, spatiotemporal; HC, healthy controls; Nsign, non-significative differences; *, significative differences; tSw, terminal Swing; St, stance; Sw, swing; iS, initial stance; iC, initial contact; midS, midstance; tS, terminal stance; Gc, Gait cycle; pts, patients; SD, spastic diplegia cerebral palsy; TD, typical development; ROM, range of movement; minAP, minimum ankle power; maxAP, maximum ankle power. The studies are ordered by year and within the same year by alphabetic order.

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TABLE 4 Results on adult GA pattern studies.

Author /design	HSP ST results	HSP Kinematic results	HSP Kinetic results	HSP sEMG or other functional results
Klebe et al. (6) case–control	Lower* gait velocity, stride length, and cadence than HC. Increased* step width and variation of the stride length. Nsign in foot angle. The sum score of the MAS correlated* with the velocity, the cadence, the step height, and the step width.	Nsign between SSP and HSP. Reduced* knee ROM, increased* minimal knee angle. Nsign in hip and ankle ROM. Increased maximum ankle ROM (equinovarus foot) and reduced* maximum hip angle, lower* step height, and increased coefficient of variation of the step height.	/	The CMCT was abnormal in 12 patients (delay in 2, reduced amplitude, and a polyphasic pattern in 10). No correlation between the CMCT and the MAS, age, disease duration, or gait abnormality
de Niet et al. (35) case–control	Lower walking speed than HC.	/	/	Increased activity levels during the first half of the St. Greater* MAearly than HC. MLV was relatively constant without distinct peaks in HSP. Lower* MLVmax during the St. Nsign in the proportions of phase shifts observed within the SLR time window, which were low.
Marsden et al. (38) case–control	Slower* normal and maximal walking speed and cadence. Slower standing up/sitting down times and lower scores on the Berg balance scale.	Reduced knee flexion and knee extension in the swing phase, decrease* in peak-to-peak knee amplitude.	During preswing: reduced peak ankle power generation and increased* knee extensor torque. Increased* peak hip flexor power. The reduction in ankle power and the increase in knee extensor torque were associated with a reduction in knee flexor velocity in preswing. Correlations: The ankle power generation was correlated to the isometric ankle plantar flexion strength, and the size of the knee extensor moment was correlated with the degree of passive stiffness in the knee extensors.	/
Serrao et al. (41) case–control	Nsign in mean speed value between groups. Increased* step width and reduced* step length vs. HC. Effect* of patients' subgroup (s): higher* walking speed in s3 than in s1, lower stance duration in s3 than in s1, higher swing duration in both s2 and s3 than in s1, lower second double support duration in s3 than in s1 and higher step length in s3 than in both s1 and s2 and in s2 than in s1.	Three subgroups (s) of patients were identified. s1: reduction* of ROM at hip, knee, and ankle joints; s2: reduced* ROM of knee and ankle joint, but hip joint ROM Nsign than HC; s3: increased* of hip joint ROM, but ankle and knee joint ROM Nsign than HC. Lower* knee and ankle ROM and higher* trunk lateral bending, flexion extension, and rotation ROM and pelvis rotation ROM in patients than in controls. Higher* hip ROM in s2 and s3 than in s1, higher values of knee ROM in s2 and s3 than in s1 and in s3 than in s2, higher values of ankle ROM in s3 than in both s1 and s2 and lower values of pelvis tilt ROM in both s2 and s3 than in s1.	Higher* only knee first and second extensor AI during the stance phase than controls. Lower hip extensor AI during the first double support subphase in s3 than s1.	Higher* values in the TMCf Area of ankle antagonistic muscles (MG-LG vs. TA) than controls (coactivation index). Nsign effect of the subgroup.

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TABLE 4 (Continued)

Author /design	HSP ST results	HSP Kinematic results	HSP Kinetic results	HSP sEMG or other functional results
Rinaldi et al. (42) case–control	Slower* walking speed. At matched speed higher* values for step width. Nsign in step length, stance duration, and swing duration.	At matched speed: lower* values in knee and ankle ROM. Nsign in hip ROM. Increased CI of both knee and ankle muscles throughout the gc and during the subphases of gait. Positive correlations*: between the MAS for both the knee and ankle joints and CI for VL–BF (knee) and TA–SOL (ankle) muscles, respectively. Negative correlation* between the knee CI and walking speed. Nsign partial correlations between the CI and other ST and kinematic parameters. Positive partial correlations* between ankle CI in St and both AWA and APS and between TEC and knee and ankle CI. Negative partial correlations* between R-step and knee and ankle CI. Knee and ankle muscle CI positively correlated with energy consumption and negatively correlated with energy recovery.	Lower* values of AWA and APS (vertical GRF) than HC.	At matched speed, higher* values of CI throughout the gait cycle both for the VL–BF and the TA–SOL pairs of antagonist muscles. Higher* CI in St and Sw for TA–SOL muscles and in the St for the VL–BF muscles, NO diff in the Sw phase for the VL-BF muscles. Energetic parameters: Higher* value of TEC and R-step at matched speed.
Martino et al. (43) case–control	s3: reduction* of walking speed vs. s1, s2 and HC. Reduction* of walking speed in s2 vs. s1. Stance duration is longer in s2 and s3 than in s1 and HC, and shorter stride length in s3 than in s1, s2, and HC. Larger* stride width in s2 than in HC.	Three patient subgroups (s): Increase* of hip joint angle ROM in s1, reduction* of knee and ankle ROM in s2 and s3, and of hip ROM in s3. Inter-subgroup: higher values of ankle joint ROM in s1 than in s2 and s3, higher hip ROM angle in s1 and s2 than in s3, higher knee ROM in s1 and s2 than in s3, and in s1 than in s2. Correlations: with the SPRS score*: walking speed, stride length, ankle ROM, knee ROM, FWHM of spinal activation of L2, L3, and L4. ROM of the knee (most sensitive parameter) correlates with FWHM of all segments.	/	Increased* distal leg muscles (TA, PL, SO, MG, LG) and hamstrings (BF and ST) duration of the major bursts in s2 and s3 vs. HC. Trend for the progressive widening of EMGs with the severity of the disease. Higher* coactivation indexes for TA vs. MG-LG in all patient subgroups vs. HC. Mapping in HSP the activity timings in lumbar and sacral segments tend to be quasi-synchronous vs. HC. Maps are characterized by distinct loci of activation of sacral and lumbar segments during late and early stance, respectively. Different* timing of the peak of sacral segments' activity significantly (s3 vs. HC in S2, and s2 and s3 vs. HC and s1 in S1, while Nsign between subgroups).
Serrao et al. (44) case–control	Nsign between groups. Nsign between CA and HSP patients in single and paired ST parameters. Difference* between CA and HSP patients in Mean of step width (triplets and Quadruples of parameters) and Mean, stride-to-stride CV in Quadruples of parameters.	Difference* between CA and HSP patients' ankle ROM (triplets and Quadruples of parameters)	/	/

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TABLE 4 (Continued)

Author /design	HSP ST results	HSP Kinematic results	HSP Kinetic results	HSP sEMG or other functional results
Van Lith et al. (45) case–control	Nsign differential effect of the SAS between HSP patients and HC in step onset and step length. Nsign effects of the SAS on step length. HSP patients made shorter steps than HC, with and without SAS	/	/	Without SAS: delay in step onset, TA and RF onsets, SOL offset, APA onset compared to HC. SAS accelerated TA and RF onsets in both groups, more in HSP, resulting in near-normal latencies. The SAS accelerated the SO offsets, but greater in HC. The SAS accelerated APA without differential effects between the two groups. APA amplitudes were smaller in HSP patients compared to HC, both with or without SAS. No effect of the SAS on APA amplitudes in either group. The occurrence of the startle reflex in SCM during SAS trials was 64% in HSP patients and 65% in healthy controls, with no difference in TA onset.
Martino et al. (46) case–control	/	Lower* ROM of the knee and ankle joint and lower* foot lift with respect to HC. Smaller* oscillations of the distal segment (shank and foot) (along with smaller ROM in the knee and ankle joints) respect HC. Smaller leg swing and smaller changes in limb length.	/	4 EMG pattern (P) in HSP and HC: Comparable structure of the motor output between the two groups (number of modules and similar synergies, but wider* basic temporal activation patterns P2 and P4 in HSP (FWHM greater* for P2 and P4 in HSP). Correlations*: with the SPRS score: shank ROM, foot ROM, FWHM of P2.
Van Vugt et al. (70) case–control	Slower walk velocity, lower cadence, wider* step width, longer step time, and more time spent in the double support phase than HC. Nsign in step length and in single support time between groups.	Higher* lateral trunk flexion than the HC. Nsign in pelvic obliquity between groups. Nsign between-group difference in the AP direction at heel strike or the AP direction at mid-St. Nsign between the groups for the COP-COM separation in the ML direction at heel strike or mid-St. Lower* MOS in the ML direction at heel strike and at mid-St and in AP MOS at mid-St. Nsign in AP MOS at heel strike. Longer* to reach the limits of stability (MOST in the AP direction at heel strike). Nsign in the MOST in the AP direction at mid-St.	/	/

HSP, Hereditary Spastic Paraplegia; SSP, Sporadic Spastic Paraplegia; ST, spatiotemporal parameters; Nsign, non-significative differences; * significative differences; HC, healthy controls; ROM, range of movement; CMCT, Central motor conduction time (rTMS); FWHM, the full width at half maximum; CI, coactivation Index (antagonist muscles at sEMG); St, stance phase; Sw, swing phase; gc, gait cycle; TA, tibialis anterior; MG, medial gastrocnemius; LG, lateral gastrocnemius; VL, vastus lateral; BF, biceps femoris; SOL, soleus; AWA, area under GRF curve within the weight acceptance; APS, area under GRF curve within the preswing; TEC, total energy consumption; R-step, fraction of mechanical energy (R-step) recovered during each walking step; GRF, Ground reaction force; AP, anterior–posterior direction; ML, medio-lateral direction; MOS, Margin of Stability; MOST, Temporal Margin of Stability; COP, center of pressure; COM, center of mass. SAS, startling acoustic stimulus; RF, rectus femoris; APA, anticipatory postural adjustments; CA, cerebellar ataxia patients; CV, coefficient of variation; AI, angular impulse; TMCf, time-varying multi-muscle coactivation function. MAearly, mean amplitude during the first half of the stance phase; MLV, muscle-lengthening velocity; MLVmax, maximum of MLV. SLR, short-latency stretch response. The studies are ordered by year and within the same year by alphabetic order.

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decreased foot lift (46), compared to healthy subjects. An increased and premature calf muscle activity was observed both in HSP and stroke subjects, compared to controls, but the contribution of the stretch reflex was excluded (35). Marsden et al. (38) demonstrated that the shorter latency stretch-evoked plantar flexor activity correlated with the increased passive stiffness found at the gastrosoleus in HSP patients, compared to controls. Conversely, no significant difference in knee extensor stiffness was recorded, by comparing HSP and controls. A significant reduction of strength was described, in particular, at the plantar flexors and knee extensors (38). Patterns of coactivation at the electromyography (EMG) were described at dorsi-plantar flexors (41–43) and extensors–flexors of the knee (41, 42). Furthermore, mapping the motor neuron activation in the lumbosacral enlargement of HSP subjects, the activity timings in lumbar and sacral segments tended to be quasi-synchronous because of a progressive widening of the activity involving the sacral segments (43). Conversely, healthy subjects showed distinct loci of activation of sacral and lumbar segments during late and early stance, respectively. Coactivation resulted to correlate with higher energy consumption during gait, based on center of mass (COM) displacements during the gait cycle (42).

Van Vugt et al. (70) analyzed the dynamic postural instability of HSP subjects starting from the distance between the center of pressure and the center of mass (COP-COM separation) to the margin of stability (61) (MOS). The authors found a significantly lower MOS in medio-lateral direction at heel strike and midstance, and in antero-posterior direction at midstance, compared to healthy subjects. van Lith et al. (45) enquired about the anticipatory postural adjustments (APAs) at gait initiation in HSP and controls by studying the StartReact effect. Delayed APAs were observed in HSP subjects, though a starling acoustic stimulus (45) (SAS) positively affected their response, by reducing the activation delay of tibialis anterior (TA) and rectus femoris (RF), close to controls' values. Conversely, the soleus (SO) inhibition was not accelerated upon administration of the SAS.

Finally, lower velocity (35, 42, 43, 70), lower cadence (38, 70), longer double support phase (70), increased step width (41, 42), and increased lateral flexion of the trunk were reported (70). Contrasting data emerged regarding step length and stance duration, being reduced or similar to controls (41–43).

3.2.4. Intervention studies

Included intervention studies focused on adult subjects and no study was found including minors. Population characteristics are summarized in Table 5. Most studies considered pure forms of HSP. Very few patients presented complicated forms, including ataxia, peripheral neuropathy, retinopathy, and epilepsy (53). The methods and results of these studies are reported in Table 6.

Seven studies researched botulinum toxin injections to reduce spasticity (49, 52, 54–57, 69). Four were cohort prospective studies (49, 52, 55, 56), one was a double-blind randomized crossover study (69), and two were retrospective studies (54, 57). Xeomin (54, 56, 57), Prosigne (69), Dysport (52, 55, 57), and Botox (49, 57) were used (whenever indicated, dilution was 2 to 5 ml). The most frequently injected muscles were gastrocnemius, soleus, adductors magnus and longus, and gracilis (52, 54, 55, 69). One study included tibialis posterior (49). Two studies extended injections to other targets: hamstrings and quadriceps (56, 57); quadratus lumbi, tibialis anterior, flexor digitorum and hallucis, and extensor longus hallucis (56). The sample size ranged from 15 to 55 subjects. A total of 170 subjects were included in the seven studies, of which 98 were male subjects. An overall synthesis of age range was not feasible because data were differently reported as mean, median, or range values, but all patients were over 18 years old. After the injections, self-administered daily stretching (10 min for 2–3 times) (52, 56) or physiotherapy (49, 54, 57) was prescribed. The follow-up ranged from 8 weeks to 5 months (49, 52, 54, 56, 57, 69), only the study by Servelhere et al. (55) did not provide any follow-up assessment. Studies reported a transient reduction of spasticity according to the Modified Ashworth Scale (MAS) and of the injected muscles' strength according to the Medical Research Council (MRC) scale, in the short term. Both receded at 4–5 months follow-up assessment. Furthermore, an increase in range of movement (ROM) within 3 months after injection was reported as increased dorsiflexion, knee flexion, and hip abduction depending on the targeted muscle. Short-term improvement in gait velocity was reported by all studies (49, 52, 54, 56), except Servelhere et al. (55) and De Lima et al. (69). No significant differences were demonstrated at functional tests, except by Paparella et al. (57). This study reported significant improvements at the following tests, 3 months after botulinum and intensive physiotherapy, in 18 subjects: Spastic Paraplegia Rating Scale (SPRS), Walking Handicap Scale (WHS), 10-m walking test (10MWT), 2-min walking test (2MWT), Timed UP and Go test (TUG), the visual analogical scale (VAS), and numeric rating scale (NRS) which assessed the perceived quality of life and pain.

Transient side effects were reported in 19 subjects: muscle strength reduction (52, 55, 69), bruise, transient pain, paresthesia in the site of the injection (69), impairing gait quality (55, 69), sleepiness, and blurred vision in one subject (55). Paparella et al. (57) denied adverse effects.

Four studies researched intrathecal baclofen to reduce spasticity (59–61, 63). Three were case reports (59, 61, 63) and one was a retrospective cohort study (60). Gait analysis at a self-chosen comfortable speed was recorded before and after intrathecal bolus testing (59, 60) or before and after pump implantation. Increased gait velocity and step length were reported by all authors. Klebe et al. (60) described improvement in 5 patients over 10; among them, 2 subjects refused pump implantation because they experienced weakness and unsteadiness. Dan et al. (59) showed that ITB normalized the planar covariation of elevation angles of the thigh, shank, and foot over the gait cycle, thus improving the coordination of the lower limb and reducing mechanical energy expenditure. Heetla et al. (63) reported the reduction of spasticity using MAS, without strength loss and improvement at TUG, which lasted 6 months after implantation. Molteni et al. (61) observed a reduction in the slope of the moment–angle curve of the ankles, which lasted 2 years after pump implantation. The overall baclofen dose range was 25–108 μg, and the overall number of patients involved was 13.

Functional electrical stimulation (71) was enquired by two studies. One case report by Pease et al. (58) reported improvements in gait velocity and knee extension in the stance phase, after FES

TABLE 5 Population characteristics of the intervention studies. Studied are grouped based on the treatment and among the same treatment are ordered by year.

Interv.		Author	Population (M) phenotype	HSP age Y *mean* ± *SD* (Y range)	Population characteristics (gait and functional features to meet inclusion criteria)
BONT-A + various physiotherapic protocol		Rousseaux et al. (49)	15 pure HSP (10)	48 (25–75% =41–53.5%).	Independent walk with or without assisting devices. 12 pts: extensor gait pattern (knee hyperextension, reduced hip and knee flexion in swing). 3: flexor hip and knee pattern. 9 patients used canes, 2 orthopedic shoes, and 1 ankle–foot orthosis. Spasticity of hip adductors and/or ankle plantar flexors. Difficulties in walking and transfers.
		de Niet (52)	15 pure HSP (12)	47.7 ± 12.3 (20–66)	Community ambulator; bilateral premature calf muscle activity during the loading and/or midstance phase at EMG; balance- and/or gait-related activity limitations in daily life, symptomatic calf muscle spasticity and preserved calf muscle strength.
		Marvulli et al. (54)	10 HSP (7)	40.2 ± 3,6	Paraparetic deambulation with reduced support of back feet, spasticity.
		Servelhere et al. (55)	33 pure HSP (15)	41.7 ± 13.6	With shoes and aid if necessary
		van Lith (56)	25 pure AD HSP (12)	>18	Able to walk > 50 m independently with (adapted) shoes and/or orthoses (but without walking aids) and comfortable gait velocity > 0.4 m/s. Balance- and/or gait-related activity limitations in daily life. Bilateral hip adductor spasticity;
		Paparella et al. (57)	18 HSP (9)	53.9 ± 12.2 (30.7–5.2)	Able to walk with ($n = 6$) or without ($n = 12$) walking aids on a level surface
		Diniz de Lima et al. (69)	55 HSP (36) 41: pure	43 ± 13.4 (19–72)	Able to walk for at least 14 m without stopping. Assistive devices permitted. 22 (60%) walked without device. At least 6 months elapsed since the last injection of Bont-A.
Intrathecal Baclofen (ITB)		Dan et al. (59)	1 pure AD HSP	41	Spastic gait
		Klebe et al. (60)	10 HSP/SSP	Unknown	Unknown
		Molteni et al. (61)	1 HSP	31	Walking impairments, lower limb spasticity, poor balance, nystagmus
		Heetla et al. (63)	1 HSP (1)	49	Able to walk only 100m with assistive devices. Progressive walking difficulties during last 5 years, wheelchair for most activities.

(Continued)

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TABLE 5 (Continued)

Interv.		Author	Population (M) phenotype	HSP age Y *mean* ± *SD* (Y range)	Population characteristics (gait and functional features to meet inclusion criteria)
Stimulation	FES	Pease (58)	1 pure HSP (1)	26	Normal velocity and crouched gait pattern, excessive EMG activity of hamstrings and gastrocnemius. Gait adductor scissoring. Hip flexion contractures. Flexion and extension synergic patterns. Articular impairment because of spastic tone. No strength deficit.
		Marsden et al. (38)	11 HSSP (9) fam.history	57.7 ± 14.2	Able to walk at least 10m with or without a walking aid. Five pts used walking aids. Long-term (>0.5 years) users of FES.
	rTMS	Antczak et al. (67)	9 HSP (7) 7pure/2 compl	40.5	Able to walk 10 meters without or with crutches
	ETOIMS	Shin et al. (56)	1pure HSP (1)	59	Could walk on their own even with the use of an assistive device. Complaining of low back pain. Scissoring, waddling, and feet dragging gait pattern.
	tsDCS	Ardolino et al. (68)	11 HSP (6)	37.3 ± 8.1	Unknown
	SCS	Pinto de Souza et al. (8)	1 HSP (type4)	51	Unable to walk without orthosis
Robot trainiing		Bertolucci et al. (51)	13 pure HSP (6)	46.3 ± 8.9 (31–62)	Able to walk independently for 6 min, with or without walking aids
		Seo et al. (64)	1 pure HSP	28	Walk without assistance using a single cane and bilateral AFO, gradually gait deteriorating. Spastic gait with excessive lumbar lordosis. Bilateral lower limb spasticity and weakness.
MPH		Klebe et al. (48)	22 SSP/HSP (11)	47.5	Unknown
Physical therapy		Zhang et al. (50)	9 late-onset HSP	Adult	Unknown
		Denton et al. (53)	22 pure/complHSSP (11)	55 ± 13	Able to walk at least 20 m with (78%) or without a walking aid and have bilateral spasticity in the ankle plantar flexors
		Denton et al. (66)	21 pure/compl HSSP (9)	51.2 ± 12.05	Able to independently walk for at least 20 m with/without a walking aid. The majority (76%) require a walking aid, orthoses, or assistance to walk.
		Samuel et al. (76)	2 pure HSP	45 and 43	1st: exaggerated foot arches bilaterally with typical features of equinovarus deformity. 2nd: bilateral genu recurvatum, equinovarus deformity, and pes cavus with evident toe walking on left

ES, functional electrical stimulation; ETOIMS, electrical twitch obtaining intramuscular stimulation; SCS, spinal cord stimulation; tsDCS, transcutaneous spinal direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; MPH, methylphenidate.

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TABLE 6 Details about methods and results of the intervention studies.

Author and design	Sample	Treatment and protocol	Gait outcome measure	Outcome time point	Significant improvement results
Rousseaux et al. (49) pre-post	15 HSP	BoNT-A + usual PT (no in 2 pts) Dose: Botox, different depending on spasticity Site: depending on spasticity SO, GN, TP, FDL, AL, AM	10mWT: step length and w.speed at comfortable and max w.speed (with aids) RMA (leg and trunk), FAC	• Before (d1) and after 2–3 w • After 2–3 m – 5m	W.speed in 10 MWT
de Niet (52) pre-post	15 HSP 10 Ctrl	BoNT-A + home calf stretch (18 ws) Dose: Dysport, 500–750 U dependent on spasticity Site: Triceps Surae, bilateral (electrical stimulation)	10 MWT, Comfortable and max w.speed TUG, BBS, GA parameter	• T0 • T1 (4 w) • T2 (18 w)	Pre-post comfortable w.speed *HSP-Ctr w.speed and balance at T0*
Marvulli et al. (54) pre-post	10 HSP	BoNT-A + PT Dose and site: bilateral with middle dosage of AddM 125 U, GNM e GNL 110U, SO 132 U of Xeomin	Postural and s-t gait parameter	• Before and after 30 d • after 3 m – 4 m - 5 m	W.speed Increase back foot loading
Servelhere et al. (55) pre-post	22 HSP	BoNT-A Dose: Dysport, depending on spasticity Site: leg muscles depending on spasticity	10 MWT, SPRS mFIS (for fatigue)	• Before and after	mFIS (reduction)
van Lith et al. (56) pre-post	25 HSP	BoNT-A + home stretch (10 min 3tpd × 16 w) Dose: Xeomin 150 – 200 U depending on MAS Site: adductors (gracilis, AddM, AddL, palpatory + US)	Gait analysis, w.speed, width in 4.88 m Comfortable and max speed, 6MWT, TUG, Balance (Fall Simulate platform).	• T1: 6 w • T2: 16 w	Gait width, Comfortable w.speed Leg degree in moveable platform
Paparella et al. (57) pre-post	18 HSP	BoNT-A + inpatient intense PT (2 h × 10 times) 2nd treatment injection after 1, 2 y Different dosages of Xeomin, Dysport, Botox Site: depending on spasticity (> HS, RF, GN, ADD)	10 MWT, Comfortable w.speed TUG, WHS, 2mWT, SPRS	• Baseline • 1 m • 3 m	10 MWT, WHS, 2MWT, SPRS (at 1st and 2nd injection) Comfortable w.speed, TUG
Diniz de Lima et al. (69) RCT Crossover	55 HSP	BoNT-A + home PT (1/d × 3 tpw × 8 w) Dose: Prosigne 400U or placebo inj (saline solution) Site: bilateral AddM and TS 100 U (palpatory)	10 MWT, Comfortable and max w.speed SPRS	• T1 (1st inj) - T2 (8 w ± 1 w) • T3 (24–28 w crossover 2nd inj) • T4(8 w)	No significant results
Dan et al. (59) case report	1 HSP *7 Ctrl*	ITB test (75 mcg)	GA on 10MWT at self-selected speed: w.speed, stride length, cadence	• Before test and after 2–4–6h	W.speed; Stride length at 2–4–6h and before vs. ctrl, Cadence at 4–6h
Klebe et al. (60) pre-post	10 HSP	ITB (test and implant + ongoing oral antispastic drugs and PT)	Gait speed, length, width Kinematic parameter on the treadmill (20 s)	• Before • After ITB test (25/50 mcg) • After ITB implant (25 mcg) • After 6 m	w.speed, step length, and step width
Molteni et al. (61) case report	1 HSP	ITB (test 25 mcg and implant)	*Before After test* Time (sec) and N. strides in 10 mWS and 50MWS at self-select max w.speed *Before and After implant* self-select w.speed, step width, stride length, step length (L and R)	• 2 h Before and 3 h after test • Before implant (0 mcg/d) • 6 m (65 m cg/d) • 12 m (85 mcg/d) • 16 m (80 mcg/d) • 24 m (895 mcg/d) after implant	w.speed after test self-select w.speed step length stride length (kinematic parameter no data)

(Continued)

TABLE 6 (Continued)

Author and design	Sample	Treatment and protocol	Gait outcome measure	Outcome time point	Significant improvement results
Heetla et al. (63) case report	1 HSP	ITB (continuous test and implant)	Step length, comfortable w.speed Knee flex degrees at IC, LR, MS, TS TUG during the ITB test	• TUG at 0.36–72–108 mcg/d • Before implant • 6 m after implant (105 mcg/d)	TUG, Step length, w.speed Knee flex degree in LR (improved)
Pease (58) case report	1 HSP	FES bilateral (QF, anterior leg mm) 2–3/w × 3 m + home stretching same days	w.speed, cadence, bilateral step length stride length, stance width, time of stance and single limb support (%) during free walking (without stimulation)	• Before • After 7 m	Right hip and knee extension in MS and TS; Symmetry of gait pattern Reduced QF activity in stance (EMGs)
Marsden et al. (38) pre-post	11 HSP 11 Ctrl	Chronic users (2.6 y +- 1.6y) of FES different sequence of stimulation for each pt.	GA in 10MWT: w.speed, max dorsiflex in sw, toe clearance max knee and hip flex PCI (physiological cost index)	• Non-stimulation • After 15 min, Stim bilat on common peroneal • After 15 min, Different Stim	w.speed, toe clearance, dorsiflex in swing
Antczak et al. (67) RCT crossover	15 HSP	rTMS (10 Hz, bilateral 1ary motor area of leg) or sham per 5 time + usual PT (crossover after 1–3 m)	10MWT, TUG	• Before and after 6 w • 2m f-up	No significant results (spasticity reduction at Ashworth)
Shin et al. (65) cohort	1 HSP (5 pts)	ETOIMS (bilateral Q.lomb, mutifidus L4-5, gluteus medius), 2 mA 0,2 ms 1 Hz × 10 s at each point	AMI (Ambulatory Motor Index) 50MWT, w.speed, gait pattern	• Before • Immediately after 1 session	Waddling (reduced)
Ardolino et al. (68) RCT crossover	11 HSP	tsDCS (spinal) anodal or sham. 20 mA, 20 min × 2/die, 5 d/w, At least 3 m. NO PT	5MWT SPRS	• Before and after, 2 m f-up	No significant results (improvement in the anodal group at 5MWT)
Pinto de Souza et al. (8) case report	1 HSP	Chronic Spinal Cord Stimulation implant	GA in 10 MWT: Step length, Step time, Stance and Swing (%), Double limb support (%), Stride length and time, Cadence, w.speed, speed variability (%) SPRS	• 24 m after • ON condition • OFF condition • ON + condition	Lower knee flex-ext muscle torque. Step length (In ON and ON+) Stance%, double limb support% (in OFF), Worsening hip extension in stance, SPRS
Bertolucci et al. (51) pre-post	13 HSP	Lokomat 3/w per 6 w	10MWT, BBS, TUG, 6MWT PCI (O2)	• 1 d before • 3 days after training	10MWT, TUG Decrease cadence, speed, step width, and length, duration of swing phase; Improve left hip extension moment in stance, and hip rotation; worsen pelvic obliquity and left hip abduction during left stance phase
Seo et al. (64) case report	1 HSP	Robot gait training (exoskeleton with partial body weight support) 25 sessions in 6 wks (1/die) + PT 30 min (+30 min)	GA over 8-meter walkway: s-t parameter, kinematic and kinetic hip, knee, and ankle in three planes. 10MWT, 6MWT, FAC, TUG, and BBS	• Baseline and after 6w • 6 m	No significant results
Klebe et al. (48) pre-post	22 HSSP	MPH (methylphenidate) (max 60 mg/day per 6 m)	GA on treadmill: w.speed, cadence, stride length	• Baseline • After 30 min of heating • After 30 min-insulation or not	w.speed between T1-T2 and T3 –T1. No inter groups

(Continued)

TABLE 6 (Continued)

Author and design	Sample	Treatment and protocol	Gait outcome measure	Outcome time point	Significant improvement results
Zhang et al. (50) pre-post	9 HSP *Ctrl from database*	Hydrotherapy 45 min, 10 w (group—5 w individual—group—5 w individual)	GA: s-t parameter, kinematics, kinetics	• Pre-post	w. speed, cadence, step length GA pre to post: decrease in the hip, knee, and ankle rotation
Denton et al. (53) RCT pre-post	22 HSSP *19 ctrl*	Warming or cooling worst leg for 30 min (random leg for ctrl)—after 24 h repeat	10MWT max w.speed Foot tapping time	• Before and after • f-up	No significant results
Denton et al. (66) RCT crossover	21 HSSP	Superficial Heating and insulation (30 min or 1 h)—crossover after 24 h.	10MWT, Max w.speed Foot tap time	• Before • Immediately after	*w.speed vs. ctr at baseline* w.speed after worming and (mostly) after cooling as w.speed in ctrl after cooling
Samuel et al. (76) Case report	2 HSP	Intensive PT program (SEIRP: stretching, strengthening, and functional exercise, 60–90 min/d, 6 d/w, per 8 w)	TUG, FRT (Functional Reach Test) 10MWT, 2MWT	• Before and after 4 w • 8 w	10MWT and TUG at 8 w

Studies are grouped based on the treatment and within the same treatment are ordered by year.
Ctr, control; w.speed, walking speed; PT, physiotherapy; US, Ultrasound; w, week; Add, adductor; AddM, adductor magnus; AddL, adductor longus; HS, hamstring; RF, rectus femoris; ADD, adductor; SO, soleus; GNM, medial gastrocnemius; GNL, lateral gastrocnemius; TP, tibialis posterior; TS, triceps surae; FDL, flexor digitorum longus; AL, adductor longus; AM, adductor magnus; s-t, spatiotemporal; 10MWT, 10-m walking test; TUG, Time Up and Go; BBS, Berg Balance Scale; SPRS, Spastic Paraplegia Rating Scale; WHS, Walking Handicap Scale; 2MWT, 2-min walking test; 6MWT, 6-min walking test; FAC, Functional Ambulation Classification; PCI, Physiological Cost Index; 5MWT, 5-min walk test; 50MWT, 50-m walk test; mFIS, modified Fatigue Impact Scale; ITB, Intrathecal baclofen; IC, initial contact; LR, loading response; MS, midstance; TS, terminal stance.

on the quadriceps and anterior compartment of the leg. Marsden et al. (71) examined a cohort of 11 long-term users of FES (at least 6 months) with and without stimulation and compared them with matched controls. With stimulation (mainly at dorsiflexion, and in some cases also at hip abductors and extensors), an increase in gait velocity and dorsiflexion torque was reported. Long-term follow-up was missing.

One study (65) explored the effect of Electrical Twitch Obtaining Intramuscular Stimulation over the low back and gluteal area, in a mixed population, including one HSP adult. The patient experienced increased speed and reduction of falls and back pain.

Ardolino et al. (68) presented a double-blind, randomized, crossover, and sham-controlled study about anodal transcutaneous spinal Direct Current Stimulation delivered over the thoracic spinal cords (T10–T12). Eleven HSP subjects were involved. They maintained their usual pharmacological treatment but no other intervention (i.e., physiotherapy) was performed during the trial. A significant reduction of spasticity was observed at the Ashworth scale, in particular, at knee extensors and hip flexors, 2 months after treatment. No other functional outcome was improved.

De Souza et al. (8) reported a subject who underwent chronic spinal cord stimulation (SCS) implantation in the posterior epidural space of T11–T12. Alternating ON/OFF phases allowed studying the effect of SCS: improvements in muscle strength and spasticity and at SPRS were reported in ON phases.

Antczak et al. (67) researched the effect of repetitive transcranial magnetic stimulation (rTMS) by means of a blinded, randomized, crossover, and sham-controlled study. Fifteen patients were enrolled, with one dropping out due to a seizure that occurred during a stimulating session. Other adverse effects were headache (several subjects) and sleeplessness (one subject). Usual physiotherapy and oral drugs (59) were provided during the trial. The strength of the proximal and distal muscles of the lower limbs increased, and the spasticity of the proximal muscles decreased. Nonetheless, no functional improvements were observed at the TUG and the 10-m walk test (10MWT).

Two studies (51, 64) researched robot-assisted gait training with partial body weight support: one case report (64) and a cohort study (51) involving 13 pure HSP patients. The treatment lasted 6 weeks. The case report (64) included physiotherapy and overground walking, while the study by Bertolucci et al. (51) provided a gradual reduction of the robotic guidance force and increased workload. An overall improvement in functional tests was observed, with non-significant change in strength, spasticity, and pattern of gait. In the cohort study (51), the improvement was maintained at a 2-month follow-up.

The outcome of an 8-week intensive physiotherapy program including stretching, strengthening, and functional exercise, in two HSP subjects, was described by Samuel et al. (76). The authors reported an improvement in all tests after completing the intervention period: TUG, Functional Reach Test (FRT), 10mWT, and 2mWT.

Zhang et al. (50) researched gait analysis changes after a 10-week hydrotherapy program in 11 HSP subjects. A significant improvement in gait velocity was reported. A significant decrease in the transverse plane rotation of hip, knee, and ankle and an increase in hip and knee peak extension moment were reported.

Klebe et al. (48) performed an open-label study with a longitudinal follow-up at 6 months, in 22 patients treated with 60 mg of methylphenidate per day. Non-significant improvement was observed at gait analysis, MAS, or MRC, at the last assessment. Nausea and sleep disturbances were reported as collateral effects,

TABLE 7 Relevant statistics for the meta-analysis.

Studies	T_0			T_1			T_2		
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Maximum gait velocity									
de Niet (52)	15	1.33	0.34	15	1.33	0.33	15	1.33	0.37
van Lith et al. (56)	25	1.31	0.41	22	1.33	0.35	22	1.36	0.41
Diniz De Lima et al. (69)	54	1.02	0.57	52	1.01	0.59	n.a.	n.a.	n.a.
Comfortable gait velocity									
Rousseaux et al. (49)	15	0.69	0.28	14	0.74	0.24	13	0.68	0.24
de Niet (52)	15	0.90	0.18	15	0.98	0.22	15	1.01	0.19
van Lith et al. (56)	25	0.96	0.25	22	1.04	0.26	22	1.07	0.28
Diniz De Lima et al. (69)	54	0.77	0.38	52	0.74	0.37	n.a.	n.a.	n.a.
SPRS									
Servelhere et al. (55)	22	21.60	9.00	22	21.40	9.10	n.a.	n.a.	n.a.
Diniz De Lima et al. (69)	54	16.80	8.25	52	16.40	8.04	n.a.	n.a.	n.a.
TUG									
de Niet (52)	22	15	10.4	2.8	15	10.5	2.3	15	10.9
van Lith et al. (56)	54	25	10.6	3.8	22	10.7	4.2	22	10.5

SPRS, Spastic Paraplegia Rating Scale; TUG, Time Up and Go; n, number of patients included in the study at the time point; mean, sd, mean value and standard deviation of the considered outcome measure.

but only one dropout was recorded, based on worsening of pre-existing urinary disturbances.

Two studies by Denton et al. (53) (randomized treatment with healthy controls) and in Denton et al. (66) (randomized crossover) researched the role of lower limb superficial heating in a total of 43 HSP subjects and 19 controls. The authors demonstrated that heating reduced spasticity, increased dorsiflexor rate of force generation and nerve conduction velocity, and slightly improved gait speed while cooling (53) induced the opposite effects. The application of heating or cooling wrap lasted 30 min.

3.3. Meta-analysis

Considering the aim of this review, the meta-analysis was limited to gait and functional outcome measures. Because of the wide variability of the type of interventions and outcomes, and the small number of studies using the same treatment, a meta-analysis was conducted only on studies describing BoNT-A intervention. Two were excluded because the authors did not specify the data results (54) or presented results in terms of median values, which were not comparable with the others (57). Five studies regarding BoNT-A were included. Comparisons were performed regarding the comfortable gait velocity in four (49, 52, 56, 69), the max gait velocity in three (52, 56, 69), the SPRS in two (55, 69), and the TUG results in two (52, 56) studies. In the study by Servelhere et al. (55), the 10mWT was reported as a global value of mean time and SD; then, it was not comparable with other studies, in which the authors reported the gait velocity. In the study by Rousseaux et al. (49), the results were expressed in terms of median values, but it was possible to calculate the mean gait velocity directly from individual raw data. Considering the heterogeneity of time points of evaluations among the studies, data were compared at baseline (t_0), before 2 months as the first time point (t_1), and after 2 months as the follow-up time point (t_2). The analysis was performed estimating the mean and the standard deviation of the change from baseline to each endpoint.

Table 7 summarizes the data used for the meta-analysis for estimating the effect of the BoNT-A; for each selected study, the number of observations (*n*), the mean value, and the standard deviation (*sd*) of the three time points are reported.

Figure 4 summarizes the weighted means estimates of the various meta-analyses and the relative standard errors, for each time period. An important variability of the estimates for all the considered parameters was generally evidenced. A non-significant effect of BoNT-A was observed in the comparison of the three time periods on the four considered parameters, except for comfortable gait velocity evaluated from t_0 to t_2.

To estimate the effect of botulinum for each of the outcomes of interest, four independent meta-analyses were performed, as represented in Figures 5–8 using forest and funnel plots. The forest plot typically summarizes the results of the meta-analysis. The funnel plot shows the estimated treatment effects in terms of standardized mean difference on the x-axis against the standard

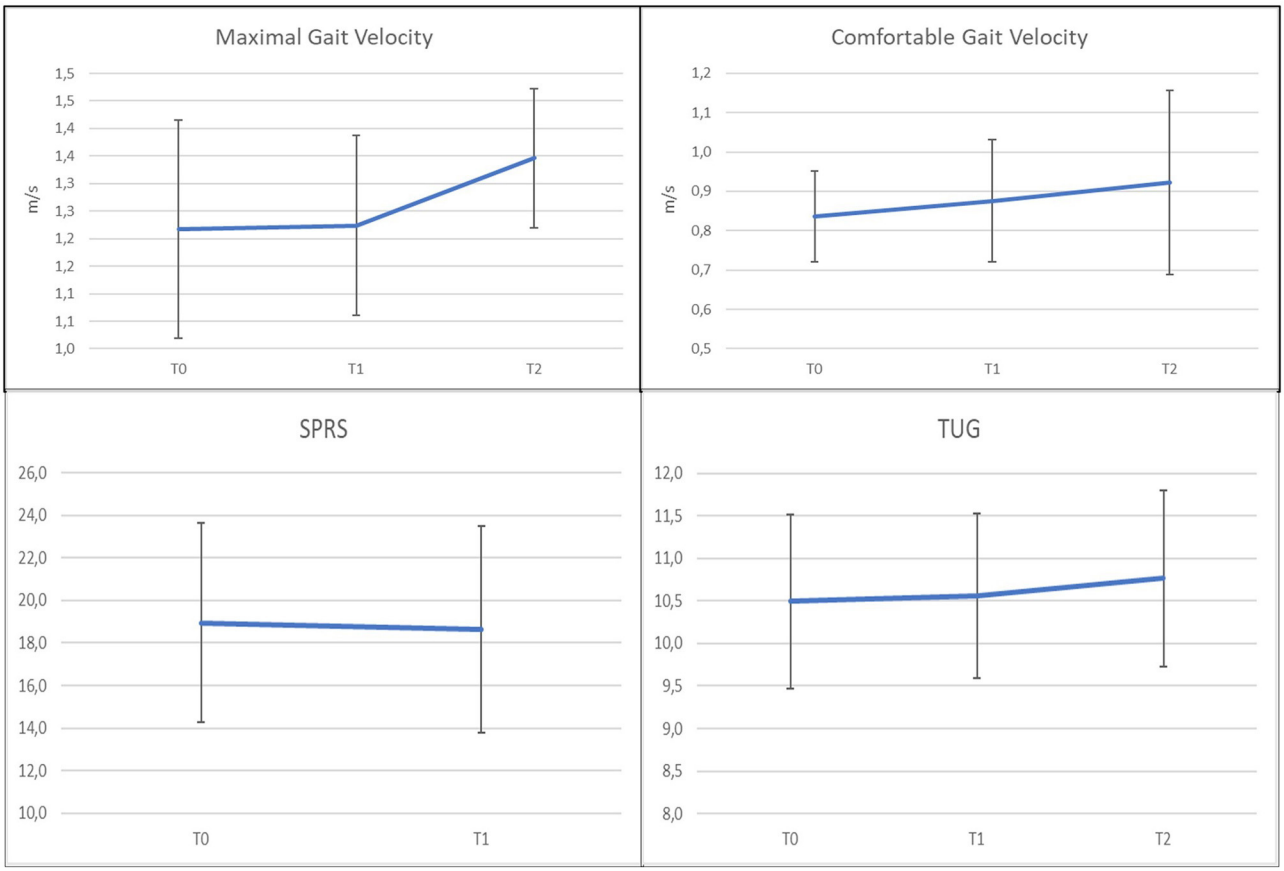

FIGURE 4
Mean estimates obtained from the meta-analyses relative to Maximal and Comfortable Walking Velocity, SPRS, and TUG, for each examined time period. The error bars represent the standard errors of the estimates of the individual means from the meta-analysis models.

error (in an inverted scale) on the y-axis. It shows the form of a triangle symmetric to the average treatment effect, with broad variability for small imprecise studies at the bottom of the plot and small dispersion for large, precise studies at the top.

3.3.1. Maximum gait velocity

The meta-analysis (Figures 5A–F) included three studies (52, 56, 69) that presented an overall heterogeneity ($Q = 9.35$, $p = 0.009$ in t_0; $Q = 10.40$, $p = 0.005$ in t_1), so a random effect model was used.

The estimated means were 1.217 in t_0 ($n = 94$; CI [1.019; 1.416]), 1.224 in t_1 ($n = 89$; CI [1.015; 1.432]), and 1.346 ($n = 37$; CI [1.219; 1.473]) in t_2.

The change of the maximum gait velocity was not significant from t_0 to t_1 (SMD = 0.003; CI [−0.287, +0.293], $p = 0.983$) nor from t_0 to t_2 (SMD = 0.073; CI [−0.374, +0.520], $p = 0.749$). Therefore, the change from t_1 to t_2 was not significant (SMD = 0.046; CI [−0.409, +0.517], $p = 0.843$).

This non-significance may depend on the great variability of the individual data, but also on the peculiarities of Diniz De Lima et al. (69), in which the average of the maximum gait velocity was considerably lower than that of the other two studies, both in t_0 and in t_1. The exclusion of Diniz De Lima et al. (69) from the meta-analysis made the other studies homogeneous ($Q = 0.05$, $p = 0.817$), but the changes in the maximum gait velocity remained non-significant.

3.3.2. Comfortable gait velocity

For the comparison of the comfortable gait velocity, four studies were included (49, 52, 56, 69) in the meta-analysis (Figures 6A–F). A random effects model was used, due to the substantial heterogeneity among the studies ($Q = 13.26$, $p = 0.004$ in t_0; $Q = 23.63$, $p < 0.001$ in t_1; $Q = 21.98$, $p < 0.001$ in t_2). The estimated means were 0.837 in t_0 ($n = 109$; CI [0.721; 0.953]), 0.876 in t_1 ($n = 103$; CI [0.721; 1.030]), and 0.922 ($n = 50$; CI [0.688; 1.157]) in t_2. The mean change was not significant from t_0 to t_1 (SMD = 0.108; CI [−0.163; 0.378]; $p = 0.435$), weakly significant in the comparison between the baseline and t_2 (SMD = 0.335; CI [−0.052; 0.723]; $p = 0.089$), and again not significant t_1 to t_2 (SMD = 0.025; CI [−0.365; 0.416]; $p = 0.898$). Also, in this case, Diniz De Lima (69) was peculiar compared to the other studies, because it presented a negative change of the comfortable gait velocity from t_0 to t_1 (SMD = −0.08; CI [−0.46; 0.30]). Meta-analysis was then repeated excluding this study. The new results showed a positive estimate of the mean change from t_0 to t_1, with a noticeably lower p-value, but in any case, non-significant at 95% (SMD = 0.297; CI [−0.086; 0.680]; $p = 0.129$).

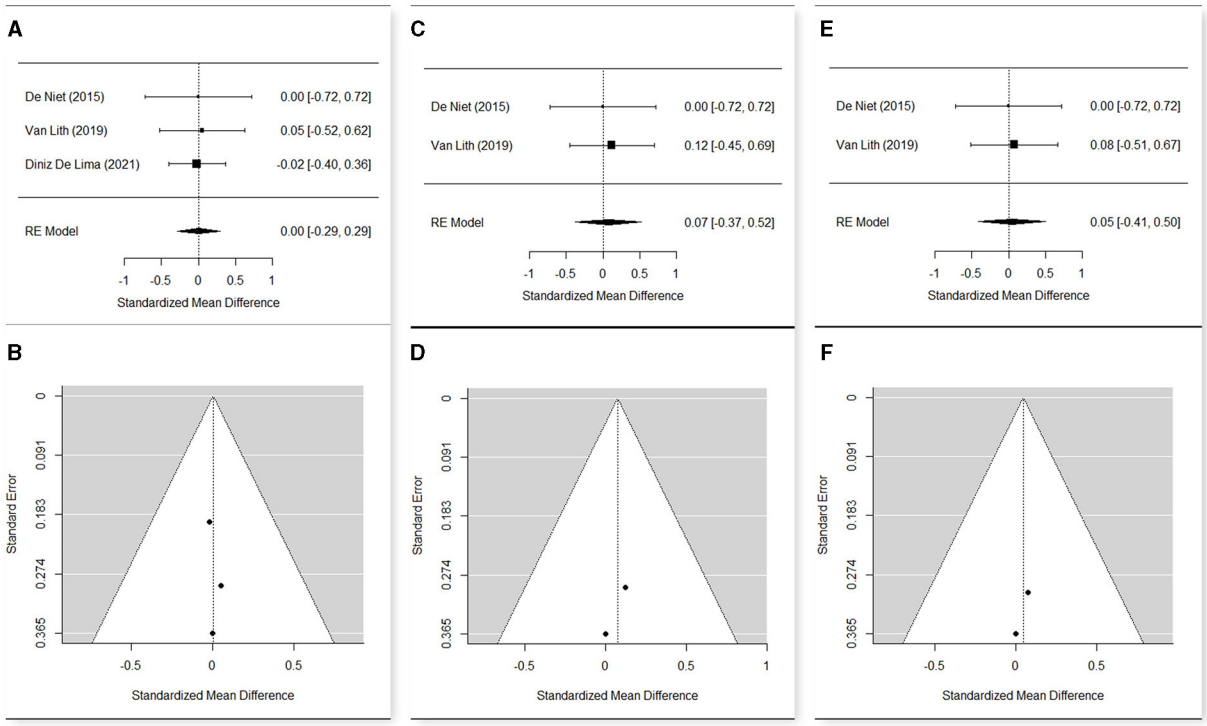

FIGURE 5
Forest plot **(A)** and funnel plot **(B)** for meta-analysis relative to Maximal Gait Velocity t_1 vs. t_0; Forest plot **(C)** and funnel plot **(D)** for meta-analysis relative to Maximal Gait Velocity t_2 vs. t_0; Forest plot **(E)** and funnel plot **(F)** for meta-analysis relative to Maximal Gait Velocity t_2 vs. t_1.

3.3.3. Spastic paraplegia rating scale

Only two studies (55, 69) were included in the meta-analysis (Figures 7A, B), and in both cases, no follow-up data were present. Data presented heterogeneity in t_0 ($Q = 4.66$, $p = 0.0308$) and also in t_1 ($Q = 504$, $p = 0.0248$), so a random effects model was performed. The estimated means of SPRS were 18.948 in t_0 (n = 76; CI [14, 269; 23.626]) and 18.643 in t_1 (n = 76; CI [13.769; 23.517]), showing a substantial stability of this parameter (SMD = −0.041; CI [−0.359; 0.277]; $p = 0.801$).

3.3.4. Time up and go

The meta-analysis included two studies (52, 56) (Figures 8A–F) for this parameter that resulted quite homogeneous in the three time points ($Q = 0.04$, $p = 0.849$ in t_0; $Q = 0.03$, $p = 0.852$ in t_1; $Q = 0.13$, $p = 0.721$ in t_2). The estimated means were 10.495 in t_0 ($n = 40$; CI [9.468; 11.512]), 10.561 in t_1 ($n = 37$; CI [9.591; 11.531]), and 10.765 ($n = 37$; CI [9.733; 11.802]) in t_2. Due to the large variability of the data, the mean change was not significant from t_0 to t_1 (SMD = 0.0300; CI [−0.417; 0.477]; $p = 0.896$), from t_0 to t_2 (SMD = 0.056; CI [−0.391; 0.504]; $p = 0.804$), and from t_1 to t_2 (SMD = 0.038; CI [−0.418; 0.494]; $p = 0.870$).

4. Discussion

One objective of the review was to provide knowledge concerning the characteristics of gait in HSP subjects, which might reveal specific functional compensations and needs, with the secondary purpose of adequately addressing the treatment strategies.

The frame of HSP gait patterns appeared wide and the severity of symptoms varied either among members of the same family (9) or among different ages (7), given an overall progression over time (5, 9). Relevant indicators of HSP progression were identified, such as knee flexion and non-sagittal pelvic movements (5), reduced ROM at the knee, ankle, and hip (41, 46), which appeared to be associated with coactivation and increased energy consumption (42, 46), decreased foot lift (46), and reduced gait velocity (6, 7, 9, 34, 39, 42–44, 70).

Based on the included studies, pathological gait analysis patterns were described in HSP by comparison with healthy subjects, with attempts to identify clusters of gait patterns either in pediatric (5, 7) or in adult (41, 43) HSP subjects. Nonetheless, most of the GA patterns described appeared similar to DCP and stroke for young HSP patients and adults, respectively. Some authors applied cerebral palsy classifications to categorize HSP sagittal kinematics (7, 37).

Nonetheless, some features distinguished HSP from other similar pathological conditions.

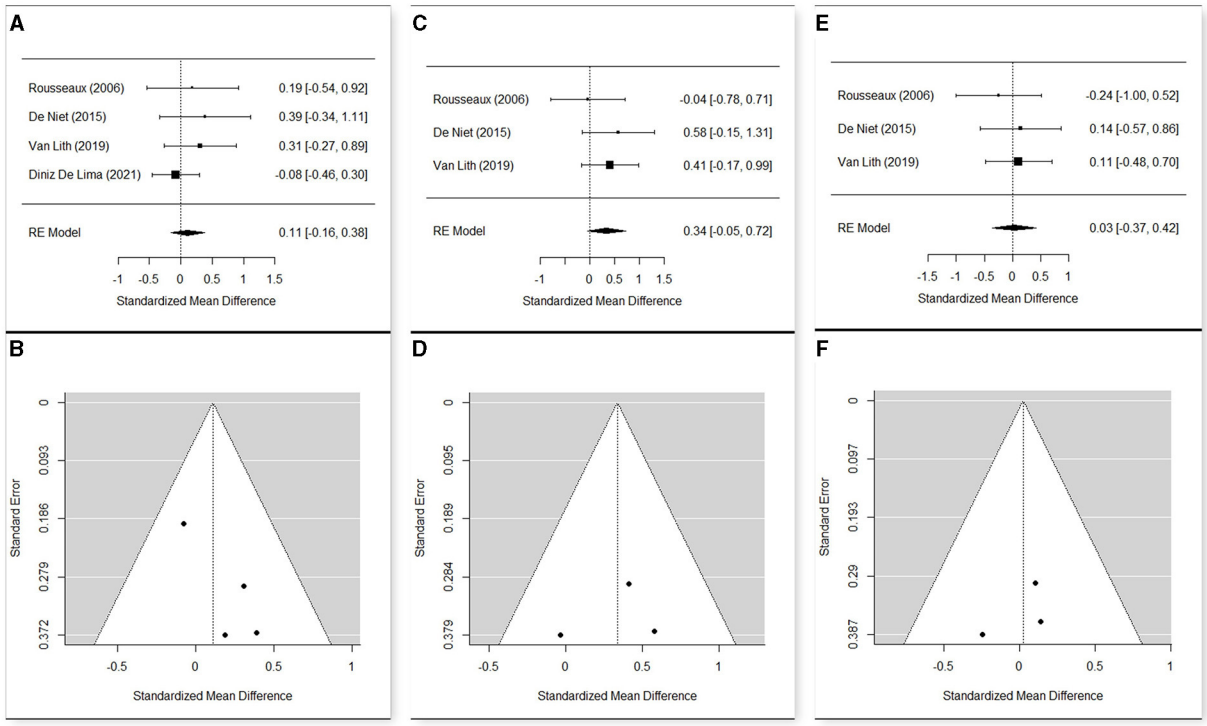

FIGURE 6
Forest plot **(A)** and funnel plot **(B)** for meta-analysis relative to Comfortable Gait Velocity t_1 vs. t_0; Forest plot **(C)** and funnel plot **(D)** for meta-analysis relative to Comfortable Gait Velocity t_2 vs. t_0; Forest plot **(E)** and funnel plot **(F)** for meta-analysis relative to Comfortable Gait Velocity t_2 vs. t_1.

Authors who compared the subgroup of young HSP patients to DCP substantially agreed focusing on the knee kinematics as the most typically involved. Similar to DCP, HSP patients presented stiff knee gait with reduced knee and hip flexion in the swing phase, insufficient knee extension in terminal swing, and insufficient hip extension in stance (5, 39, 40). Nonetheless, longer knee hyperextension was often observed during midstance compared to DCP (5, 34, 36, 37). This may be interpreted as compensation to rectus femoris weakness/hypoactivation (quadriceps avoidance pattern) (34, 36) to achieve a supportive reaction and avoid joint collapse during walking, rather than one manifestation of spasticity, as suggested by EMG pattern (36). While DCP subjects presented higher rectus femoris and hamstring activation, low activation of knee extensors was reported in HSP, with increased absorbed power and decreased generated power at the knee (34, 36). Knee extensor weakness was confirmed at the MRC assessment (36). Based on these observations, ankle–foot orthoses, often recommended in DCP to reduce recurvatum of the knee, might interfere with the HSP knee stabilization strategy (34).

Along with HSP progression, an important increase of knee flexion in midstance and at initial contact was observed, which is similar to the crouch pattern in DCP. This condition might be related to hamstring spasticity/over-activity (5), or most probably to failure of the knee extensor moment (47) because of abnormal quadriceps function, associated with inadequate hip extensor moment, due to weakness of hip extensors (5). Furthermore, a crouch gait pattern was observed following Achilles tendon lengthening surgeries in two HSP patients (39).

Differently from DCP, the ankle joint kinematics, such as the mean foot progression and the global ankle functioning, appeared more or less similar to healthy controls, with global normal foot orientation (34, 36, 39).

An increased anterior pelvic tilt with reduced hip extension appeared to be a typical pattern, explained by iliopsoas muscle spasticity (5) or by hip extensors and hamstring weakness with increased lumbar lordosis (40).

Several studies researched upper body behavior, which is a novelty in GA studies. Increased trunk movements in the sagittal and coronal plane with retroposed trunk and lateral flexion were the most recurrent features. They may be attributed to compensatory patterns to muscle weakness, to assist limb clearance in the swing phase, resembling the "hip abductor avoiding gait" and "hip extensor avoidance gait", respectively, previously described in people with spina bifida (39, 40). Trunk movements were also characterized by a Double-bump trunk pattern, with twice occurring large peaks of the out-of-phase thorax and pelvis movements, throughout the gait cycle (39, 40). This might be a compensation for distal deficits, related to good control of spinal segments, which is typically maintained in HSP patients (39). Moreover, while DCP patients used synchronized (co-contraction) upper limb and pelvis–thorax movements to increase equilibrium, conversely, HSP patients showed significant and rapid spine tilt, with almost normal shoulder and elbow movements (37, 39).

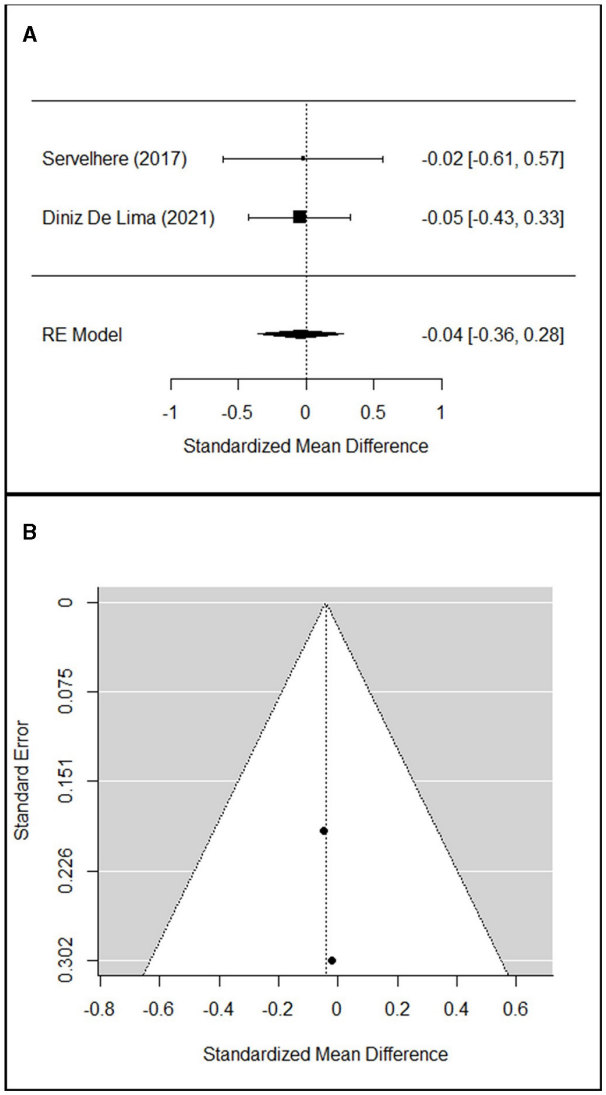

FIGURE 7
Forest plot **(A)** and funnel plot **(B)** for meta-analysis relative to SPRS t_1 vs. t_0.

Nonetheless, excessive lateral and posterior trunk movements might also lead to increased energy expenditure, then require the use of mobility devices to help energy conservation and prevent future joint deterioration (40).

Compared to DCP, HSP patients presented a more physiological position of the hip in the transversal plane (36, 40), and this was interpreted as a physiological correction of neonatal femur anteversion in the first years of life in HSP patients, compared to a persistence of this condition in DCP patients, where neuromotor anomalies are present at birth (36). Also, Klebe et al. (6) in an adult cohort denied inward foot rotation.

The stiff knee was also reported as the most common pattern in adults affected by HSP, with a reduced ROM at the knee and ankle (38, 42, 44, 46). Similar to younger patients, these patterns were almost unanimously attributed to weakness, confirmed at MRC, and increased stiffness of plantar flexors and quadriceps, rather than spasticity (35, 38). Furthermore, patterns of EMG coactivation at dorsi-plantar flexors (41–43) and extensors–flexors of the knee (41, 42) were described. They were attributed to decreased cortical inhibition, related to the degeneration of the corticospinal tract, which was not completely compensated by extrapyramidal pathways. One alternative pathway, i.e., the reticulospinal system, was studied by van Lith et al. (45), enquiring the APA after SAS. The authors demonstrated that the reticulospinal pathway might compensate for the corticospinal tract degeneration, accelerating TA and RF activation. Conversely, it failed acceleration of SO inhibition, with a persisting deficit of inhibitory motor control.

Finally, increased step width (6, 41, 42, 44, 70) was often reported and might be interpreted as one strategy to increase stability.

The predominant role of weakness above spasticity was confirmed by the intervention studies. Because of secondary weakness, oral baclofen was mostly withdrawn and only 50% of patients responded to bolus infusion test according to Klebe et al. (60). One case report (59) showed improved lower limb locomotor coordination, speed, stride length, and cadence after ITB bolus. Heetla et al. (63) reported improvement after ITB implantation in terms of gait velocity and spasticity reduction, without strength loss, lasting at a 6-month follow-up. The authors suggested that a continuous infusion test was more effective because it allowed a slight dose increase, reducing adverse effects and providing sufficient time for patients to explore positive outcomes. Regarding studies on botulinum injections, the meta-analysis demonstrated a significant improvement limited to the comparison between the baseline and t_2 at the comfortable gait velocity, which was not relieved as significant at t_0-t_1. This might be attributed to an initial limiting role of post-botulinum weakness (52) that was subsequently overcome. Nonetheless, a significant improvement was not observed at maximum gait velocity. This might be related to an increase in spasticity (even after pharmacological inhibition) and more impaired motor control, associated with augmented velocity. Functional improvements were reported, in particular, in the study by Paparella et al. (57), but botulinum was followed by intensive physiotherapy, which might have contributed to the improvements, based on increased physical activity and reconditioning as observed after gait training. In addition, some concerns should be considered regarding the analysis and the reporting of results in the study by Paparella et al. (57).

A meta-analysis was not possible; however, functional improvements were reported by individual studies after intensive active interventions, such as physical therapy training (including stretching, strengthening, and functional exercises), hydrotherapy, and robotic gait training. Significant or close to significant improvements were reported, in particular, for gait velocity, and, whenever measured, for BBS, TUG, and 10MWT. Only one case report by Seo et al. (64) reported a contradictory reduction of TUG and 6MWT after robot-assisted gait training, while other outcome measures improved (speed, 10MWT, and BBS). The positive rebound of such intensive active interventions might rely on reconditioning through augmented physical activity, as in other pathological conditions (77, 78). Nonetheless, no significant changes in kinematics and kinetics were observed, suggesting that physical activity might improve fitness and the ability to perform compensatory strategies rather than modifying gait patterns.

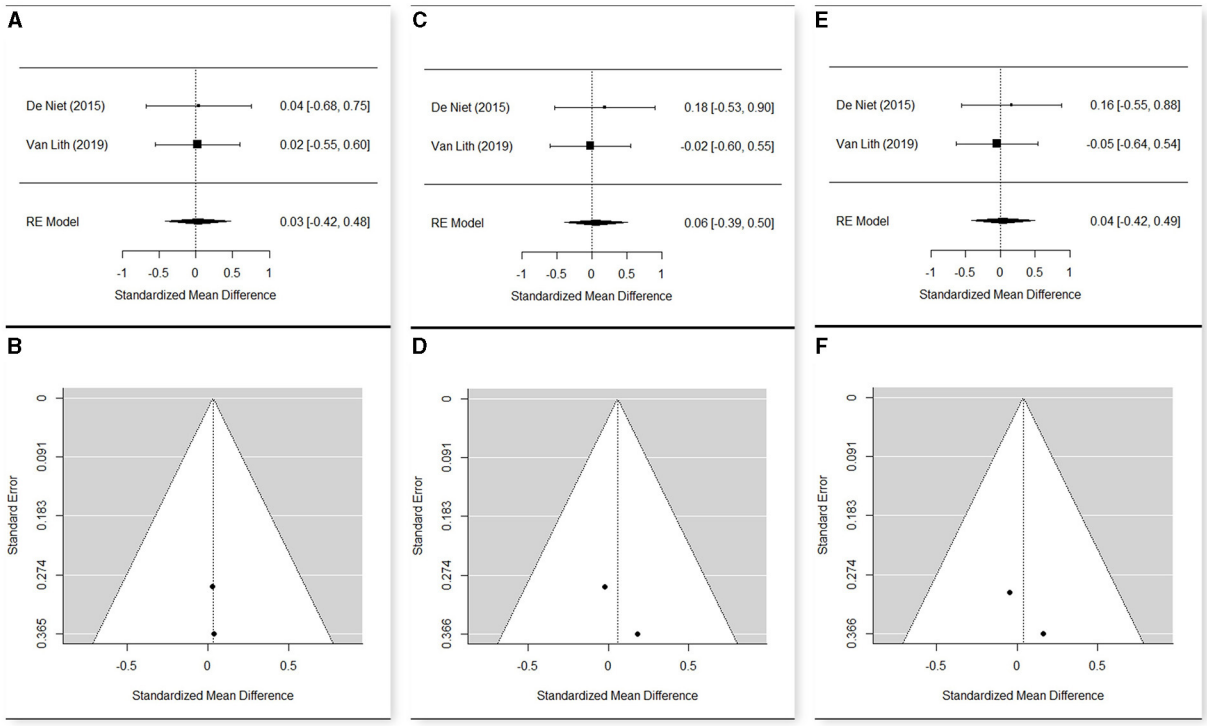

FIGURE 8
Forest plot **(A)** and funnel plot **(B)** for meta-analysis relative to TUG t_1 vs. t_0; Forest plot **(C)** and funnel plot **(D)** for meta-analysis relative to TUG t_2 vs. t_0; Forest plot **(E)** and funnel plot **(F)** for meta-analysis relative to TUG t_2 vs. t_1.

Furthermore, the evidence is limited by a lack of follow-up and very small samples. The benefits might recede following the withdrawal of the training, as it is, for example, in cerebral palsy (77), which has the advantage of being a non-progressive disease. As for the general population, it is advisable to increase physical activity, hopefully integrated into daily life, to maintain or improve fitness, with a possible positive impact on gross motor activities. Nonetheless, this is limited to subjects with sufficient motor skills to be able to undertake training.

Two studies by Denton et al. (53, 66) demonstrated that superficial warming of the legs may reduce spasticity and increase nerve conduction velocity in the very short term, while the opposite effect may be expected by cooling. This confirms previous data (79) supporting the application of such techniques in immediate pre-stretch or pre-exercise periods.

FES (58, 71) determined an improvement limited to gait velocity, but long-term follow-up was missing and samples were small. No improvement was reported at the functional test (SPRS, gait velocity, TUG, 5MWT, and 10MWT) after rTMS (67), tsDCS (68), and ETOIMS (65). Furthermore, sample size and follow-up were very limited. Only one case report (8) researching SCS described improvements at SPRS at 12 months after implantation. Nonetheless, increased difficulty in controlling gait balance and uncomfortable paresthesia was referred by the patient. The authors attributed it to the SCS-induced block of proprioceptive pathways (8). Information about any adverse effects was missing in the other studies, except for rTMS. Antczak et al. (67) reported one case of a seizure occurring during the third session of stimulation, which induced the patient to drop out of the trial. One patient complained of sleeplessness and several subjects reported headaches during the first and second sessions of stimulation, but they all completed the study. Based on the included studies, further evidence is needed to support the role of previous techniques, which might be considered complementary interventions.

4.1. Safety and feasibility aspects

Computerized gait analysis is a safe procedure in patients with HSP of any age (no unfavorable events were reported), and only in one study, did six patients require a safety belt suspended from the ceiling of the laboratory, without weight support.

Muscle weakness was the main adverse effect reported following botulinum injections and intrathecal baclofen test. Nonetheless, it resolved at the termination of the pharmacological effect. Minor and uncommon side effects, after botulinum injections, were bruising, transient pain, paresthesia, falls or stumbles, decreased balance confidence (52, 69), slurred speech, handwriting incoordination, and inability to stand up and walk (55). Seizure (one subject) was reported as a major adverse effect following rTMS (67). Minor side effects were sleeplessness (one subject) and headache.

4.2. Limitations

One limitation of the present study was not considering the study design as an exclusion criterion, intending to collect as much data as possible in such a rare pathological condition and maintain a more powerful study design. Furthermore, we did not distinguish between the internal validity and statistical analysis validity of the studies, and a statistical analysis of quality score assessment was not performed.

The principal limitation concerning studies researching the GA pattern was that they included only subjects who could walk, without assistive devices, for a sufficient distance to carry out the exam. Therefore, more compromised patients were excluded from the pattern analysis.

Furthermore, limited to young HSP subjects, almost all studies performed the GA once, except Armand et al. (9), and longitudinal information about gait patterns is lacking. Therefore, any possible change related to growth or HSP progression has not been studied.

Relative to intervention studies, several limitations must be underlined: short or lacking follow-up, small samples, wide variability in treatment protocol, and most of all, the absence of studies involving younger HSP subjects.

Finally, most of the included studies, in particular, those researching the GA patterns, were limited to pure forms of HSP. This met the need to select uniform samples and reduce confounders. Nonetheless, a partial representation emerged of the more complex and wide range of HSP clinical phenotypes.

5. Conclusion

Knee kinematics and kinetics represent the most peculiar patterns in HSP, compared to DCP and stroke, in particular, related to knee hyperextension in midstance, as compensation to plantar flexor-knee extensor couple deficit.

Other typical patterns are non-sagittal pelvic movements and reduced ROM at the knee, ankle, and hip, which relates to coactivation and increased energy consumption.

Spasticity in HSP hinders muscle weakness, so caution is required while considering interventions to reduce spasticity. Botulinum induced a significant improvement in gait at a comfortable velocity approximately 2–3 months after the injection. This improvement resulted as non-significant immediately after the treatment, probably due to initial weakness.

Limited evidence suggests that intensive physical activity (overground or robot-assisted gait training, functional exercises, and hydrotherapy) and FES might determine improvement in the very short term in gait velocity-related outcomes. Future studies are needed to study the effectiveness of these approaches in HSP subjects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SF: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review and editing. AC: Investigation, Methodology, Writing – original draft. NF: Data curation, Formal analysis, Methodology, Writing – original draft. GM: Investigation, Writing – original draft. IS: Investigation, Writing – original draft. SS: Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1256392/full#supplementary-material

References

1. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. *Exp Neurol Nov.* (2014) 261:518–39. doi: 10.1016/j.expneurol.2014.06.011

2. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol Dec.* (2008) 7:1127–38. doi: 10.1016/S1474-4422(08)70258-8

3. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Disorders TFoCM. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics.* (2003) 111:e89–97. doi: 10.1542/peds.111.1.e89

4. Fink JK, Heiman-Patterson T, Bird T, Cambi F, Dubé MP, Figlewicz DA, et al. Hereditary spastic paraplegia: advances in genetic research. Hereditary Spastic Paraplegia Working group. *Neurology.* (1996) 46:1507–14. doi: 10.1212/WNL.46.6.1507

5. Pulido-Valdeolivas I, Gómez-Andrés D, Martín-Gonzalo JA, Rodríguez-Andonaegui I, López-López J, Pascual-Pascual SI, et al. Gait phenotypes in paediatric hereditary spastic paraplegia revealed by dynamic time warping analysis and random forests. *PLoS ONE.* (2018) 13:e0192345. doi: 10.1371/journal.pone.0192345

6. Klebe S, Stolze H, Kopper F, Lorenz D, Wenzelburger R, Volkmann J, et al. Gait analysis of sporadic and hereditary spastic paraplegia. *J Neurol.* (2004) 251:571–8. doi: 10.1007/s00415-004-0366-7

7. Van Beusichem AE, Nicolai J, Verhoeven J, Speth L, Coenen M, Willemsen MA, et al. Mobility characteristics of children with spastic paraplegia due to a mutation in the KIF1A gene. *Neuropediatrics.* (2020) 51:146–53. doi: 10.1055/s-0039-3400988

8. Pinto de Souza C, Coelho DB, Campos DDSF, Dos Santos Ghilardi MG, de Oliveira Vicente EC, González-Salazar C, et al. Spinal cord stimulation improves motor function and gait in spastic paraplegia type 4 (SPG4): clinical and neurophysiological evaluation Parkinsonism. *Relat Disord.* (2021) 83:1–5. doi: 10.1016/j.parkreldis.2020.12.008

9. Armand S, Turcot K, Bonnefoy-Mazure A, Lascombes P, De Coulon G. Gait evolution in a family with hereditary spastic paraplegia. *Eur J Paediatr Neurol.* (2015) 19:87–92. doi: 10.1016/j.ejpn.2014.08.001

10. Fink JK. Hereditary spastic paraplegia. *Curr Neurol Neurosci Rep.* (2006) 6:65–76. doi: 10.1007/s11910-996-0011-1

11. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol.* (2013) 126:307–28. doi: 10.1007/s00401-013-1115-8

12. Harding AE. Classification of the hereditary ataxias and paraplegias. *Lancet.* (1983) 1:1151–5. doi: 10.1016/S0140-6736(83)92879-9

13. Harding AE. Hereditary "pure" spastic paraplegia: a clinical and genetic study of 22 families. *J Neurol Neurosurg Psychiatry.* (1981) 44:871–83. doi: 10.1136/jnnp.44.10.871

14. Nonnekes J, van Lith B, van de Warrenburg BP, Weerdesteyn V, Geurts ACH. Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med.* (2017) 49:369–77. doi: 10.2340/16501977-2227

15. Patrick JH, Keenan MA. Gait analysis to assist walking after stroke. *Lancet.* (2007) 369:256–7. doi: 10.1016/S0140-6736(07)60124-X

16. Bellofatto M, De Michele G, Iovino A, Filla A, Santorelli FM. Management of Hereditary Spastic Paraplegia: A Systematic Review of the Literature. *Front Neurol.* (2019) 10:3. doi: 10.3389/fneur.2019.00003

17. Trummer B, Haubenberger D, Blackstone C. Clinical trial designs and measures in hereditary spastic paraplegias. *Front Neurol.* (2018) 9:1017. doi: 10.3389/fneur.2018.01017

18. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* (2021) 372:n160. doi: 10.1136/bmj.n160

19. Higgins JPT. TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions, 2nd Edn.* Chichester: John Wiley &Sons. (2019).

20. McDermott CJ, Shaw PJ. Chapter 17 Hereditary spastic paraparesis. *Handb Clin Neurol.* (2007) 82:327–52. doi: 10.1016/S0072-9752(07)80020-0

21. Moola MZ, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, et al. *JBI Manual for Evidence Synthesis. Systematic Reviews of Etiology and Risk*. London: The Joanna Briggs Institute (2017).

22. George PP, DeCastro Molina JA, Heng BH. The methodological quality of systematic reviews comparing intravitreal bevacizumab and alternates for neovascular age related macular degeneration: a systematic review of reviews. *Indian J Ophthalmol Jul.* (2014) 62:761–7. doi: 10.4103/0301-4738.138615

23. National Heart Lung and Blood Institute. *Study Quality Assessment Tools*. Bethesda, MD: National Heart Lung and Blood Institute (2021).

24. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Mil Med Res.* (2020) 7:7. doi: 10.1186/s40779-020-00238-8

25. Cashin AG, McAuley JH. Clinimetrics: physiotherapy evidence database (PEDro) scale. *J Physiother.* (2020) 66:59. doi: 10.1016/j.jphys.2019.08.005

26. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* (2016) 355:i4919. doi: 10.1136/bmj.i4919

27. Available online at: https://sites.google.com/site/riskofbiastool/welcome/home/current-version-of-robins-i?authuser=0.ROBINS-I (accessed September 15, 2022).

28. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* (2019) 366:l4898. doi: 10.1136/bmj.l4898

29. Available online at: https://www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-crossover-trials.RoB2 (accessed September 15, 2022).

30. R Core Team. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing*. Vienna: R Core Team (2021).

31. Viechtbauer W. Conducting meta-analyses in R with the metafor Package. *J Stat Software.* (2010) 5:1–48. doi: 10.18637/jss.v036.i03

32. Cochran WG. The combination of estimates from different experiments. *Biometrics*. (1954) 10:101–29. doi: 10.2307/3001666

33. Morris SB. Distribution of the standardized mean change effect size for meta-analysis on repeated measures. *Br J Math Stat Psychol.* (2000) 53:17–29. doi: 10.1348/000711000159150

34. Cimolin V, Piccinini L, D'Angelo MG, Turconi AC, Berti M, Crivellini M, et al. Are patients with hereditary spastic paraplegia different from patients with spastic diplegia during walking? Gait evaluation using 3D gait analysis. *Funct Neurol.* (2007) 22:23–8. .

35. de Niet M, Latour H, Hendricks H, Geurts AC, Weerdesteyn V. Short-latency stretch reflexes do not contribute to premature calf muscle activity during the stance phase of gait in spastic patients. *Arch Phys Med Rehabil.* (2011) 92:1833–9. doi: 10.1016/j.apmr.2011.05.025

36. Piccinini L, Cimolin V, D'Angelo MG, Turconi AC, Crivellini M, et al. 3D gait analysis in patients with hereditary spastic paraparesis and spastic diplegia: a kinematic, kinetic and EMG comparison. *Eur J Paediatr Neurol.* (2011) 15:138–45. doi: 10.1016/j.ejpn.2010.07.009

37. Wolf SI, Braatz F, Metaxiotis D, Armbrust P, Dreher T, Döderlein L, et al. Gait analysis may help to distinguish hereditary spastic paraplegia from cerebral palsy. *Gait Posture.* (2011) 33:556–61. doi: 10.1016/j.gaitpost.2011.01.009

38. Marsden J, Ramdharry G, Stevenson V, Thompson A. Muscle paresis and passive stiffness: key determinants in limiting function in Hereditary and Sporadic Spastic Paraparesis. *Gait Posture.* (2012) 35:266–71. doi: 10.1016/j.gaitpost.2011.09.018

39. Bonnefoy-Mazure A, Turcot K, Kaelin A, De Coulon G, Armand S. Full body gait analysis may improve diagnostic discrimination between hereditary spastic paraplegia and spastic diplegia: a preliminary study. *Res Dev Disabil.* (2013) 34:495–504. doi: 10.1016/j.ridd.2012.09.005

40. Adair B, Rodda J, McGinley JL, Graham HK, Morris ME. Kinematic gait deficits at the trunk and pelvis: characteristic features in children with hereditary spastic paraplegia. *Dev Med Child Neurol Aug.* (2016) 58:829–35. doi: 10.1111/dmcn.13082

41. Serrao M, Rinaldi M, Ranavolo A, Lacquaniti F, Martino G, Leonardi L, et al. Gait Patterns in Patients with Hereditary Spastic Paraparesis. *PLoS ONE.* (2016) 11:e0164623. doi: 10.1371/journal.pone.0164623

42. Rinaldi M, Ranavolo A, Conforto S, Martino G, Draicchio F, Conte C, et al. Increased lower limb muscle coactivation reduces gait performance and increases metabolic cost in patients with hereditary spastic paraparesis. *Clin Biomech.* (2017) 48:63–72. doi: 10.1016/j.clinbiomech.2017.07.013

43. Martino G, Ivanenko Y, Serrao M, Ranavolo A, Draicchio F, Rinaldi M, et al. Differential changes in the spinal segmental locomotor output in Hereditary Spastic Paraplegia. *Clin Neurophysiol.* (2018) 129:516–25. doi: 10.1016/j.clinph.2017.11.028

44. Serrao M, Chini G, Bergantino M, Sarnari D, Casali C, Conte C, et al. Identification of specific gait patterns in patients with cerebellar ataxia, spastic paraplegia, and Parkinson's disease: a non-hierarchical cluster analysis. *Hum Mov Sci.* (2018) 57:267–79. doi: 10.1016/j.humov.2017.09.005

45. van Lith BJH, Coppens MJM, Nonnekes J, van de Warrenburg BPC, Geurts AC, Weerdesteyn V. StartReact during gait initiation reveals differential control of muscle activation and inhibition in patients with corticospinal degeneration. *J Neurol Nov.* (2018) 265:2531–9. doi: 10.1007/s00415-018-9027-0

46. Martino G, Ivanenko Y, Serrao M, Ranavolo A, Draicchio F, Casali C, et al. Locomotor coordination in patients with Hereditary Spastic Paraplegia. *J Electromyogr Kinesiol.* (2019) 45:61–9. doi: 10.1016/j.jelekin.2019.02.006

47. Malone A, Kiernan D, O'Brien T. Bilateral sleeve fractures of the patella in a 12-year-old boy with hereditary spastic paraparesis and crouch gait. *BMJ Case Rep.* (2013) 2013:217. doi: 10.1136/bcr-2013-202217

48. Klebe S, Deuschl G, Stolze H. Methylphenidate fails to improve gait and muscle tone in patients with sporadic and hereditary spastic paraplegia. *Mov Disord.* (2006) 21:1468–71. doi: 10.1002/mds.20973

49. Rousseaux M, Launay MJ, Kozlowski O, Daveluy W. Botulinum toxin injection in patients with hereditary spastic paraparesis. *Eur J Neurol.* (2007) 14:206–12. doi: 10.1111/j.1468-1331.2006.01617.x

50. Zhang Y, Roxburgh R, Huang L, Parsons J, Davies TC. The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. *Gait Posture.* (2014) 39:1074–9. doi: 10.1016/j.gaitpost.2014.01.010

51. Bertolucci F, Di Martino S, Orsucci D, Ienco EC, Siciliano G, Rossi B, et al. Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation.* (2015) 36:93–9. doi: 10.3233/NRE-141196

52. de Niet M. Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: a study in patients with hereditary spastic paraplegia. *J Rehab Med.* (2015) 2:147–53. doi: 10.2340/16501977-1909

53. Denton A, Bunn L, Hough A, Bugmann G, Marsden J. Superficial warming and cooling of the leg affects walking speed and neuromuscular impairments in people with spastic paraparesis. *Ann Phys Rehabil Med.* (2016) 59:326–32. doi: 10.1016/j.rehab.2016.04.006

54. Marvulli R, Lopopolo AL, Dantone A, Palmisano V, Lancioni G, Fiore P et al. Combined treatment FKT-botulinum toxin type A (BTX-A) in patients with Strumpell-Lorrain disease. *Curr Pharm Des.* (2016) 22:758–63. doi: 10.2174/1381612822666151204001830

55. Servelhere KR, Faber I, Martinez A, Nickel R, Moro A, Germiniani FMB, et al. Botulinum toxin for hereditary spastic paraplegia: effects on motor and non-motor manifestations. *Arq Neuropsiquiatr.* (2018) 76:183–8. doi: 10.1590/0004-282x20180013

56. van Lith BJH, den Boer J, van de Warrenburg BPC, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia. *J Rehabil Med.* (2019) 51:434–41. doi: 10.2340/16501977-2556

57. Paparella G, Vavla M, Bernardi L, Girardi G, Stefan C, Martinuzzi A. Efficacy of a combined treatment of botulinum toxin and intensive physiotherapy in hereditary spastic paraplegia. *Front Neurosci.* (2020) 14:111. doi: 10.3389/fnins.2020.00111

58. Pease WS. Therapeutic electrical stimulation for spasticity: quantitative gait analysis. *Am J Phys Med Rehabil.* (1998) 77:351–5. doi: 10.1097/00002060-199807000-00021

59. Dan B, Bouillot E, Bengoetxea A, Cheron G. Effect of intrathecal baclofen on gait control in human hereditary spastic paraparesis. *Neurosci Lett.* (2000) 280:175–8. doi: 10.1016/S0304-3940(00)00778-3

60. Klebe S, Stolze H, Kopper F, Lorenz D, Wenzelburger R, Deuschl G, et al. Objective assessment of gait after intrathecal baclofen in hereditary spastic paraplegia. *J Neurol.* (2005) 252:991–3. doi: 10.1007/s00415-005-0792-1

61. Molteni F, Carda S, Cazzaniga M, Magoni L, Rossini M, Caimmi M. Instrumental evaluation of gait modifications before and during intrathecal baclofen therapy: a 2-year follow-up case study. *Am J Phys Med Rehabil.* (2005) 84:303–6. doi: 10.1097/01.PHM.0000156892.04239.B6

62. Samuel AA, Vencita K, Trapthi P. Physical therapy interventions for the patient with hereditary spastic paraparesis – An exploratory case reports. *Int J Physiother Res.* (2013) 24:110–3.

63. Heetla HW, Halbertsma JP, Dekker R, Staal MJ, van Laar T. Improved gait performance in a patient with hereditary spastic paraplegia after a continuous intrathecal baclofen test infusion and subsequent pump implantation: a case report. *Arch Phys Med Rehabil.* (2015) 96:1166–9. doi: 10.1016/j.apmr.2015.01.012

64. Seo HG, Oh BM, Kim K. Robot-assisted gait training in a patient with hereditary spastic paraplegia. *PMR.* (2015) 7:210–3. doi: 10.1016/j.pmrj.2014.09.008

65. Shin S, Park J, Hong J, Park JH. Improved gait speed in spastic paraplegia: a new modality. *BMJ Support Palliat Care.* (2020) 10:e41. doi: 10.1136/bmjspcare-2018-001738

66. Denton AL, Hough AD, Freeman JA, Marsden JF. Effects of superficial heating and insulation on walking speed in people with hereditary and spontaneous spastic paraparesis: a randomised crossover study. *Ann Phys Rehabil Med.* (2018) 61:72–7. doi: 10.1016/j.rehab.2017.12.001

67. Antczak J, Pera J, Dabroś M, Kozmiński W, Czyzycki M, Wezyk K, et al. The effect of repetitive transcranial magnetic stimulation on motor symptoms in hereditary spastic paraplegia. *Neural Plast.* (2019) 2019:7638675. doi: 10.1155/2019/7638675

68. Ardolino G, Bocci T, Nigro M, Vergari M, Di Fonzo A, Bonato S, et al. Spinal direct current stimulation (tsDCS) in hereditary spastic paraplegias (HSP): a sham-controlled crossover study. *J Spinal Cord Med.* (2021) 44:46–53. doi: 10.1080/10790268.2018.1543926

69. Diniz De Lima F, Faber I, Servelhere KR. Randomized trial of botulinum toxin type A in hereditary spastic paraplegia - the SPASTOX trial. *Mov Disor.* (2021) 36:1654–63. doi: 10.1002/mds.28523

70. van Vugt Y, Stinear J, Claire Davies T, Zhang Y. Postural stability during gait for adults with hereditary spastic paraparesis. *J Biomech.* (2019) 88:12–7. doi: 10.1016/j.jbiomech.2019.03.001

71. Marsden J, Stevenson V, McFadden C, Swain I, Taylor P. The effects of functional electrical stimulation on walking in hereditary and spontaneous spastic paraparesis. *Neuromodulation.* (2013) 16:256–60. doi: 10.1111/j.1525-1403.2012.00494.x

72. Ian Davidson VFH. Comparison of four methods of allocation for clinical trials with small sample sizes. *Physiotherapy.* (2002) 14:722–9. doi: 10.1016/S0031-9406(05)60715-8

73. Rodda JM, Graham HK, Carson L, Galea MP, Wolfe R. Sagittal gait patterns in spastic diplegia. *J Bone Joint Surg Br.* (2004) 86:251–8. doi: 10.1302/0301-620X.86B2.13878

74. Sutherland DH, Davids JR. Common gait abnormalities of the knee in cerebral palsy. *Clin Orthop Relat Res.* (1993) (288):139–47. doi: 10.1097/00003086-199303000-00018

75. Baker R, McGinley JL, Schwartz MH, et al. The gait profile score and movement analysis profile. *Gait Posture.* (2009) 30:265–9. doi: 10.1016/j.gaitpost.2009.05.020

76. Samuel AJ, Aranha VP, Kamath T, Pokhrel M. Physical therapy interventions for the patients with hereditary spastic paraparesis: an exploratory case reports. *Int J Physioth Res.* (2013) 5:110–3.

77. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE. Exercise interventions for cerebral palsy. *Cochrane Database Syst Rev.* (2017) 6:CD011660. doi: 10.1002/14651858.CD011660.pub2

78. Picelli A, Melotti C, Origano F, Waldner A, Fiaschi A, Santilli V, et al. Robot-assisted gait training in patients with Parkinson disease: a randomized controlled trial. *Neurorehabil Neural Repair.* (2012) 26:353–61. doi: 10.1177/1545968311424417

79. Gracies JM. Physical modalities other than stretch in spastic hypertonia. *Phys Med Rehabil Clin N Am.* (2001) 12:769–92. doi: 10.1016/S1047-9651(18)30032-9

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Computer-assisted cognitive rehabilitation in neurological patients: state-of-art and future perspectives

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Background and aim: Advances in computing technology enabled researchers and clinicians to exploit technological devices for cognitive training and rehabilitation interventions. This expert review aims to describe the available software and device used for cognitive training or rehabilitation interventions of patients with neurological disorders.

Methods: A scoping review was carried out to analyze commercial devices/software for computerized cognitive training (CCT) in terms of feasibility and efficacy in both clinical and home settings. Several cognitive domains responding to the different patients' needs are covered.

Results: This review showed that cognitive training for patients with neurological diseases is largely covered by several devices that are widely used and validated in the hospital setting but with few translations to remote/home applications. It has been demonstrated that technology and software-based devices are potential and valuable tools to administer remotely cognitive rehabilitation with accessible costs.

Conclusion: According to our results, CCT entails the possibility to continue cognitive training also in different settings, such as home, which is a significant breakthrough for the improvement of community care. Other possible areas of use should be the increase in the amount of cognitive therapy in the free time during the hospital stay.

KEYWORDS

rehabilitation software, telerehabilitation, cognitive rehabilitation, computer-based, rehabilitation, executive functions, memory, attention

Highlights

- Devices and software for cognitive rehabilitation are a feasible solution with increasing attention also thanks to the distancing of the COVID-19 pandemic.
- With these devices, different cognitive domains can be trained in the hospital or at home.
- These devices and software can guarantee continuity of care between hospital and home even though the same user interfaces.
- It is necessary to overcome problems of various kinds that limit the spread of these devices: geographical and socio-economic barriers.

1. Introduction

In recent years, the aging of population in the industrialized countries increased the demand for care services, including neurorehabilitation (1, 2). Then, the overload of healthcare systems and the difficulties in organizing services have required the implementation of new methodologies for rehabilitation (2). COVID-19 has affected rehabilitation processes, especially in neurological patients, harming the quality of life of both patients and their families. To face this unexpected pandemic, new innovative models of rehabilitation service have emerged. At the same time, it led to the increase of non-hospital services to guarantee the continuity of care, thanks to technological innovations (3). Moreover, rapid advances in computing technology have enabled researchers to carry out cognitive training and rehabilitation interventions with the assistance of technology (4).

Cognitive rehabilitation (CR) aims to improve residual neuropsychological capacities through specific strategies based on cognitive models. In particular, the innovative techniques mediated by personal computers (PC) use multimedia and computer resources, through hardware and software systems, to implement cognitive functioning, including attention, memory, problem-solving, language, and executive functions (5–8). Computerized methods are based on repeated training of specific cognitive domains, through the execution of tasks involving specific skills. Most of the tools use audio-video feedback as a motivational stimulus. Furthermore, these tools allow modifying the type, duration, and difficulty of the tasks to adapt the intervention to the individual abilities. The exercises are grouped according to the cognitive domain stimulated and adapt to the patient's abilities to avoid frustration due to too complex or too simple tasks (5). These devices could offer some therapeutic possibilities for the CR of various neurological diseases (4–8). It has been shown that innovative tools, such as PC-based treatments, could facilitate patient management in the rehabilitation process, allowing continuity of care at home through the telerehabilitation mode (9–13). The tools could support restorative training on cognitive functions thanks to the simulation of different cognitive domains, with positive repercussions on the patient's motivation (4–8). Various authors have also shown that telerehabilitation can improve various cognitive domains, with results comparable to those of conventional face-to-face rehabilitation (3, 10). Despite the many advantages of PC-based approaches, these devices have also some limitations such as: (a) visual interface limiting their use; (b) access prerequisites (i.e., computer skills); (c) lack of acceptability due to photosensitivity problems; (d) acceptability of devices; (e) reliability (some systems have been validated for the clinic but not remotely, or not validated on some types of the population); (f) availability (some systems are too expensive for a patient to maintain or purchase). However, there are neither clear indications nor warnings for the use of these tools, as rigorous comparisons of technical devices in different neurological populations have never been performed.

In this review, we sought to provide an overall picture of the devices on the market that can be used for CR. Furthermore, a secondary aim is to report on the strengths and weaknesses of the devices employed in inpatient or remote/home settings for continuing the rehabilitation process.

2. Search strategy

This scoping review was conducted by searching peer-reviewed articles published between 01 June 2010 and 31 December 2022 using the following databases: PubMed, Embase, Cochrane Database, and Web of Science. The aim of the search strategy was twofold: (1) to track progress in the use of software and device-based technology in terms of technological content, human-machine interaction, and cognitive domain training, and (2) to check neurological populations in which the devices and software for cognitive neurorehabilitation are used. To this end, a comprehensive search was carried out using the search terms: ("Cognitive Rehabilitation" OR "Computer-based" OR "Telerehabilitation") AND ("Stroke" OR "Traumatic Brain Injury" OR "Dementia" OR Multiple Sclerosis" OR "Parkinson" OR "Rehabilitation"). After the removal of the duplicates, all articles were evaluated based on the titles and abstracts. The inclusion criteria were: (i) patients with neurological disease; (ii) a computerized approach applied to cognitive rehabilitation; (iii) English language; and (v) published in a peer-reviewed journal. We excluded articles that described theoretical models, methodological approaches, algorithms, basic technical descriptions, and validation of experimental devices providing no clear translation to clinical practice. Furthermore, we excluded: (i) animal studies; (ii) conference proceedings, or reviews; (iii) studies focusing only on other innovative approaches (such as virtual reality, exergaming, or serious games), (iv) cognitive remediation relating to physiological condition (i.e., the developmental stage or the elderly), (v) study concerning the mobile-app device, which is too far from the traditional CR program.

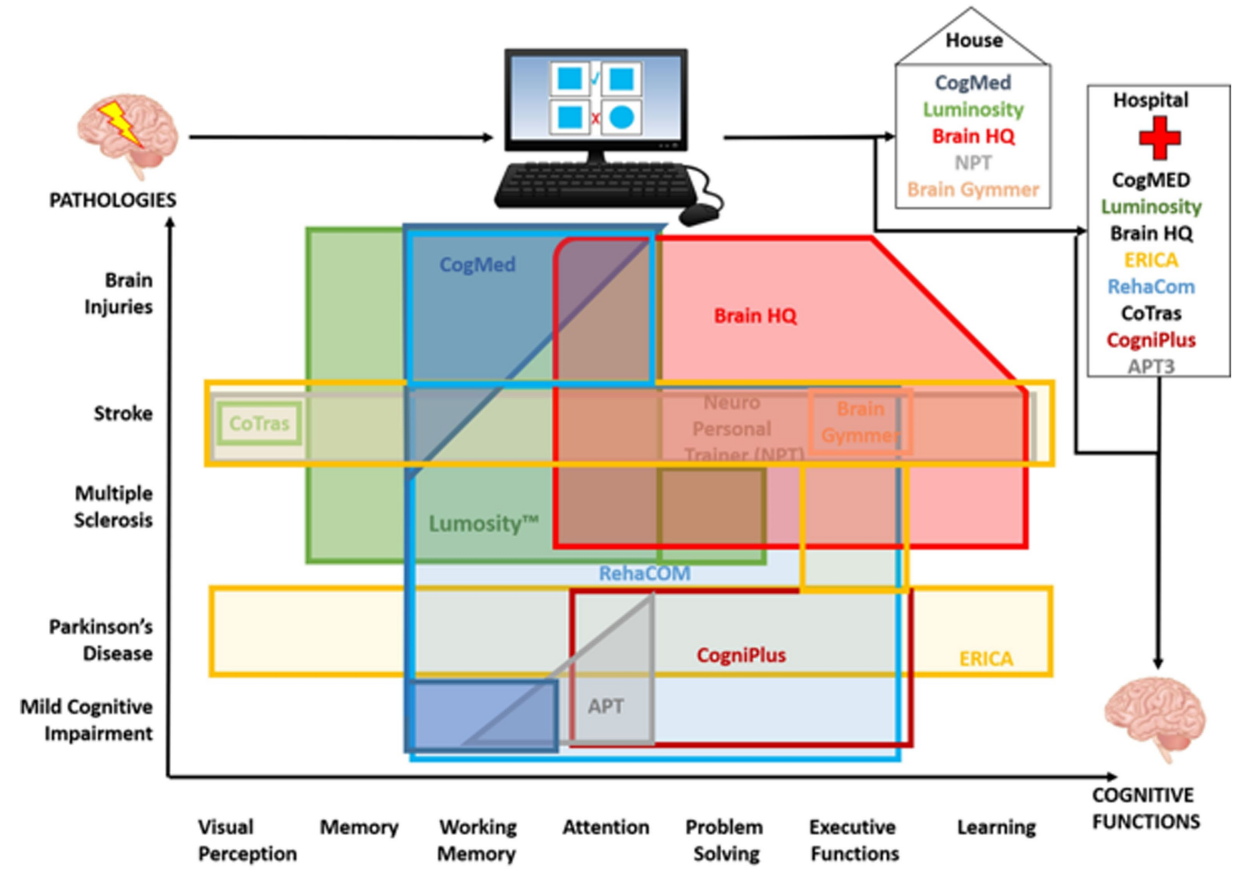

FIGURE 1
Schematic representation of the clinical use of the different cognitive devices and software. The figure illustrates the different devices and cognitive functions trained in the different pathologies and in which setting they were used (home or in hospital). The figure reflects the fields of application as evident from the literature selected in this review.

The list of articles was then refined based on relevance and summarized according to the inclusion/exclusion criteria. Furthermore, to ensure a greater homogeneity in the results, after the removal of duplicates, the articles were evaluated on the basis of the titles and abstracts by two independent researchers (DDB and MGM). These researchers read the full text of articles suitable for the study and performed the data collection to reduce the risk of bias (i.e., language bias; publication bias; time-lag bias). In case of disagreement on the inclusion and exclusion criteria, the final decision was made by two senior investigators (RSC and GM).

Data extraction was performed on 190 articles. Data were considered for the following information: year and type of publication (e.g., clinical studies, pilot study), characteristics of the participants involved in the study, and purpose of the study (Figure 1). After a thorough review of the complete manuscripts, 34 studies articles met the exclusion/exclusion criteria (Table 1). We reported as a primary outcome the one identified by the researchers, for each study, as between-group (in RCT design) or within-subjects difference (for studies with only one group) on the first-level test, and secondary outcome as differences within groups (for RCT) or on second-level tests (for single-group studies). For every study, we selected only significant results adjusted for multiple comparisons.

3. Results

Although our research in PubMed, Embase, Cochrane Database, and Web of Science has found many technological devices used in CR, only the 10 most cited devices were selected. The information obtained from the selection of studies was organized in two tables. Table 1 reports the list of devices and their main characteristics, as well as the studies and clinical populations on which they were tested. Table 2, indeed, shows what type of study was carried out, how the device was used, and what the results are in terms of treatment efficacy. Most of the selected devices (6 out 11) are supplied in software mode. Then, they can be used by purchasing a stand-alone license, which has a limited duration to the subscription chosen on the manufacturer's website. Of these, only CogMED (14–19) provides a special license for its usage and a specific training for the online tutor. Three devices (Lumosity, Brain HQ, Brain Gymmer) are either available as PC software or can be installed as an app on tablet/phone devices. Finally, only one represents a telerehabilitation platform (NeuroPersonalTrainer) that allows patients to carry out Hospital and home rehabilitation. In most studies included in Table 2, these devices were tested to evaluate their effectiveness compared to conventional rehabilitation. This review reveals that cognitive training for patients with

TABLE 1 List of devices and their main characteristics, main studies, and clinical populations on which they have been tested.

Device	Device description	License	Type of feedback	Adaptive training approach	Studies	Neurologic population	Cognitive domains
CogMED QM training, Pearson Company, Stockholm, Sweden, 2011 (www.cogmed.com) Type: Software	The CogMed is a computer-based solutions software for cognitive training of attention problems caused by poor working memory (WM). Use of Cogmed requiringes a computer and/or tablet with speakers, stable broadband internet connection of 0.5 Mbit/s or higher, Adobe Flash plugin version 10.0 or later, and minimal hard drive space to store results. It is programmed for Mac, PC, and Android devices, but. It is most commonly run online through the Cogmed website where users are provided a unique ID and password.	Professionals use only. Available on subscription	Coach online	Available	Akerlund et al. (2013) (14)	ABI	Working Memory
					Johansson & Tornmalm (2012) (15)	ABI	Working Memory, Activity of Daily Living (ADL)
					Lundqvist et al. (2010) (16)	ABI	Spatial and Verbal Working Memory
					Svaerke et al. (2022) (17)	ABI	Working Memory
					Blair et al. (2021) (18)	MS	Spatial and Verbal Working Memory
					Nyberg et al. (2018) (19)	Stroke	Working Memory
Lumosity™ Brain Games Lumos Labs. Lumosity: Reclaim Your Brain™. San Francisco, CA: Dakim, Inc.; 2010 (www.lumosity.com) Type: Web platform/software app	LumosityTM is a commercially available CCT software providing brain games designed to improve cognitive processing speed, flexibility, attention, memory, and problem-solving skills. Game complexity increases and decreases systematically based on an individual's performance data. Multiple forms of each game level are available to prevent task learning with continued practice.	Full version available on payment. Free- version mode (with a smaller number of exercises chosen randomly)	Real-time feedback on errors; Lumosity performance index at the end of each exercises	Available	Withiel et al. (2019) (20)	Stroke	Everyday Memory
					Wentink et al. (2016) (21)	Stroke	Working Memory, Attention, Fluency, Quality of Life
					Stuifbergen et al. (2018) (22)	MS	Memory, Attention, Problem Solving Skills
					Zickefoose et al. (2013) (23)	TBI	Attention
BrainHQ program, Posit Science Corporation, San Francisco CA, 2015 (www.brainhq.com) Type: Web platform/software app	BrainHQ is a software designed for brain stimulation of: Attention, Brain Speed, Memory, People Skills, Intelligence, and Navigation. It is an adaptive software, easy to use, and can be implemented on home computers, tablets, and laptops. Based on scientific research results, it allows choosing different levels/types of training based on individual needs.	Full version available on payment. Free- version mode (with a smaller number of exercises chosen randomly)	Graphic and numeric feedback regarding patients' performance within and across sessions per game and category of cognitive function, adjusted to matched demographics	Available	Yeh et al. (2019) (24)	Stroke	Attention, Executive Functions
					Charvet et al. (2017) (25)	MS	Attention, Information processing, Learning
					O'Neil-Pirozzi & Henry Hsu (2016) (26)	TBI	Attention, Memory, Executive Functions

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TABLE 1 (Continued)

Device	Device description	License	Type of feedback	Adaptive training approach	Studies	Neurologic population	Cognitive domains
NeuroPersonalTrainer™®, GNPT®. Guttmann Institute, Badalona, Spain, 2011. Type: Tele-rehabilitation platform	GNPT® allows the provision of individualized and personalized treatments, improving the traditional on-site rehabilitation processes. It is based on a testing and training approach, so after a first baseline the software select specific training and store patients' scores by organizing them in a therapeutic index on which next exercises will be adjusted.	Professionals use only. No free trial available	The program will then calculate a cognitive profile using these results, taking into account the patient's age and educational level.	Available	Gil-Pages et al. (2018) (27)	Stroke	Multiple domains.
ERICA, Giunti Psycometrics, Italy, 2013 (www.giuntipsy.it) Type: Software	Erica is software for customized cognitive rehabilitation involving 5 specific cognitive domains: attention process, memory abilities, spatial cognition, verbal and nonverbal executive functions. The training is characterized by modularity, flexibility, and uniformity of the administered program.	Professionals use only. Three years license based on subscription.		Not available automatically, therapist may adjust the preferred exercises based on patients' performance	De Luca et al. (2019) (28)	Parkinson's Disease (PD)	Multiple domains
					De Luca et al. (2017) (29)	Stroke	Multiple domains
					Barbarulo et al. (2018) (30)	MS	Executive Functions.
CogniPlus, Schuhfried GmbH, Vienna, Austria, 2008 (www.schuhfried.com) Type: Software	CogniPlus software has various modules for the training of specific cognitive abilities. The content of CogniPlus is closely linked to the Vienna Test System. This software combines treatment and evaluation exploiting the role of the therapeutic assessment CogniPlus is an intelligent interactive system that adapts to patients' abilities by offering exercises based on performance.	Professionals use only. No free trial available.	Feedback is provided by testing patient's ability. This software combines a testing and training approach	Available	Hagovská et al. (2017) (31)	older adults with MCI	Multiple domains
					Zimmermann et al. (2014) (32)	Parkinson's Disease (PD)	Executive Functions, Focused Attention.
Attention Process Training (APT), Lash & Associates Publishing/ Training Inc., Youngsville, North Carolina, 2010 (https://lapublishing.com). Type: Software	APT is software for cognitive rehabilitation of attention abilities, based on structured exercises for training specific cognitive domains of attention. A graphical interface allows the clinician to select exercises and associated parameters in order to create customized exercise easily modifiable as the patient progresses.	Full version available on payment. The software is licensed for a period of one year.	Feedback is provided as scores on each exercise at the end of session.	Not reported	Pantoni et al. (2017) (33)	MCI	Attention, working memory
					Walton et al. (2018) (34)	Parkinson's Disease (PD)	Attention, ADL

(Continued)

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TABLE 1 (Continued)

Device	Device description	License	Type of feedback	Adaptive training approach	Studies	Neurologic population	Cognitive domains
CoTras, RPIO Co., Ltd., Geumcheon-gu, Seoul, 2010 (www.rpio.co.kr). Type: Software with specific hardware for human-computer interaction	CoTras is a training program involving visual perception, attention, memory, orientation, and others (categorization, sequencing). A joystick and a large button on the CoTras panel make the training easy for patients who are unfamiliar with computer use.	Professionals use only. No free trial available.	Feedback is provided at the end of session with graphs and statistic report about patient's performance.	Available	Park and Park (2015) (35)	Stroke	Visual Perception
BrainGymmer, Dezzel Media, The Netherlands, 2010 (www.braingymmer.com) Type: Web platform	BrainGymmer is an online brain training program that offers brain games, brain tests, and brain teasers. It has been developed and clinically tested by clinicians and academics. Individual performance is further compared to people of the same age	Full version available on payment. Free- version mode (with a smaller number of exercises chosen randomly).	Feedback is provided at the end of session based on the Brain Fitness Index (accuracy and reaction speed of the performance)	Not reported	Van de Ven et al. (2017) (36)	Stroke	Executive Functions
RehaCom®, HASOMED GmbH, Magdeburg, Germany, 1997. www.rehacom.com Type: Software with specific tool for human-computer interaction.	RehaCom is a cognitive rehabilitation program consists of 20 modules with several subsections that are selected and used by the therapist according to the needs of the participant. The RehaCom hardware has a special keyboard with large buttons, which limits the interference of motor and coordination impairment and expertise in computer use. Online monitoring is also available for the therapist to assess the function of the participant.	Professionals use only. No free trial available.	Progress can be saved, but no direct feedback is provided at the end of exercises.	Available	Nousia et al. (2022) (37)	MCI	Multiple Domains
					Naeeni Davarani et al. (2022) (38)	Multiple Sclerosis (MS)	Attention, executive functions, working memory
					Amiri et al. (2021) (39)	Stroke	Working Memory, Processing Speed
					Messinis et al. (2020) (40)	MS	Multiple Domains
					Messinis et al. (2017) (41)	MS	Multiple Domains
					Campbell et al. (2016) (42)	MS	Attention, Processing Speed
					Bonavita et al. (2015) (43)	MS	Attention
					Darestani et al. (2020) (44)	MS	Verbal performance
					Veisi-Pirkoohi et al. (2020) (45)	Stroke	ADL, attention
					Fernandez et al. (2017) (46)	ABI	Attention, memory
					Cerasa et al. (2014) (47)	PD	Attention, Information Processing

(Continued)

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TABLE 1 (Continued)

Device	Device description	License	Type of feedback	Adaptive training approach	Studies	Neurologic population	Cognitive domains
GRADIOR (INTRAS Foundation, Spain) Type: Software	GRADIOR is multimedia software for cognitive stimulation, neuropsychological assessment, and rehabilitation. It consists of personalized exercises that train various cognitive domains, such as attention, memory, orientation, calculation, perception, reasoning, and language.	Professionals use only.	The evaluation profile generated by the program offers a description of cognitive performance	Not Reported	Diaz Baquero et al. (2022) (8)	MCI and mild Dementia	Executive functioning, attention, phonological verbal fluency, cognitive flexibility
					Diaz Baquero et al. (2022) (48)	MCI and mild Dementia	Executive functioning, attention, phonological verbal fluency, cognitive flexibility
					Góngora Alonso et al. (2020) (49)	Severe and prolonged mental illness	Psychosocial skills
					Vanova et al. (2018) (50)	MCI dementia	Cognition, mood, quality of life, activities of daily living, quality of patient-carer relationship

ABI, Acquired Brain Injury; EG, Experimental group; CG, Control group; MCI, Mild Cognitive Impairments; MS, Multiple Sclerosis; PD, Parkinson's Disease; TBI, Traumatic Brain Injury.

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neurological diseases is covered by several efficient devices that are widely used and validated in the hospital setting, but with few translations in remote applications.

3.1. CogMED

CogMed (*QM Training, Pearson Company, Stockholm, Sweden, 2011*) is a computer-based software system for training of attention and working memory (WM). CogMed can be accessed via computer and tablet with speakers, and it is mainly used online through the Cogmed website. It has been shown that this device could have positive effects on the rehabilitation of WM. Akerlund et al. carried out a randomized study of 47 patients with acquired brain injury (ABI) in the subacute phase. The authors demonstrated that the device not only improved WM but also cognition and psychological health (14), as well as activity of daily living, as reported also by Johansson & Tornmalm (15). According to these results, Lundqvist et al. (16) performed a cross-over design controlled experimental study using CogMed software on 21 subjects with ABI. They observed significant improvement in WM tasks, occupational performance, performance satisfaction, and overall health rating (16). Svaerke et al. found similar results in a randomized study of 72 patients (17). Moreover, these findings could be generalized to the life context, as suggested by Johansson et al. (15). Improvements have been observed also in other neurological populations, including multiple sclerosis (MS) (18). A study on older adults with Mild Cognitive Impairment (MCI) showed an improvement in cognitive skills, especially in information processing speed and WM, after specific home interventions (51).

On the other hand, Nyberg et al. (19) conducted a study in 26 stroke patients trained with CogMed for 6 weeks. The authors found changes in performance related to the trained computerized task, but no microstructural changes in white matter between rest and training condition ($p = 0.99$).

3.2. Lumosity™

Lumosity™ (*Brain Games Lumos Labs. Lumosity: Recover Your Brain™. San Francisco, Calif.: Dakim, Inc.; 2010*) is a CR software that provides access to games to improve cognitive processing speed, flexibility, attention, memory, and problem-solving skills. However, the results of its effectiveness are conflicting.

Withiel et al. found a good usability of the device, especially for its playful aspects, but without improvements in daily memory, in 20 stroke survivors (20). These results were confirmed by Wentink et al. that carried out an experimental study on chronic stroke patients. The authors showed no effect of training on cognitive functioning, QoL, or self-efficacy regarding the control condition, except for minimal effects on WM and speed (21).

Conversely, Stuifbergen et al. performed a study on 183 MS patients, noting that the device is feasible with promising effects in improving cognitive functioning (22). Furthermore, Zickefoose et al. evaluated whether the treatment of severe traumatic brain injury (TBI) survivors could be generalized to comparable, untrained tasks. They found that participants made significant improvements but with limited generalization (23). Finally, evidence is inconsistent regarding the effectiveness of this device on subjective or objective memory or other cognitive components.

3.3. BrainHQ

BrainHQ (*Posit Science Corporation, San Francisco CA, 2015*) is an online cognitive training system for cognitive exercises. Each user can be monitored throughout the entire training, which is automatically modified according to the skill level reached. BrainHQ has multiple exercises for training different cognitive skills, including attention, speed, memory, sociability, orientation, and intelligence. The program appears to have good feasibility and effective results in CR.

Yeh et al. performed a randomized controlled trial to evaluate the efficacy of a combination of aerobic exercise and cognitive training using BrainHQ on stroke survivors. The authors noticed that, compared to the control group, the experimental group significantly improved global cognitive functioning and memory scores after training (24). These results were confirmed by Charvet et al. (25) in patients with MS, demonstrating how home computer-based cognitive training can improve cognitive functioning. Furthermore, they observed that this telerehabilitation approach enabled good patient compliance and rapid recruitment (25). Finally, an interesting pilot study by O'Neil-Pirozzi et al. explored the feasibility and effects of participating in a computerized cognitive fitness exercise program on ABI adults with positive results (26).

3.4. Neuro PersonalTrainer®

Neuro PersonalTrainer®-MH (*GNPT®, Guttmann Institute, Badalona, Spain, 2011*) is a module for neurocognitive rehabilitation provided by a computerized tele-rehabilitation platform. It allows one to carry out cognitive training in an intensive and personalized mode (27). Gil-Pages et al. in their cross-over, randomized, controlled, double-blind clinical study observed that chronic stroke patients with cognitive impairment may benefit from cognitive training using this innovative tool (27). On the contrary, Aparicio-López et al., in a randomized clinical trial of 28 stroke patients, found no statistically significant differences when comparing patients using the Neuropersonal-Trainer to those receiving traditional pc-based rehabilitation (52).

3.5. ERICA

ERICA (*Giunti Psychometrics, Italy, 2013*) is a tool composed of a series of computerized exercises for cognitive rehabilitation. These exercises are dedicated to the rehabilitation of specific skills, such as attention, spatial cognition, memory, verbal executive functions, and non-verbal executive functions, and can be used in patients with neuropsychological deficits resulting from brain injury, developmental disorders, degenerative pathologies, and psychiatric pathologies. The studies using this device mainly involve subjects suffering from Parkinson's disease (PD), and multiple sclerosis (MS). DeLuca et al. (28) performed a randomized clinical study on 70 PD patients, noting significant improvement after CR in both

groups. However, the group receiving the Erica training achieved greater outcomes, especially in attention, orientation, and visuospatial domains (28). The same research group observed similar significant improvements in people with MS (29). The positive effects of Erica on the emotional, motor, and cognitive aspects in MS patients were also highlighted by Barburulo et al. in a study of 63 MS patients (30).

3.6. CogniPlus

CogniPlus (*Schuhfried GmbH, Vienna, Austria, 2008*) is a tool related to the Vienna Test System, which integrates the diagnosis, treatment, and assessment of various cognitive functions, such as attention, executive functions, memory, spatial processing, and visuomotor abilities. Cogniplus has been shown to be effective in CR. Hagovská et al. (31) performed a study to compare the effectiveness of two types of cognitive training in 60 older adults with MCI. The results showed that although both traditional and experimental groups had an improvement, the Cogniplus group reported better scores in quality of life and better attention (31).

Cogniplus is also effective in combination treatments. Westerhof-Evers et al. (53) conducted a study to evaluate the effects of treatment using Cogniplus combined with T-scEmo (a tool that affects emotions) on social cognition and emotion regulation in 61 TBI patients. The authors noticed that this combined approach may be effective in rehabilitating impairments in social cognition (53). Another study by Hagovská et al. (54) on 80 elderly participants with MCI showed that Cogniplus can improve balance control, cognitive functions, gait speed, and activities of daily living, when combined to motor interventions (54).

In contrast to these studies, Zimmerman et al. (32) performed a study on patients with Parkinson's disease (PD) using cognitive training with Cogniplus and motor training with a movement game in different groups. They found that specific computer training for cognition is not superior to a motion-controlled computer game in improving cognitive performance (32).

3.7. Attention process training

APT (*Lash & Associates Publishing/Training Inc, Youngsville, North Carolina, 2010*) is a clinical program used for attention process training in adolescents, adults, and older adults with ABI. It was developed by Sohlberg & Mateer, and it is based on scientific evidence, as it has demonstrated its effectiveness in the rehabilitation of patients with cognitive disorders (55).

Pantoni et al. (33) carried out a single-blind randomized clinical trial to evaluate the effects of CR in 46 patients with MCI, using the Attention Process Training (APT) program. The authors found that APT potentially enhances focused attention and WM and appears to increase activity in brain circuits involved in cognition (33). APT training also seems to be effective in other patient populations. Walton et al. (34) carried out a randomized study of 65 PD patients to evaluate whether targeted training could improve freezing and executive dysfunction. The results highlighted that APT training can be an effective method to improve processing speed and reduce daytime sleepiness (34).

3.8. CoTras

The CoTras program (*RPIO Co., Ltd., Geumcheon-gu, Seoul, 2010*) is a computer-based cognitive rehabilitation device. It consists of real-life training content which is defined according to the environment in Korea. It has several exercises that adapt to the patient's cognitive abilities, including difficulty, time, and speed of exercise execution. Park and Park (35) carried out a study to investigate the effects of CoTras on cognition in thirty acute stroke patients. The results showed that the tool can stimulate the recovery of global cognitive function, with regard to and visual perception (35).

3.9. BrainGymmer

BrainGymmer (*Dezzel Media, The Netherlands, 2010*) consists of computer-based cognitive training exercises via a website. The training tasks consist of games designed to be challenging and customized to the characteristics of the user.

Van de Ven et al. (36) carried out a double-blind, randomized controlled trial to investigate whether the computer-based training improves executive functioning after stroke. The results showed that patients submitted to Braingymmer training had the same improvement in executive and general cognitive functioning as control groups. This improvement was likely due to non-specific training effects. Therefore, the Braingymmer program does not seem to make significantly different improvements compared to conventional methods. Nevertheless, other studies on larger samples should be implemented to ascertain the effectiveness of this tool.

3.10. RehaCom®

RehaCom (*HASOMED GmbH, Magdeburg, Germany, 1997*) is a software for computer-assisted cognitive rehabilitation useful in the management of different cognitive disorders. The system supports recovery and replacement processes, potentiating cognitive strategies and offering targeted therapeutic solutions for rehabilitation.

Various studies have shown positive results of intervention using Rehacom, even in telerehabilitation modality, to improve or stabilize cognitive decline. Nousia et al. (37) carried out a study on 46 Greek patients with MCI. The authors demonstrated the efficacy of Rehacom on delayed and semantic memory, word recognition, and attentional shifting. The results have been confirmed by other authors. Naeeni Davarani et al. (38) investigated the effect of RehaCom on attention, response control, processing speed, working memory, visuospatial skills, and verbal/nonverbal executive functions in 60 MS patients. They observed that RehaCom treatment improved all cognitive functions, and this effect was maintained over time (i.e., at three-month follow-up) (38). Moreover, Amir et al. (39) carried out a study of 50 stroke survivors. They showed a significant improvement in working memory and processing speed in the experimental group compared to the control group after a 5-week training with the software (39). These results were confirmed by Messinis et al. (40), who carried out a randomized controlled study to examine the efficacy of at-home intervention using RehaCom software in 36 patients with secondary progressive MS. The authors found that the tool can be effective in improving cognitive functioning and mood with

TABLE 2 Performance results reported in the selected studies of this review.

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
CogMED QM training, Pearson Company, Stockholm, 2011 Sweden, (www.cogmed.com).	Akerlund et al. (2013) (14)	38 Acquired Brain Injury (18 CG)	RCT	Both groups underwent integrated rehabilitation. The experimental group also implemented the computerized training program Cogmed	5-week training program (30–45 min, 5 days). In Hospital Supervision of a therapist	BNIS ($p_b = 0.044$), Digit Span ($p_b = 0.045$), Digit Span reverse ($p_b = 0.003$)
	Johansson & Tornmalm (2012) (15)	18 chronic stage patients with ABI: traumatic brain injury (5), brain tumor (6), stroke (7) (severe impairment)	Cross-over study with no CG	Customize training program	7–8 weeks (20–25 sessions) 30–45 min in Hospital Group of 5–6 participants, under supervision of a therapist	QM index ($p_w = 0.000$), Cognitive Failures Questionnaire ($p_w = 0.018$), Canadian Occupational Performance Measure ($p_w = 0.008$)
	Lundqvist et al. (2010) (16)	21 chronic stage patients with ABI: stroke (1), trauma (11), infection (5), tumor (2), subarachnoidal hemorrhage (2) (mild to moderate neurologic disorder).	Cross-over study with no CG	Remember the position of stimuli in a four-by-four grid, reproduce stimuli order, remember sequences of letters and digits forwards and/or backward.	5 weeks (25 sessions) 45–60 min In Hospital Under a coach supervision	PASAT ($p_w < 0.001$), Listening Span ($p_w < 0.001$), Block Span forward ($p_w = 0.002$), backward ($p_w = 0.001$)
	Svaerke et al. (2022) (17)	72 patients with ABI	RCT	Treatment was diversified into four different groups: two groups trained with the "Cogmed" and "Brain + Health" programs, respectively, and one group completed active control training. All three groups received ongoing support from a health professional. The last group trained under the 'Brain+ Health' program but received no support	12-week intervention. In Hospital Supervision of a therapist	Both CBCR programs improved working memory when administered with support from a health professional. The programs have improved several subcomponents of working memory.
	Blair et al. (2021) (18)	22 chronic stage patients with MS (moderate impairment) (CG:11)	Single blind RCT	Remember the position of stimuli in a four-by-four grid, reproduce stimuli order, remember sequences of letters and digits forwards and/or backward. CG patients received a TAU.	5 weeks (25 sessions) 30–45 min At home Coaching online	DKEFS ($p_w = 0.02$) Colour-Word Interference test ($p_w = 0.016$), Digit span ($p_w = 0.01$).
	Nyberg et al. (2018) (19)	22 chronic stage patients with Stroke (mild impairment)	Cross-over study with no CG	"Grid" (visuospatial working memory); "Numbers" (verbal and visuospatial working memory); "Cube" (visuospatial working memory) and "Hidden numbers" (verbal working memory)	5 weeks (25 sessions) 40 min training In Hospital Individual feedback once a week	Performance improvement for WAIS subtest Grid, Numbers, Cube, Hidden numbers ($p < 0.001$), no FA changes.

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TABLE 2 (Continued)

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
Lumosity™ Brain Games Lumos Labs. Lumosity: Reclaim Your Brain™. San Francisco, CA: Dakim, Inc.; 2010. (www.lumosity.com)	Withiel et al. (2019) (20)	65 chronic stage patients with Stroke (mild impairment).	3-group, single-blind RCT	Recall semantic information (names, conversations, birthday dates); prospective memory tasks. (two control groups, MSG group followed a TAU for memory skills (24), the WC group (19) did not any add-on rehab activity)	6 weeks (30 sessions) 120 min training At Home Weekly update with a therapist	Goal Attainment Scores ($p_b = 0.00$), Verbal WM ($p_b < 0.05$) and Prospective memory ($p_b < 0.01$) for MSG group
	Wentink et al. (2016) (21)	107 stroke patients (GC 57)	RCT	The intervention consisted of a brain training program (Lumosity Inc.®). The control group received general information about the brain week	8-week (24 sessions) At home Not specified	TMT-B, Time B, ($p_b = 0.04$) and flexibility (TMT-A/TMT-B), Difference time A and time B, ($p_b < 0$ 0.01)
	Stuifbergen et al. (2018) (22)	183 chronic stage patients with MS (mild-to-moderate impairment). (CG 90)	RCT	CCT followed the MAPSS-MS approach (Memory, Attention, Problem-Solving Skills in MS). CG patients, performed a generic computerized training	8 weeks (24 sessions) 45 min training At Home Not specified	CVLT delayed ($p_b = 0.012$), PASAT 3″ ($p_b = 0.006$), CESD ($p_b = 0.006$).
	Zickefoose et al. (2013) (23)	4 chronic stage patients with TBI (severe impairment)	Repeated treatment design (A-B-A-C-A).	Five attention-oriented Lumosity games: Birdwatching, Monster Garden, Playing Koi, Rotation Matrix, and Top Chimp.	4 weeks (16 sessions) 30 min training In Hospital with the therapist.	Pre-post analysis of performance level measured in Lumosity ($p_w < 0.001$).
BrainHQ program, Posit Science Corporation, San Francisco CA, 2015. (www.brainhq.com)	Yeh et al. (2019) (24)	30 subacute stage patients with Stroke (mild impairment) (GC 15)	Single-blind, multisite RCT	Sequential training (motor aerobic exercises followed by CCT). Computerized cognitive exercises consisted of tasks involving color and shape identification, calculation, visuospatial object recognition. CG received a modified program of aerobic motor activity	12–18 weeks (36 sessions) 30 min training In Hospital Under the supervision of a therapist.	MoCA ($p_b = 0.030$), Spatial Span ($p_b = 0.012$), 6MWT ($p_b = 0.025$).
	Charvet et al. (2017) (25)	135 chronic stage patients with MS (mild impairment) (CG: 61)	Double-blind, with active-placebo RCT	Speed, Attention, Working Memory, and Executive Functions (visual and auditory domains). CG patients followed a nonspecific training with Hoyle Puzzle and Board Games	12 weeks (60 sessions). 60 min training At Home Remote control of compliance and online supervision through WorkTime Software.	Compliance rates ($p_b = 0.0056$), PASAT 2″ ($p_b < 0.05$), DKEFS ($p_b < 0.05$).
	O'Neil-Pirozzi & Henry Hsu (2016) (26)	14 chronic stage patients with TBI (moderate-to-severe impairment) (CG: 7)	Mixed methods design pilot study	Customize exercises program. CG patients received a general computerized training TAU	20 weeks (98 sessions) 60 min training In Hospital Under the supervision of a therapist (with active feedback).	Hopkins Verbal Learning Test-Revised ($p_b = 0.0068$), TMT A-B ($p_b = 0.0761$)
NeuroPersonalTrainer"®, GNPT®, Guttmann Institute, Badalona, Spain, 2011.	Gil-Pages et al. (2018) (27)	40 chronic stage patients with Stroke (mild impairment)	Double-blind, crossover RCT with two arms.	Customize exercises program adjusted on NPE.	6 weeks (30 sessions) 60 min training At Home Under remote control of a therapist, (ongoing study)	Study protocol.

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TABLE 2 (Continued)

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
ERICA Giunti Psychometrics, Italy, 2013. (www.giuntipsy.it)	De Luca et al. (2019) (28)	60 chronic stage patients with PD (mild-to-moderate) (CG:30)	RCT	Customize exercises program. CG patients received a TAU	8 weeks (24 sessions) 60 min training In Hospital. Under the supervision of a therapist.	ACE-R ($p_b = 0.026$§), WEIGL Test ($p_b = 0.026$§), Hamilton Rating Scale ($p_b = 0.031$§).
	De Luca et al. (2017) (29)	35 subacute stage patients with Stroke (moderate impairment) (CG:15)	RCT	Customize exercises program. CG patients received a general computerized training TAU	8 weeks (24 sessions) 45 min training In Hospital Under the supervision of a therapist.	MMSE ($p_w < 0.01$), Attentive Matrices ($p_w < 0.021$), Letter Verbal Fluency ($p_w < 0.06$), Categorial Verbal Fluency ($p_w < 0.03$).
	Barbarulo et al. (2018) (30)	63 chronic stage patients with MS (mild-to-moderate impairment). (CG:32)	RCT	Dual-task exercises, plus additional exercises tailored to the single patient's neuropsychological impairments. CG patients received only motor TAU	24 weeks (48 sessions) 60 min training In Hospital Not specified	Spatial Span ($p_w < 0.003$), Forward/ Backward verbal span ($p_w < 0.032$, $p_w < 0.027$), Phonological Fluency ($p_w < 0.001$), SRT-D ($p_w < 0.001$§), WLG ($p_w = 0.002$§), Tinetti scale ($p_w < 0.001$)
CogniPlus, Schuhfried GmbH, Vienna, Austria, 2008. (www.schuhfried.com)	Hagovská et al. (2017) (31)	60 MCI patients: (CG 30)	RCT	Group A ($n = 30$) underwent CogniPlus, a computer-based, cognitive training. Group B ($n = 30$) underwent classical group-based cognitive training	8 weeks (24 sessions) Not specified	QOL ($p_w < 0.001$), attention (increased load score), ($p_w < 0.05$), errors ($p_w < 0.001$). No group difference.
	Zimmermann et al. (2014) (32)	39 chronic stage patients with PD (moderate impairment) (CG:20)	RCT	Tasks involved four modules: FOCUS, for focused attention; NBACK, for working memory; PLAND, for planning and action skills and HIBIT, for response inhibition. CG patients underwent a cognitive stimulation with Nintendo Wii	4 weeks (12 sessions) In Hospital Under the supervision of a therapist	Attentional Performance Test ($p_w = 0.024$§), TMT B/A ($p_w = 0.431$§), Executive function ($p_w = 0.462$§), WAIS Block Design Test ($p_w = 0.055$§), e California Verbal Learning Test ($p_w = 0.093$§).
Attention Process Training (APT), Lash & Associates Publishing/Training Inc., Youngsville, North Carolina, 2010. (https://lapublishing.com).	Pantoni et al. (2017) (33)	43 MCI patients (CG 22)	RCT	CG received the standard care and EG performed the attention training	40h (2-h weekly sessions for 20 weeks) Not specified	Rey Auditory-Verbal Learning Test immediate recall (change score 6 versus 12 months: 1.8 ± 4.9 and -1.4 ± 3.8, $p = 0.021$; baseline versus 12 months: 3.8 ± 6.1 and 0.2 ± 4.4, $p = 0.032$)
	Walton et al. (2018) (34)	38 chronic stage patients with PD (mild-to-moderate impairment) (CG:18)	Double-blind active RCT	Customize exercises program based on NPE. CG patients received an aspecific cognitive training	7 weeks (14 sessions) In Hospital Group of ten participants, under supervision of a therapist.	Baseline and Follow-Up Geometric Means for the FoG in on-phase ($p_b = 0.002$).
CoTras, RPIO Co., Ltd., Geumcheon-gu, Seoul, 2010. (www.rpio.co.kr).	Park and Park (2015) (35)	30 subacute stage patients with Stroke (moderate impairment) (CG:15)	RCT	Tasks involving object recognition, object constancy, figure-ground organization, visual discrimination, and visual organization. CG patients received a paper and pencil training for perception rehabilitation	4 weeks (20 sessions) 30 min training In Hospital Under the supervision of a therapist.	Lowenstein Occupational Therapy Cognitive Assessment ($p_b < 0.05$§), Motor-free Visual Perception Test-3 ($p_b < 0.05$§)

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TABLE 2 (Continued)

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
BrainGymmer, Dezzel Media, The Netherlands, 2010. (www.braingymmer.com)	Van de Ven et al. (2017) (36)	97 subacute-to-chronic stage patients with Stroke (moderate impairment) (CG 59)	Double-blind RCT	Cognitive flexibility tasks (updating, set-shifting, inhibition). CG groups: AC 35 patients followed a mock training, WLC 24 patients received TAU	12 weeks (58 sessions) At Home Under the supervision of a therapist.	TMT-B ($p_w < 0.001$§), LNS ($p_w < 0.01$§), ToL ($p_w < 0.01$§).
RehaCom®, HASOMED GmbH, Magdeburg, Germany, 1997. (www.rehacom.com) Type: Software with specific tool for human-computer interaction.	Nousia et al. (2021) (37)	46 MCI patients (GC 21)	RCT	Multidomain cognitive training intervention program. CG received TAU	30 60-min individual sessions over a period of 15 weeks (i.e., two sessions per week) At home Not specified	Delay memory, Semantic Fluency, TMT-A ($p_b < 0.001$), Boston Naming Test ($p_b = 0.030$), Clock Drawing Test ($p_b = 0.017$), Digit Span Backward ($p_b = 0.045$) TMT-B ($p_b = 0.010$)
	Naeeni Davarani et al. (2022) (38)	60 MS patients (CG 30)	RCT	The cognitive trained was focused on: attention, response control, processing speed, working memory, visuospatial skills, and executive functions; CG group received no any intervention,	5 weeks (two 60-min sessions per week)	Visuospatial and motor skills ($p_b < 0.01$); Verbal executive functions ($p_b < 0.01$); Non-verbal executive functions ($p_b < 0.01$); Processing speed (SDMT) ($p_b < 0.001$); Working memory ($p_b < 0.001$)
	Amiri et al. (2021) (39)	50 chronic stage patients with Stroke (mild-to-moderate impairment) (CG: 25)	RCT	Customize exercises program. CG patients engaged in routine physiotherapy rehabilitation sessions without any extra cognitive stimulation	5 weeks (10 sessions) 30 min training In Hospital Group of 10 participants, under supervision of a therapist.	N-back ($p_b < 0.05$), PASAT ($p_b < 0.001$), SDMT ($p_b < 0.001$).
	Messinis et al. (2020) (40)	36 MS (CG 17)	Randomized, multi-site, sham controlled trial	Treatment with the RehaCom modules consisted of 24 domain and task specific. The CG completed nonspecific computer based activities	45 min per (3 sessions per week) for 8-week At home Not specified	Verbal learning ($p_b < 0.0005$), visuospatial memory ($p_b < 0.0005$) and information processing speed ($p_b < 0.0005$)
	Messinis et al. (2017) (41)	58 MS patients (CG 26)	RCT	Multidomain computerized treatment, CG received TAU.	10 week (2 days a week for approximately 60 min) At home Not specified	RTLTS ($p_w = 0.000$), SRTDR ($p_w = 0.001$), BVMT-R ($p_w = 0.001$), TMT-A ($p_w = 0.000$), TMT-B ($p_w = 0.000$), SNST ($p_w = 0.000$).

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TABLE 2 (Continued)

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
	Campbell et al. (2016) (42)	38 patients with MS (CG 19)	RCT	Treatment sessions consisted of training in three specific modules involving working memory, visuospatial memory, and divided attention. CG watched a series of natural history.	45 min, 3 times weekly for 6 weeks At home Not specified	SDMT ($p_w = 0.005$)
	Bonavita et al. (2015) (43)	32 chronic stage patients with MS (mild impairment) (CG:14)	RCT	The training program included: "attention and concentration," "plan a day," "divided attention," "reaction behavior," and "logical thinking" sessions. CG patients received a TAU and an aspecific cognitive stimulation	8 weeks (16 sessions) 50 min training In Hospital Under the supervision of a therapist.	SDMT ($p_w = 0.01$), PASAT 3″($p_w = 0.00$), PASAT 2″ ($p_w = 0.03$), SRT-D ($p_w = 0.02$), 10/36 SPART-D ($p_w = 0.04$), MRI fractal anisotropy ($p_w = 0.05$).
	Darestani et al. (2020) (44)	60 patients with MS (CG 30)	RCT	Multidomain treatment, CG received no treatment	10 sessions for 5 weeks (2 60 min sessions per week) At home Not specified	CVLT-II ($p < 0.001$) and COWAT ($p < 0.001$)
	Veisi-Pirkoohi et al. (2020) (45)	50 stroke patients (CG 25)	RCT	Multidomain treatment, CG received no treatment	10 sessions (45-min for each) in 5 weeks At home Not specified	ADL, attention and response control ($p_b < 0.001$)
	Fernandez et al. (2017) (46)	80 ABI patients (GC 30)	RCT	Specific training for attention. CG received TAU	5 session (50 min. For each) per 8 week Not specified	TMT-A, Digit Span and logical memory ($p_b < 0.001$)
	Cerasa et al. (2014) (47)	20 chronic stage patients with PD (mild impairment) (CG:10)	RCT	Customize exercises program. CG patients performed a simple visuomotor coordination tapping task by using an in-house software	6 weeks (12 sessions) 60 min training In Hospital Group of participants, under supervision of a therapist.	SDMT ($p_b = 0.04$), Digit Span Forward ($p_b = 0.01$)

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TABLE 2 (Continued)

Device	Studies	Sample characteristic	Type of study	Training protocols	Treatment duration location supervision	Outcome measures & efficacy
GRADIOR (INTRAS Foundation, Spain)	Diaz Baquero et al. (2022) (8)	43 MCI and mild dementia patients	RCT	computer-based cognitive rehabilitation program and allows CCT on cognitive functions, each of these cognitive modalities includes various sub-modalities to customize the exercises according to the user's cognitive profile	GRADIOR consisted of attending 2–3 weekly sessions for 4 months with a duration of 30 min	Digit Symbol of WAIS-III ($p = 0.02$), Arithmetic of WAIS-III ($p = 0.02$) and lexical verbal fluency (LVF)-R ($p = 0.03$)
	Diaz Baquero et al. (2022) (48)	Eighty-nine patients with MCI and Dementia (CG = 32)	RCT			Mini-Mental State Exam (MMSE), Trail Making Test (TMT)-A ($p = 0.03$; =0.019)
	Góngora Alonso et al. (2020) (49)	83 subjects with severe and prolonged mental illness	Usability			Gradior has 81.2% acceptance and 83.7% general assessment
	Vanova et al. (2018) (50)	400 people with MCI and mild dementia	RCT		three to four times per week for 30 min per session.	ADASCog Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADL activities of daily living, CAMCog Cambridge Cognition Examination, EQ5d-5 L EuroQoL 5 dimensions, 5 levels, GDS Geriatric Depression Scale, MMSE Mini Mental State Examination, QCPR Quality of Patient-carer Relationship, SUS System Usability Scale, TMT Trail-making test

Significance is reported as p_w (for within groups) and p_b (for between groups) value of primary and secondary outcomes measures, with § for significance found in primary outcomes measure also for the control group. For every study, we selected only significant results adjusted for multiple comparisons. MS, multiple sclerosis; PD, Parkinson's Disease; ABI, acquired brain injury; TBI, Traumatic Brain Injury; RCT, randomized controlled trial; CG, control group; DKEFS, Delis-Kaplan Executive Function System; MRI, magnetic resonance imaging; IQ, Intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; TAU, treatment as usual; WM, working memory; CCT, cognitive computerized training; CVLT, California Verbal Learning test; CESD, Center for Epidemiologic Studies Depression Scale; COWAT, Controlled Oral Word Association Test; MoCA, Montreal Cognitive Assessment; 6MWT, six-minute walking test; TMT A-B, Trial Making Test part A-B; MMSE, Mini-Mental State Examination; ACE-R, Addenbrooke Cognitive Examination Revised; SDMT, Symbol Digit Modalities Test; SPART-D, Spatial Recall Test-Delayed; LNS, Letter Number Sequencing; ToL, Tower of London; FoG, freezing of gait.

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positive results on fatigue and health-related quality of life (40). These findings were confirmed by a multicenter study carried out by the same authors (41) on 58 MS patients. In fact, the authors showed significant improvements in episodic memory, information processing speed/attention, and executive functions with a positive perception of patients in using the training software RehaCom (41). Moreover, Campbell et al. (42) explored the efficacy of home-based computer-aided cognitive rehabilitation in 38 patients with MS using neuropsychological assessment and advanced structural and functional MRI. The treatment group had greater activation in the bilateral prefrontal cortex and right temporoparietal regions. In addition, improved cognitive performance was noted in patients treated with Rehacom (42). Finally, Bonavita et al. (43) performed a study on 18 relapsing–remitting MS patients treated with Rehacom software. They demonstrated that training with the software can induce an adaptive cortical reorganization as well as better cognitive performance (43).

Darestani et al. (44) conducted research to investigate the effect of RehaCom treatment on verbal performance in 60 MS patients. The results showed that treatment with the software can improve speech fluency, verbal learning, and memory in MS patients (44).

Veisi-Pirkoohi et al. (45) found that RehaCom rehabilitation software was effective on ADL, attention, and response control in 50 chronic stroke patients due to middle and anterior cerebral arteries occlusion (45). Yoo et al. (7), in their study on 46 patients with stroke, found that computer-assisted cognitive rehabilitation with the RehaCom program improved cognitive function. This raises the idea that the tool may be helpful for stroke patients who have cognitive impairment (7). Fernández et al. (46) investigated the effectiveness of the software on patients with ABI. The authors showed a good efficacy of the training procedure in focused attention, digit span, and logical and working memory (46). In another study performed on 50 hospitalized patients (56), the same authors found an improvement in the trained functions in all patients. However, adverse effects, including mental fatigue, headaches, and eye irritation, have been found to negatively affect the usability of the tool (56).

Finally, an interesting randomized controlled trial (47) was carried out on 8 patients with PD. The authors found that the patients improved attention and processing speed with changes in neural plasticity, as investigated by fMRI (47).

3.11. GRADIOR

GRADIOR (INTRAS Foundation, Spain) is a multimedia software for cognitive stimulation, neuropsychological assessment, and rehabilitation. It consists of personalized exercises that train various cognitive domains, such as attention, memory, orientation, calculation, perception, reasoning, and language. This software creates a multimedia environment with high flexibility and demanding challenges that boost the cognitive components. The use of the software requires the presence of a qualified therapist to support the user during the assessment and training. Few studies have evaluated its usability and effectiveness in the rehabilitation field. Diaz Baquero et al. performed an RCT study on 43 patients with MCI and mild dementia, highlighting good adherence to treatment, good acceptability, and potential efficacy of the device (8). Another RCT performed by the same authors on 89 people with MCI and dementia demonstrated the benefit of this training on several cognitive domains (48). These promising results were confirmed by Gongora Alonso et al., who observed good acceptability of the tool in patients with severe and prolonged mental illness (49). Finally, Vanova et al. performed an RCT of 400 people with MCI and mild dementia treated with Gradior. They found significant improvements in most patients, with long-term maintenance of the results (50).

4. Discussion

This review aimed to identify suitable technological devices for the CR of chronic neurological patients. Specifically, our literature research has shown how these devices can be used with different neurological pathologies, including stroke, MS, TBI and PD. In detail, it emerges that the clinical population with the most trials is stroke ($N = 10$) (19–21, 24, 29, 35, 36, 39, 45, 52), followed by MS ($N = 9$) (18, 22, 25, 30, 38, 40–43), PD ($N = 4$) (28, 32, 34, 47), and traumatic and acquired brain injury ($N = 4$, respectively) (14, 17, 23, 26). Only two studies investigating patients with different neurological pathologies were recruited (15, 16), as reported in Table 2. The misrepresentation of RCT studies with such a different neurological population could be intrinsically linked to the difficulty in managing patients affected, e.g., by TBI and dementia. For dementia, there is some evidence that computer-based cognitive rehabilitation may be of help in improving different cognitive domains (57). In particular, the software "GRADIOR" looks promising in the CR field (8, 48–50). Moreover, previous studies have applied computerized approaches using photos of the patient and his/her personal surroundings, with positive results (58, 59). However, these studies were excluded for temporal reasons.

Moreover, most studies reported a statistically significant efficacy of using the PC-based devices in reparative CR. However, only in some cases they were superior to conventional treatments. Training duration, frequency and timing is still unclear. For CogMed, 5 weeks of intervention with each session lasting between 30 and 45 min seems to be the best solution for different populations of patients. However, the efficacy was mainly observed within the group, and not with respect to the control group (14–19). Luminosity™ was mainly used in patients with stroke, but also with MS and TBI, with an intervention duration ranging from 4 to 12 weeks (each session lasting from 20 to 45 min) and with an efficacy higher than that observed for the control group (20–23). Brain HQ needed longer intervention times (12–20 weeks, each session lasting 30–60 min), but with a higher efficacy reported with respect to control intervention for patients with stroke, MS and TBI (24–26). Three studies investigated the use of ERICA for 8–24 weeks (each session 45–60 min), demonstrating significant results only within the experimental group (28–30). CogniPlus (31, 32) and APT (33, 34) have been used for patients with MCI or PD with high variability in the duration of interventions. CoTras (35) and BrainGymmer (36) were both tested in a single study on patients with stroke, the former for a shorter period (4 vs. 12 weeks) and with between group significant differences.

RehaCom was the device more widely tested, especially in patients with MS. The high number of studies increased the variability of the adopted protocols, with a duration of the intervention going from 5 to 15 weeks (each session ranged between 30 and 60 min). However,

literature on this device reports solid statistically significant results about its efficacy also when compared to conventional interventions (7, 37–47).

Therefore, we noticed that the importance of training cognitive functions is increasingly evident in the literature, also for facilitating learning processes in motor recovery (4, 60). Indeed, computerized cognitive rehabilitation has proven effective in combination with other methods. A practical example can be the application of acupuncture coupled to transcranial direct current stimulation with computerized cognitive rehabilitation. This method showed good results in cognitive performance in individuals with vascular cognitive impairment (61) and people with stroke (62). A recent study by Shaker et al. (62) demonstrated significant improvement in scores of attention and concentration domains, figural memory, logical reasoning, and reaction times performance. People with cognitive disabilities are treated intensively in the subacute stage of the disease, while unfortunately, they have little access to treatment in the chronic stage. This problem is due to the burden of the Local Health Care Institutions. The underestimation as well as the reduced possibility of effective cognitive training after subacute rehabilitation regards both subjects with central nervous system pathology and those affected by other conditions, such as for example non-CNS cancer (63). This is why new solutions, including telemedicine and home devices/software for cognitive rehabilitation, may be helpful to guarantee the continuity of care. In fact, they should be used when geographical and socio-economic barriers prevent the patient from reaching primary clinics. This will allow each patient to receive monitoring and rehabilitation, through remote devices (3, 64–66).

Moreover, the patient's perception of the device usability is a key point of rehabilitation. In fact, recent studies have pointed out that the adaptability of technology also includes adapting to patients' emotions or perceptions. An interesting study by Norman et al. (65) pointed out that perception of a device influences the use of that device itself (37). Nonetheless, this aspect deserves further investigation, as some tools could have high costs and reduce the possibility of customizing the design of the tools. Although in the last period very flexible low-cost proposals have been advanced, also based on smartphones and apps to download for free. We have not explored this field as they are out of the scope of this review. Possible problems concerning the diffusion and use of such devices at home could concern: (i) the absence of a caregiver to supervise the training, especially for patients with greater impairment and with a greater need for therapy; (ii) the lack of experience with technological interfaces and PCs by both patient and caregiver; (iii) the lack of structural technical requirements such as not having a PC or an internet connection. Similar issues have recently been raised by Mantovani et al. (67) concerning the use of Virtual Reality as a home therapy for CR.

In general, it seems that the use of technological devices for CR is promising, but with inconsistencies due to the variations in study design. However, we must bracket the proposal with a caveat. Although these technological devices have features that make them highly adaptive to the patient's performance. For more severe and subacute subjects they cannot replace conventional CR, in which neuropsychologists and speech therapists play a fundamental role. In fact, their optimal use always remains integrated with conventional CR, or they are part of a rehabilitation process following discharge, to support the patient remotely. However, the protocols of the various studies are very different both in the frequency and the duration of the sessions. This makes it difficult to judge the effectiveness of the tool, so new randomized trials with large samples should be conducted to confirm this aspect. Moreover, it is important that clinicians are familiar with the different devices, in order to facilitate the selection of the appropriate device for the treatment to be performed. Finally, another problem is related to the difficulty of standardizing tests for patients with different neurological pathologies. This implies the need to validate tests for different patients, favoring the continuous updating of devices and tests. Indeed, young subjects, such as those with MS, are more familiar with computerized devices and may require different tests than patients with MCI. Often young patients stop testing because they get bored, or quickly reach the various levels of the tests. On the other hand, patients with dementia and severe cognitive decline may have serious difficulties in using the devices. This could be the main reason why we did not find studies in patients with dementia.

Our review had the ambitious aim of offering an overview of the devices currently in use in clinical practice for the computerized CR of neurological patients. We have collected many studies with the aim of describing the devices and highlighting their strengths and weaknesses. A wide variability among the revised papers was noted in terms of primary as well as secondary outcome measures, even when aiming at measuring the same cognitive domain. This is accompanied by a wide variability also in the duration of treatments, including both session duration and length of rehabilitative period in which a specific device was used (as shown in Table 2). There is the need to standardize assessment and rehabilitative protocols by identifying the key parameter for each device. The inter-rater reliability in the coding and interpretation of these parameters, which in this review cannot be performed given the wide variability among the studies. Thus, this work has limitations. Unlike validation studies, it is not possible to operationalize and define the key parameters being analyzed in the identified literature and then demonstrate inter-rater reliability in the coding or interpretation of each of the defined parameters. The scientific literature on this topic is very varied: different devices are used, for different types of patients, administering a different amount of therapies/duration. Further meta-analysis reviews are needed to fulfill this purpose. In the near future, various factors can consolidate and improve the possibility of carrying out cognitive therapy using software and platforms at home. They include: (i) better accessibility (in terms of lower costs and greater geographical coverage), (ii) higher attention to the chronic and territorial phase of neurorehabilitation and (iii) a growing sensitivity to the possibility of ensuring a better quality of life for brain injury survivors.

With this in mind and considering the aforementioned limitations, PC based approaches could be valuable complementary tools to improve cognitive function and partly guarantee the continuity of care in neurological patients.

Author contributions

MM: Conceptualization, Formal analysis, Methodology, Writing – original draft. DB: Formal analysis, Investigation, Methodology,

Writing – original draft. RC: Investigation, Methodology, Writing – original draft, Writing – review & editing. IC: Supervision, Validation, Writing – review & editing. AC: Validation, Writing – review & editing, Supervision. PT: Supervision, Visualization, Writing – review & editing. FI: Software, Validation, Writing – review & editing. SP: Software, Writing – review & editing. GA: Software, Validation, Writing – review & editing. GM: Methodology, Visualization, Writing – review & editing. MI: Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Md Fadzil NH, Shahar S, Rajikan R, Singh DKA, Mat Ludin AF, Subramaniam P, et al. A scoping review for usage of Telerehabilitation among older adults with mild cognitive impairment or cognitive frailty. *Int J Environ Res Public Health*. (2022) 19:4000. doi: 10.3390/ijerph19074000

2. Xiang YT, Zhao YJ, Liu ZH, Li XH, Zhao N, Cheung T, et al. The COVID-19 outbreak and psychiatric hospitals in China: managing challenges through mental health service reform. *Int J Bio Sci*. (2020) 16:1741–4. doi: 10.7150/ijbs.45072

3. Maggio MG, De Luca R, Manuli A, Calabrò RS. The five 'W' of cognitive telerehabilitation in the COVID-19 era. *Expert Rev Med Devices*. (2020) 17:473–5. doi: 10.1080/17434440.2020.1776607

4. Morone G, Spitoni GF, De Bartolo D, et al. Rehabilitative devices for a top-down approach. *Expert Rev Med Devices*. (2019) 16:187–95. doi: 10.1080/17434440.2019.1574567

5. Vilou I, Bakirtzis C, Artemiadis A, Ioannidis P, Papadimitriou M, Konstantinopoulou E, et al. Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: an explorative study. *J Integr Neurosci*. (2020) 19:341–7. doi: 10.31083/j.jin.2020.02.35

6. Sampanis DS, Mevorach C, Shalev L, et al. Cognitive deficits after stroke through computerized progressive attentional training (CPAT): a pilot study. *Phys Med Rehabil Int*. (2015) 2:1058.

7. Yoo C, Yong MH, Chung J, Yang Y. Effect of computerized cognitive rehabilitation program on cognitive function and activities of living in stroke patients. *J Phys Ther Sci*. (2015) 27:2487–9. doi: 10.1589/jpts.27.2487

8. Diaz Baquero AA, Perea Bartolomé MV, Toribio-Guzmán JM, Martínez-Abad F, Parra Vidales E, Bueno Aguado Y, et al. Determinants of adherence to a "GRADIOR" computer-based cognitive training program in people with mild cognitive impairment (MCI) and mild dementia. *J Clin Med*. (2022) 11:1714. doi: 10.3390/jcm11061714

9. Zhou X, Snoswell CL, Harding LE, Bambling M, Edirippulige S, Bai X, et al. The role of telehealth in reducing the mental health burden from COVID-19. *Telemed J E Health*. (2020) 26:377–9. doi: 10.1089/tmj.2020.0068

10. De Cola MC, De Luca R, Bramanti A, Bertè F, Bramanti P, Calabrò RS. Tele-health services for the elderly: a novel southern Italy family needs-oriented model. *J Telem Telecare*. (2016) 22:356–62. doi: 10.1177/1357633X15604290

11. Burns SP, Terblanche M, Perea J, et al. mHealth intervention applications for adults living with the effects of stroke: a scoping review. *Arch Rehabil Res Clin Transl*. (2020) 3:100095. doi: 10.1016/j.arrct.2020.100095

12. Meulenberg CJW, de Bruin ED, Marusic U. A perspective on implementation of technology-driven Exergames for adults as Telerehabilitation services. *Front Psychol*. (2022) 13:840863. doi: 10.3389/fpsyg.2022.840863

13. Bernini S, Panzarasa S, Sinforiani E, Quaglini S, Cappa SF, Cerami C, et al. HomeCoRe for Telerehabilitation in mild or major neurocognitive disorders: a study protocol for a randomized controlled trial. *Front Neurol*. (2021) 12:752830. doi: 10.3389/fneur.2021.752830

14. Akerlund E, Esbjörnsson E, Sunnerhagen KS, Björkdahl A. Can computerized working memory training improve impaired working memory, cognition and psychological health? *Brain Inj*. (2013) 27:1649–57. doi: 10.3109/02699052.2013.830195

15. Johansson B, Tornmalm M. Working memory training for patients with acquired brain injury: effects in daily life. *Scand J Occup Ther*. (2012) 19:176–83. doi: 10.3109/11038128.2011.603352

16. Lundqvist A, Grundström K, Samuelsson K, Rönnberg J. Computerized training of working memory in a group of patients suffering from acquired brain injury. *Brain Inj*. (2010) 24:1173–83. doi: 10.3109/02699052.2010.498007

17. Svaerke K, Pyke SB, Tjoernlund M, Humle F, Mogensen J. Effects of computer-based cognitive rehabilitation on working memory in patients with acquired brain injury in the chronic phase, a pilot-study. *Brain Inj*. (2022):1–11. doi: 10.1080/02699052.2022.2034965

18. Blair M, Goveas D, Safi A, Marshall C, Rosehart H, Orenczuk S, et al. Does cognitive training improve attention/working memory in persons with MS? A pilot study using the Cogmed working memory training program. *Mult Scler Relat Disord*. (2021) 49:102770. doi: 10.1016/j.msard.2021.102770

19. Nyberg CK, Nordvik JE, Becker F, Rohani DA, Sederevicius D, Fjell AM, et al. A longitudinal study of computerized cognitive training in stroke patients – effects on cognitive function and white matter. *Top Stroke Rehabil*. (2018) 25:241–7. doi: 10.1080/10749357.2018.1443570

20. Withiel TD, Wong D, Ponsford JL, Cadilhac DA, New P, Mihaljcic T, et al. Comparing memory group training and computerized cognitive training for improving memory function following stroke: a phase II randomized controlled trial. *J Rehabil Med*. (2019) 51:343–51. doi: 10.2340/16501977-2540

21. Wentink MM, Berger MA, de Kloet AJ, Meesters J, Band GP, Wolterbeek R, et al. The effects of an 8-week computer-based brain training programme on cognitive functioning, QoL and self-efficacy after stroke. *Neuropsychol Rehabil*. (2016) 26:847–65. doi: 10.1080/09602011.2016.1162175

22. Stuifbergen AK, Becker H, Perez F, Morrison J, Brown A, Kullberg V, et al. Computer-assisted cognitive rehabilitation in persons with multiple sclerosis: results of a multi-site randomized controlled trial with six month follow-up. *Disabil Health J*. (2018) 11:427–34. doi: 10.1016/j.dhjo.2018.02.001

23. Zickefoose S, Hux K, Brown J, Wulf K. Let the games begin: a preliminary study using attention process training-3 and Lumosity™ brain games to remediate attention deficits following traumatic brain injury. *Brain Inj*. (2013) 27:707–16. doi: 10.3109/02699052.2013.775484

24. Yeh TT, Chang KC, Wu CY. The active ingredient of cognitive restoration: a multicenter randomized controlled trial of sequential combination of aerobic exercise and computer-based cognitive training in stroke survivors with cognitive decline. *Arch Phys Med Rehabil*. (2019) 100:821–7. doi: 10.1016/j.apmr.2018.12.020

25. Charvet LE, Yang J, Shaw MT, Sherman K, Haider L, Xu J, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: results from a randomized controlled trial. *PLoS One*. (2017) 12:e0177177. doi: 10.1371/journal.pone.0177177

26. O'Neil-Pirozzi TM, Hsu H. Feasibility and benefits of computerized cognitive exercise to adults with chronic moderate-to-severe cognitive impairments following an acquired brain injury: a pilot study. *Brain Inj*. (2016) 30:1617–25. doi: 10.1080/02699052.2016.1199906

27. Gil-Pagés M, Solana J, Sánchez-Carrión R, Tormos JM, Enseñat-Cantallops A, García-Molina A. A customized home-based computerized cognitive rehabilitation platform for patients with chronic-stage stroke: study protocol for a randomized controlled trial. *Trials*. (2018) 19:191. doi: 10.1186/s13063-018-2577-8

28. De Luca R, Latella D, Maggio MG, et al. Computer assisted cognitive rehabilitation improves visuospatial and executive functions in Parkinson's disease: preliminary results. *NeuroRehabilitation*. (2019) 45:285–90. doi: 10.3233/NRE-192789

29. De Luca R, Leonardi S, Spadaro L, et al. Improving cognitive function in patients with stroke: can computerized training be the future? *J Stroke Cerebrovasc Dis*. (2018) 27:1055–60. doi: 10.1016/j.jstrokecerebrovasdis.2017.11.008

30. Barbarulo AM, Lus G, Signoriello E, Trojano L, Grossi D, Esposito M, et al. Integrated cognitive and Neuromotor rehabilitation in multiple sclerosis: a pragmatic study. *Front Behav Neurosci*. (2018) 12:196. doi: 10.3389/fnbeh.2018.00196

31. Hagovská M, Dzvoník O, Olekszyová Z. Comparison of two cognitive training programs with effects on functional activities and quality of life. *Res Gerontol Nurs*. (2017) 10:172–80. doi: 10.3928/19404921-20170524-01

32. Zimmermann R, Gschwandtner U, Benz N, Hatz F, Schindler C, Taub E, et al. Cognitive training in Parkinson disease: cognition-specific vs nonspecific computer training. *Neurology*. (2014) 82:1219–26. doi: 10.1212/WNL.0000000000000287

33. Pantoni L, Poggesi A, Diciotti S, Valenti R, Orsolini S, Della Rocca E, et al. Effect of attention training in mild cognitive impairment patients with subcortical vascular changes: the RehAtt study. *J Alzheimers Dis*. (2017) 60:615–24. doi: 10.3233/JAD-170428

34. Walton CC, Mowszowski L, Gilat M, Hall JM, O'Callaghan C, Muller AJ, et al. Cognitive training for freezing of gait in Parkinson's disease: a randomized controlled trial. *NPJ Parkinsons Dis*. (2018) 4:15. doi: 10.1038/s41531-018-0052-6

35. Park JH, Park JH. The effects of a Korean computer-based cognitive rehabilitation program on cognitive function and visual perception ability of patients with acute stroke. *J Phys Ther Sci*. (2015) 27:2577–9. doi: 10.1589/jpts.27.2577

36. van de Ven RM, Buitenweg JI, Schmand B, Veltman DJ, Aaronson JA, Nijboer TC, et al. Brain training improves recovery after stroke but waiting list improves equally: a multicenter randomized controlled trial of a computer-based cognitive flexibility training. *PLoS One*. (2017) 12:e0172993. doi: 10.1371/journal.pone.0172993

37. Nousia A, Martzoukou M, Siokas V, Aretouli E, Aloizou AM, Folia V, et al. Beneficial effect of computer-based multidomain cognitive training in patients with mild cognitive impairment. *Appl Neuropsych Adult*. (2021) 28:717–26. doi: 10.1080/23279095.2019.1692842

38. Naeeni Davarani M, Arian Darestani A, Hassani-Abharian P, Vaseghi S, Zarrindast MR, Nasehi M. RehaCom rehabilitation training improves a wide-range of cognitive functions in multiple sclerosis patients. *Appl Neuropsychol Adult*. (2022) 29:262–72. doi: 10.1080/23279095.2020.1747070

39. Amiri S, Hassani-Abharian P, Vaseghi S, Kazemi R, Nasehi M. Effect of RehaCom cognitive rehabilitation software on working memory and processing speed in chronic ischemic stroke patients. *Assist Technol*. (2021) 35:41–7. doi: 10.1080/10400435.2021.1934608

40. Messinis L, Kosmidis MH, Nasios G, Konitsiotis S, Ntoskou A, Bakirtzis C, et al. Do secondary progressive multiple sclerosis patients benefit from computer- based cognitive neurorehabilitation? A randomized sham controlled trial. *Mult Scler Relat Disord*. (2020) 39:101932. doi: 10.1016/j.msard.2020.101932

41. Messinis L, Nasios G, Kosmidis MH, Zampakis P, Malefaki S, Ntoskou K, et al. Efficacy of a computer-assisted cognitive rehabilitation intervention in relapsing-remitting multiple sclerosis patients: a multicenter randomized controlled trial. *Behav Neurol*. (2017) 2017:1–17. doi: 10.1155/2017/5919841

42. Campbell J, Langdon D, Cercignani M, Rashid W. A randomized controlled trial of the efficacy of cognitive rehabilitation in multiple sclerosis: a cognitive, behavioral, and MRI study. *Neural Plastic*. (2016) 2016:1–9. doi: 10.1155/2016/4292585

43. Bonavita S, Sacco R, Della Corte M, Esposito S, Sparaco M, d'Ambrosio A, et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. *J Neurol*. (2015) 262:91–100. doi: 10.1007/s00415-014-7528-z

44. Arian Darestani A, Naeeni Davarani M, Hassani-Abharian P, Zarrindast MR, Nasehi M. The therapeutic effect of treatment with RehaCom software on verbal performance in patients with multiple sclerosis. *J Clin Neurosci*. (2020) 72:93–7. doi: 10.1016/j.jocn.2020.01.007

45. Veisi-Pirkoohi S, Hassani-Abharian P, Kazemi R, Vaseghi S, Zarrindast MR, Nasehi M. Efficacy of cognitive rehabilitation software RehaCom in activities of daily living, attention and response control in chronic stroke patients. *J Clin Neurosci*. (2020) 71:101–7. doi: 10.1016/j.jocn.2019.08.114

46. Fernandez E, Bergado Rosado JA, Rodriguez Perez D, Salazar Santana S, Torres Aguilar M, Bringas ML. Effectiveness of a computer-based training program of attention and memory in patients with acquired brain damage. *Behav Sci (Basel)*. (2017) 8:4. doi: 10.3390/bs8010004

47. Cerasa A, Gioia MC, Salsone M, Donzuso G, Chiriaco C, Realmuto S, et al. Neurofunctional correlates of attention rehabilitation in Parkinson's disease: an explorative study. *Neurol Sci*. (2014) 35:1173–80. doi: 10.1007/s10072-014-1666-z

48. Diaz Baquero AA, Franco-Martín MA, Parra Vidales E, Toribio-Guzmán JM, Bueno-Aguado Y, Martínez Abad F, et al. The effectiveness of GRADIOR: a neuropsychological rehabilitation program for people with mild cognitive impairment and mild dementia. Results of a randomized controlled trial after 4 and 12 months of treatment. *J Alzheimers Dis*. (2022) 86:711–27. doi: 10.3233/JAD-215350

49. Góngora Alonso S, Fumero Vargas G, Morón Nozaleda L, Sainz de Abajo B, de la Torre DI, Franco M. Usability analysis of a system for cognitive rehabilitation, "Gradior", in a Spanish region. *Telemed J E Health*. (2020) 26:671–82. doi: 10.1089/tmj.2019.0084

50. Vanova M, Irazoki E, García-Casal JA, Martínez-Abad F, Botella C, Shiells KR, et al. The effectiveness of ICT-based neurocognitive and psychosocial rehabilitation programmes in people with mild dementia and mild cognitive impairment using GRADIOR and ehcoBUTLER: study protocol for a randomised controlled trial. *Trials*. (2018) 19:100. doi: 10.1186/s13063-017-2371-z

51. Wayne RV, Hamilton C, Jones Huyck J, Johnsrude IS. Working memory training and speech in noise comprehension in older adults. *Front Aging Neurosci*. (2016) 8:49. doi: 10.3389/fnagi.2016.00049

52. Aparicio-López C, García-Molina A, García-Fernández J, López-Blázquez R, Enseñat-Cantallops A, Sánchez-Carrión R, et al. Combination treatment in the rehabilitation of visuo-spatial neglect. *Psicothema*. (2016) 28:143–9. doi: 10.7334/psicothema2015.93

53. Westerhof-Evers HJ, Visser-Keizer AC, Fasotti L, Schönherr MC, Vink M, van der Naalt J, et al. Effectiveness of a treatment for impairments in social cognition and emotion regulation (T-ScEmo) after traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil*. (2017) 32:296–307. doi: 10.1097/HTR.0000000000000332

54. Hagovská M, Olekszyová Z. Relationships between balance control and cognitive functions, gait speed, and activities of daily living. *Z Gerontol Geriatr*. (2016) 49:379–85. doi: 10.1007/s00391-015-0955-3

55. Sohlberg MM, Mateer CA. Effectiveness of an attention-training program. *J Clin Exp Neuropsychol*. (1987) 9:117–30. doi: 10.1080/01688638708405352

56. Fernández E, Bringas ML, Salazar S, Rodríguez D, García ME, Torres M. Clinical impact of RehaCom software for cognitive rehabilitation of patients with acquired brain injury. *MEDICC Rev*. (2012) 14:32–5. doi: 10.37757/MR2012V14.N4.8

57. Klimova B, Maresova P. Computer-based training programs for older people with mild cognitive impairment and/or dementia. *Front Hum Neurosci*. (2017) 11:262. doi: 10.3389/fnhum.2017.00262

58. Hofmann M, Hock C, Kühler A, Müller-Spahn F. Interactive computer-based cognitive training in patients with Alzheimer's disease. *J Psychiatr Res*. (1996) 30:493–501. doi: 10.1016/S0022-3956(96)00036-2

59. Hofmann M, Hock C, Müller-Spahn F. Computer-based cognitive training in Alzheimer's disease patients. *Ann N Y Acad Sci*. (1996) 777:249–54. doi: 10.1111/j.1749-6632.1996.tb34427.x

60. Park HK, Song MK, Kim JH, Han JY. A randomized controlled trial to evaluate the effectiveness and safety of electro acupuncture and transcranial direct current stimulation with computerized cognitive rehabilitation in patients with vascular cognitive impairment. *Medicine (Baltimore)*. (2020) 99:e21263. doi: 10.1097/MD.0000000000021263

61. Jiang C, Yang S, Tao J, Huang J, Li Y, Ye H, et al. Clinical efficacy of acupuncture treatment in combination with RehaCom cognitive training to improve cognitive function in stroke: a factorial 2 × 2 design a randomized controlled trial. *J Am Med Dir Assoc*. (2016) 17:1114–22. doi: 10.1016/j.jamda.2016.07.021

62. Shaker HA, Sawan SAE, Fahmy EM, Ismail RS, Elrahman SAEA. Effect of transcranial direct current stimulation on cognitive function in stroke patients. *Egypt J Neurol Psychiatr Neurosurg*. (2018) 54:32. doi: 10.1186/s41983-018-0037-8

63. De Luca R, Torrisi M, Bramanti A, et al. A multidisciplinary telehealth approach for community dwelling older adults. *Geriatr Nurs*. (2021) 42:635–42. doi: 10.1016/j.gerinurse.2021.03.015

64. Manuli A, Maggio MG, Tripoli D, Gullì M, Cannavò A, la Rosa G, et al. Patients' perspective and usability of innovation technology in a new rehabilitation pathway: an exploratory study in patients with multiple sclerosis. *Mult Scler Relat Disord*. (2020) 44:102312. doi: 10.1016/j.msard.2020.102312

65. Norman DA. *Emotional design: Why we love (or hate) everyday things*. New York: Basic Civitas Books (2004).

66. De Bartolo D, Morone G, Lupo A, et al. From paper to informatics: the post soft care-app, an easy-to-use and fast tool to help therapists identify unmet needs in stroke patients. *Funct Neurol*. (2018) 33:200–5.

67. Mantovani E, Zucchella C, Bottiroli S, Federico A, Giugno R, Sandrini G, et al. Telemedicine and virtual reality for cognitive rehabilitation: a roadmap for the COVID-19 pandemic. *Front Neurol*. (2020) 11:926. doi: 10.3389/fneur.2020.00926

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Changes in respiratory structure and function after traumatic cervical spinal cord injury: observations from spinal cord and brain

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Respiratory difficulties and mortality following severe cervical spinal cord injury (CSCI) result primarily from malfunctions of respiratory pathways and the paralyzed diaphragm. Nonetheless, individuals with CSCI can experience partial recovery of respiratory function through respiratory neuroplasticity. For decades, researchers have revealed the potential mechanism of respiratory nerve plasticity after CSCI, and have made progress in tissue healing and functional recovery. While most existing studies on respiratory plasticity after spinal cord injuries have focused on the cervical spinal cord, there is a paucity of research on respiratory-related brain structures following such injuries. Given the interconnectedness of the spinal cord and the brain, traumatic changes to the former can also impact the latter. Consequently, are there other potential therapeutic targets to consider? This review introduces the anatomy and physiology of typical respiratory centers, explores alterations in respiratory function following spinal cord injuries, and delves into the structural foundations of modified respiratory function in patients with CSCI. Additionally, we propose that magnetic resonance neuroimaging holds promise in the study of respiratory function post-CSCI. By studying respiratory plasticity in the brain and spinal cord after CSCI, we hope to guide future clinical work.

KEYWORDS

cervical spinal cord injury (CSCI), breathing, neuroplasticity, brainstem, bulbospinal pathway, magnetic resonance imaging, neuroimaging

1. Introduction

Traumatic spinal cord injury (SCI) is an irreversible central nervous system disease with a high incidence rate of 50 per million individuals in China, with a higher incidence of cervical spinal cord injury (CSCI) at between 55.7% and 64.49% (1). Similarly, the incidence of SCI in the United States is 25–59 per million individuals (2, 3). Different degrees of respiratory dysfunction occur in patients with CSCI at different injury levels and degrees of injury and are mainly expressed as restrictive ventilatory deficits (4, 5). In addition, the degree of respiratory dysfunction following CSCI is compounded by an imbalance between the sympathetic and parasympathetic nervous systems.

Parasympathetic dominance causes airway hyper-responsiveness and increased mucus production (Figure 1) (6). Consequently, respiratory muscles such as the diaphragm, intercostal muscles, and abdominal muscles become paralyzed, resulting in reduced inspiratory and expiratory forces, as well as a diminished ability to cough up secretions. During the acute phase, severe injuries often lead to respiratory complications including pneumonia, atelectasis, hypercarbia, hypoxemia, and potentially even death (7–9). Patients with milder impairments may experience changes in vocal quality or duration (10). Sleep apnea is also common among individuals with CSCI, although the exact underlying cause is still not fully understood (11, 12).

To maintain ventilation after spinal cord injury, patients experience shallow and fast breathing (13). Simultaneous paralysis of the respiratory muscles may prompt compensation of the neck muscles (14). Regardless of the initial defect, improvement in lung function will occur within 6 months of injury (15). These improvements can be attributed to biomechanical adaptations, neuroplasticity, and rehabilitation interventions (16). Breathing is a rhythmic process that involves the generation of respiratory rhythms by the brainstem respiratory centers, with contributions from higher brain centers in respiratory control (17, 18). Neuroplasticity refers to the continuous changes in the morphology and/or function of the neural control system based on experience (19). Preclinical research has shown that changes in neurons (20), activation of the cross-phrenic pathway (21–23), and axonal regeneration (24) play crucial roles in functional recovery following CSCI.

As the spinal cord and brain are interconnected, alterations in respiratory function due to CSCI can also affect the higher respiratory centers in the brain. Recent advancements in non-invasive neuroimaging techniques have enabled the examination of changes in respiratory-related structures and functions in the brainstem and subcortical layers of patients with CSCI. This provides valuable insight into the mechanisms underlying respiratory plasticity (25, 26). Neuroimaging can also assist in clinical decision-making by assessing respiratory function in patients with CSCI.

This review aims to explore the anatomy and function of the principal respiratory centers, discuss changes in respiratory function observed in clinical research on individuals with CSCI, examine findings from preclinical research regarding the structural basis for altered respiratory center function following cervical cord damage, and propose the potential use of neuroimaging to study the structure and function of respiratory centers in individuals with CSCI.

2. Anatomic basis of neural control of respiration

Breathing is a complex and rhythmic activity that requires coordination between the respiratory and nervous systems. This section elucidates the central architecture and pathways responsible for respiration, enhancing our comprehension of disrupted respiratory neural pathways and neuroplasticity following SCI. Figure 2 visually depicts the interconnection between these domains.

2.1. Brainstem respiratory central pattern generator

The neural drive to breathe results from the integration of brainstem respiratory central pattern generators (rCPG) and the respiratory-related cortical networks (27–29). The rCPG is a hierarchical functional region; respiratory motions may result from integration among numerous brainstem nuclei (30–33). The main brainstem-associated respiratory nuclei, listed in descending order, include the periaqueductal gray (PAG) (34, 35), pontine respiratory group (PRG) (29, 36), retrotrapezoid nucleus (RTN)/parafacial respiratory group (pFRG) (37), pre-Bötzinger complex (pre-Bötc), Bötzinger complex (Bötc), ventral lateral medulla oblongata respiratory neuron group, and the nucleus tractus solitaries (NTS) (38). These nuclei harbor diverse neuron types and neurotransmitters, enabling them to perform distinct respiratory functions, as outlined in Table 1.

The respiratory rhythm originates from the ventral part of the medulla, specifically the pre-Bötc and Bötc. The pre-Bötc assumes the role of providing rhythmic excitation drive for respiration, while the Bötc engenders alternating inspiratory and expiratory patterns during normal breathing (44). The respiratory drives are conveyed to the ventral (VRG) and dorsal respiratory neuron groups (DRG) of the medulla oblongata (39). The rostral VRG is the largest group of inspiratory bulbospinal neurons and receives inspiratory drive from pre-Bötc neurons while being inhibited by expiratory Bötc neurons (39, 45). The rVRG transmits respiratory drive to phrenic motorneurons (PhMNs) via the bulbospinal respiratory neural pathway (46). The caudal VRG receives converging inputs, including those from the RTN/pFRG and BötC (39). The pons is proposed to interact with the medullary respiratory system (47). Respiratory adjustment primarily occurs in the midbrain, pons, and related cortical regions. The PAG mainly regulated the patterns of respiratory and contributed to arousal and control of sleep (34). Respiratory adjustments occur mainly in the PRG and the facial nucleus. The PRG, consisting of the Kölliker-Fuse nucleus (KF) and the parabrachial nuclei (PB), project upward to the amygdala and hypothalamus (48) and downward to the VRG through medullary raphe neurons (49). The RTN/pFRG serves as a conditioned oscillator of expiratory activity and serves as a significant generator of inspiratory rhythms (50, 51). Additionally, the lateral reticular nucleus also affects respiratory control and arousal (52).

2.2. Respiratory-related forebrain regions

Advanced respiratory centers connected to breathing include the cerebral cortex, thalamus, hypothalamus, hippocampus, extended amygdala, and limbic system (53–55). For details, please refer to this literature (29). Initial indications of a direct connection between the cortex and motor neurons were observed when the primary motor cortex was stimulated, inducing activation of the phrenic nerve in cats (56). Subsequently, the relationship between spontaneous breathing and the primary motor cortex was confirmed using transcranial electrical or magnetic cortical stimulation (57–60) and positron emission

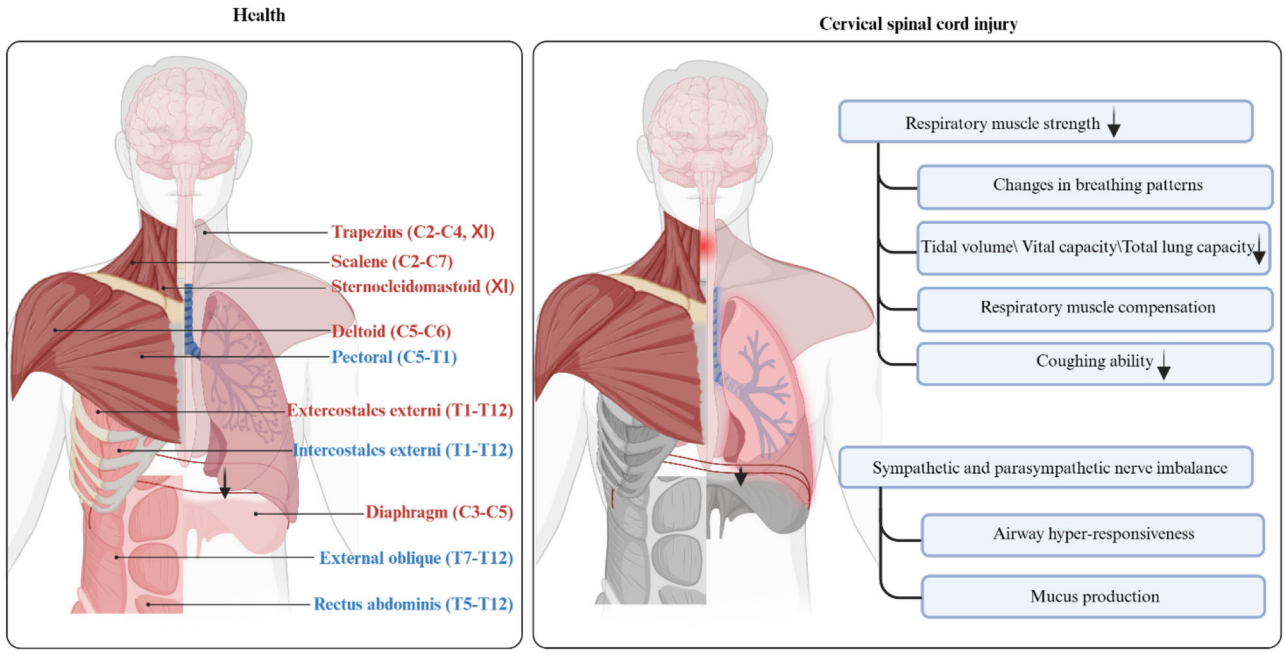

FIGURE 1
Anatomy and function of respiratory muscles in health and patients with cervical spinal cord injury. This figure shows the anatomical location and innervation of respiratory-related muscles. The inspiratory muscles are highlighted in red font, while the expiratory muscles are highlighted in blue font. Respiratory muscles that may be paralyzed after cervical cord injury are highlighted in gray. Created with BioRender.com.

tomography (61). Furthermore, evidence suggests the existence of a rapid pathway from the supplementary motor area (SMA) to the diaphragm, with the SMA exerting a more pronounced excitatory effect on the diaphragm (62). The premotor area was thought to be involved in respiratory control during articulation (63). While our understanding of the brainstem respiratory center has advanced (39), the control mechanisms of the higher respiratory centers and their performance under varying conditions remain unclear.

2.3. Respiratory afferent and efferent pathways

2.3.1. Respiratory afferent pathways

Respiratory information is collected through chemoreceptors, bronchial and pulmonary receptors, and respiratory muscle proprioceptors (Figure 2). Chemoreceptors detect CO2, O2, and pH levels, and transmit this information to the central chemical-sensitive neurons in the brainstem (37, 64). Sensory information from the lungs and the airways is conveyed via the vagus nerve, which serves as the link between the lung and brain (65, 66). Besides, the proprioceptive information from the respiratory muscle is sent to the cerebellum through the spinocerebellar tract for processing (27). The respiratory sensory information is also projected to supraspinal structures such as the hypothalamus, thalamus, cingulate gyrus, and sensory cortex, where it is integrated and further processed to regulate breathing (48, 67, 68).

2.3.2. Respiratory efferent pathways

Respiratory movements are facilitated by transmitting autonomous respiratory impulses from the rhythm-generating respiratory center and the reticular structure via the bulbar spinal cord pathway. Additionally, voluntary respiratory impulses from the respiratory-related cortex are transmitted to the respiratory-related skeletal muscles through the corticospinal lateral tract (27). The respiratory muscles can be categorized into upper respiratory muscles and trunk respiratory muscles. The upper respiratory muscles are critical to maintaining upper respiratory tract patency and airway pressure (69). The abnormalities in upper respiratory muscles may cause sleep apnea and dysphagia (11, 70, 71). Trunk respiratory muscles are closely involved in lung ventilation. The diaphragm is the primary inspiratory muscle, contributing to approximately 65% of tidal volume during calm breathing (28). Contraction of the abdominal muscles and internal intercostal muscles helps the diaphragm return to its resting position, reduces intra-abdominal pressure, and facilitates expiration (72, 73).

3. Structural basis of respiratory plasticity after CSCI

3.1. Neuronal changes

3.1.1. Respiratory motor neuron

The phrenic motor neurons and the bulbospinal nerve pathway are directly affected following C2 hemisection, leading to a reduction in tidal volume due to decreased respiratory drive to the phrenic neurons (4). In the mid-cervical spinal cord

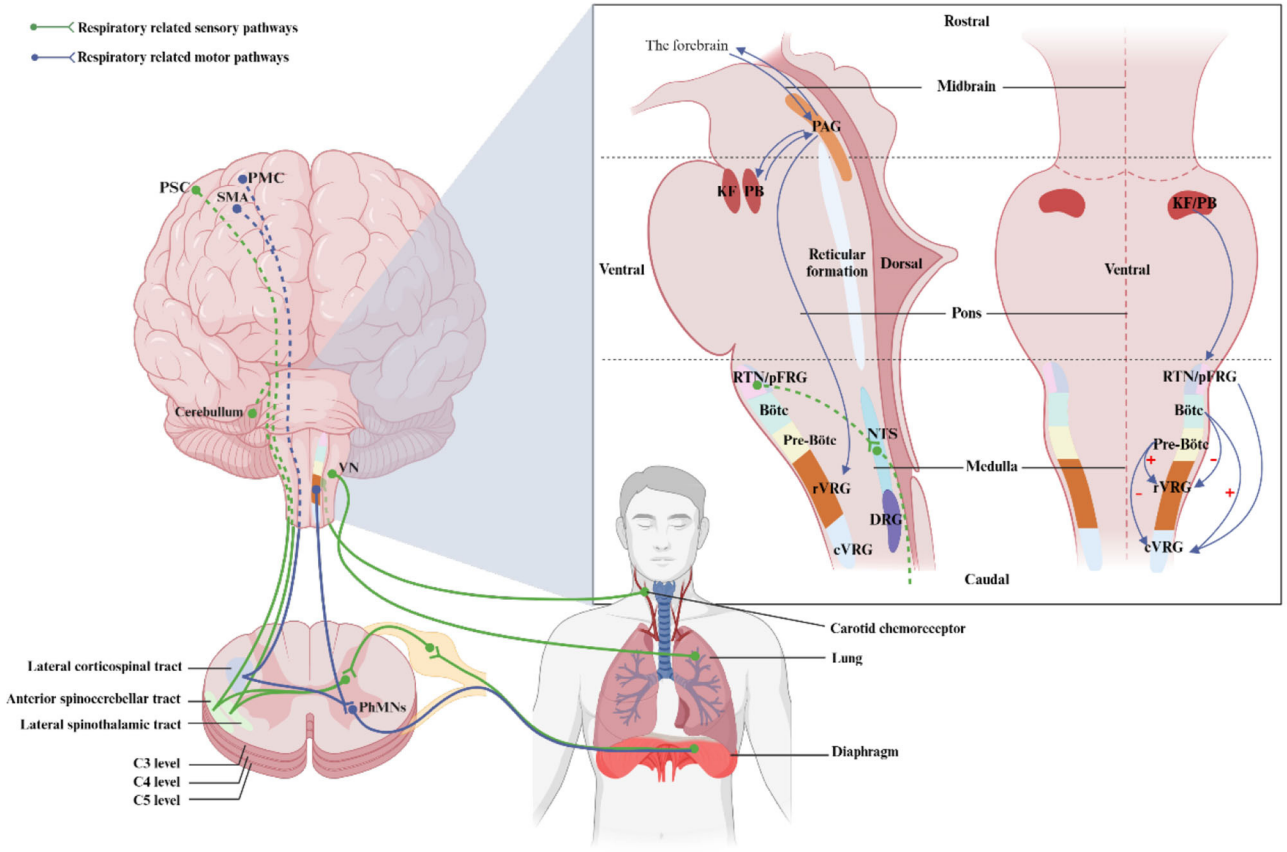

FIGURE 2
Location of regions and respiratory pathways involved in the control of breathing. This illustration shows the location of respiratory nuclei in the brainstem from a side and front view, as well as respiratory nerve pathways in a sagittal section. PMC, primary motor cortex; SMA, supplementary motor area; PSC, primary sensory cortex; rVRG, rostral ventral respiratory group; SpINs, spinal interneurons; PhMNs, phrenic motorneurons; PAG, periaqueductal gray; KF, kölliker-Fuse nucleus; PB, parabrachial nuclei; RTN, retrotrapezoid nucleus; pFRG, parafacial respiratory group; cVRG, caudal ventral respiratory group; NTS, nucleus of the Solitary Tract; DRG, dorsal respiratory group; VN, vagus nucleus. Created with BioRender.com.

contusion mice model (74) and the unilateral C4 contusion rat model (75), the same ipsilateral PhMNs can be lost within 24 h, accompanied by phrenic nerve axon deformation and denervation of the phrenic neuromuscular junction, resulting in impaired diaphragm function. Despite increasing lesion volume, there is minimal progression of the injury over an extended period (75). During the chronic phase, PhMNs of Sprague-Dawley (SD) rats tend to return to control values, potentially due to the influence of brainstem upper respiratory neurons on early PhMNs function (76). Additionally, intercostal muscle neurons are also affected by damage to the bulbospinal pathway, with recovery similar to PhMNs (77). Intercostal muscle recovery is observed in both spinal cord hemisection (77) and contusion SD rats models (78). All of the above models of CSCI confirm that respiratory motor neurons are immediately damaged, resulting in varying levels of muscle paralysis. However, with time, the paralyzed muscles all show functional recovery, which may result from replacement with other neurons or lateral bypass repair.

3.1.2. Spinal interneurons

The location of Spinal interneurons (SpINs) are distributed in the dorsal horn, around the central canal, in the gray matter of the spinal cord (79). Morphological and electrophysiology evidence has confirmed that SpINs receive their excitatory inspiratory drive from the rVRG (80–82). With our understanding of respiratory neuromodulation, it appears that SpINs play a role in promoting respiratory recovery (20, 83). During acute hypoxia, a network of spinal cord interneurons becomes activated, facilitating synaptic connections from the contralateral side of the injury (84). In chronic spinal cord injury, SpIN recruitment increases along with increased interaction with the bulbospinal pathway, suggesting a potential role for SpINs in respiratory integration (85). At the same time, thoracic SpINs may serve as reliable neurons connecting intercostal neurons after disruption of the bulbospinal pathway (86). Spinal cord proprioceptive interneurons may also be involved in the reconstruction of respiratory function after thoracic segment SCI and play a key role in functional recovery following injury (87).

TABLE 1 The location and function of respiratory nuclei in the brainstem.

Brainstem	Nucleus	Neurons or neurotransmitters	Function
Midbrain	PAG	Neurotransmitters: 5-HT and neurotensin	• Coordinates specific patterns of respiration. • Input or output information to the forebrain. • Contributes to arousal and control of REM sleep (34).
Pons	KF/PB	Neurons: laryngeal post-inspiratory premotor neurons Neurotransmitters: glutamate, glycine, GABA, acetylcholine, norepinephrine, serotonin	• Regulates vocal fold closure and controls upper airway opening in the inspiratory and expiratory phases of the transition (39). • Regulates breathing frequency and tidal volume by regulating the duration of the inspiratory discharge of the VRG (40). • Switching respiratory phases, a classical apnea center (41).
Medulla	RTN/pFRG	Neurotransmitters: VGlut2, Phox2b and NK1R Neurons: oscillatory neurons	• Receives information from the center and peripheral chemoreceptors and inputs VRG (37, 42). • Delivers exhalation drive to cVRG.
	pre-Bötc	Neurons: inspiratory neurons Neurotransmitters: glutamate, glycine, GABA	• Respiratory rhythm oscillator. • Inhibits expiratory activity.
	Bötc	Neurons: expiratory neurons Neurotransmitters: glycine, GABA	• Respiratory rhythm oscillator. • Inhibits inspiratory activity.
	rVRG	Neurons: bulbospinal premotor inspiratory neurons	• Transmits the inspiratory and expiratory drive to PhMNs.
	cVRG	Neurons: excitatory bulbospinal expiratory neurons	• Transmit exhalation drive
	DRG		• Only drives inspiratory drive to PhMNs.
	RN	Neurons: serotonergic neurons Neurotransmitters: serotonin and co-localized peptides	• Participates in chemosensory regulation of breathing and stabilizes breathing (43).
	NTS	Neurotransmitters: amino acids, biogenic amines, purines and peptides	• Coordinates respiratory and sympathetic responses to hypoxia.

PAG, periaqueductal gray; KF, kölliker-Fuse nucleus; PB, parabrachial nuclei; RTN, retrotrapezoid nucleus; pFRG, parafacial respiratory group; pre-Bötc, Pre Bötzinger; Bötc, Bötzinger; rVRG, rostral ventral respiratory group; PhMNs, phrenic motor neurons; cVRG, caudal ventral respiratory group; DRG, caudal respiratory group; RN, Raphe nucleus; NTS, nucleus of the Solitary Tract.

3.1.3. Respiratory-related neurons in the brainstem and subcortical structures

Several studies have revealed that modifications occur in the brainstem and higher brain structures during the acute phase of CSCI that go beyond the plasticity of respiratory nerves within the spinal cord segment. These changes may arise from the presence of interconnections or unidirectional connections between the rRVG and other nerve nuclei (88–90). For instance, there is a tendency for an increase in rVRG expiratory activity while cVRG expiratory activity declines (89). Similar alterations in the reticular fiber structures have been observed following spinal cord hemisection, indicating their association with the restoration of respiratory function (89–91). Researchers have utilized transcranial magnetic stimulation in mice and rats to visualize respiratory plasticity after CSCI (92, 93). Vinit discovered ipsilateral diaphragmatic motor-evoked potentials when the coil center was positioned 6 mm caudal to the pons, suggesting that stimulated PAG might influence breathing (92). Although current investigations on the remodeling of respiratory nociceptors after CSCI primarily focus on fundamental research (13). It is important to acknowledge the differences between human structure and function when extrapolating findings from animal models (94). Section 6 describes the alterations in cortical structures related to respiration after SCI.

3.2. The cross-phrenic phenomenon

The strongest evidence that potential respiratory neural pathways are activated in the weeks or months following high CSCI is the crossed phrenic phenomenon (CPP). CPP was first discovered by John Porter in 1895 through the C2 hemisection model (21). Since then, the neuroplasticity of diaphragm neuromotor control after CSCI has been studied. Cervical medullary hemisection interrupts the inspiratory drive of the ipsilateral PhMNs, paralyzes the ipsilateral diaphragm, and then achieves functional recovery of the ipsilateral diaphragm by severing the contralateral phrenic nerve to induce CPP (21, 95). The occurrence of CPP serves as a respiratory-related stressor leading to modulation of respiratory function, and the bulbospinal pathway contralateral to the injury is activated to cross over at the level of the phrenic nucleus within the spinal cord to innervate the ipsilateral PhMNs (4). Similarly, in rats with unilateral CSCI, the "crossed-spinal" pathways are also observed in the ipsilateral intercostal activity (77). Further studies have identified CPP as a state-dependent phenomenon that is induced by certain respiratory stressors, such as contralateral phrenic nerve dissection, hypercapnia, hypoxia, and asphyxia (96, 97). One study has identified CPP within a few days of injury (98), while other studies identify CPP within 2 weeks of C2 hemisection (99, 100). Beyond

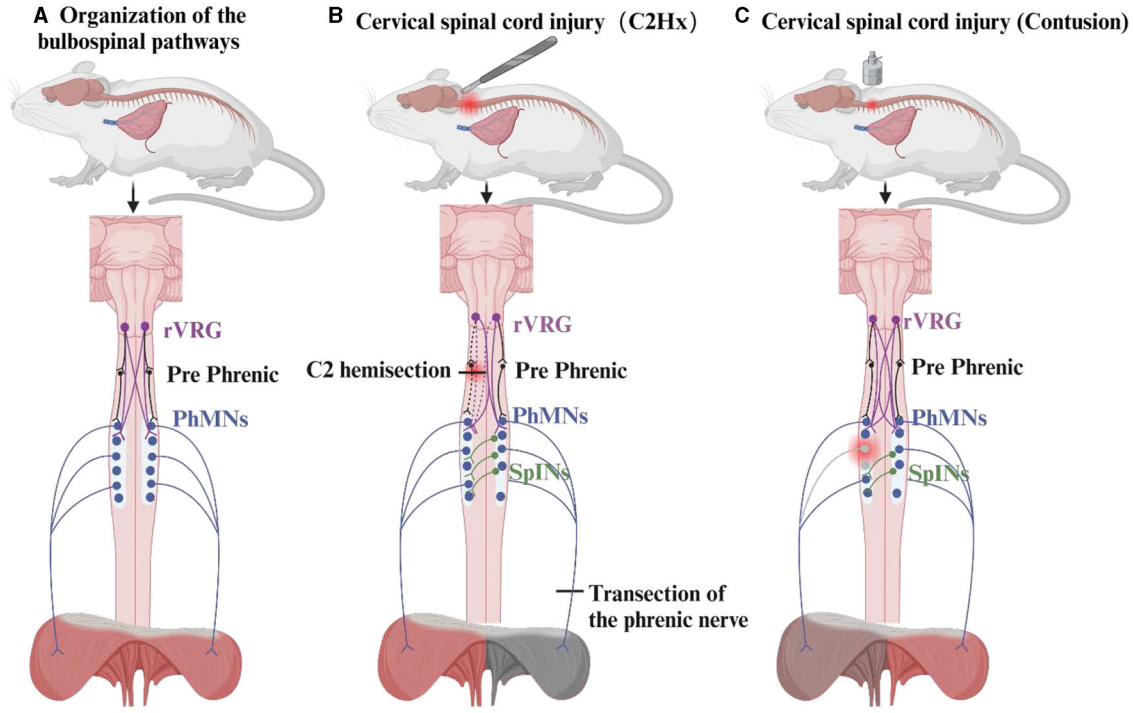

FIGURE 3
The organization of the bulbospinal pathways and the crossed phrenic phenomenon. The crossed phrenic phenomenon (CPP) of the C2 hemisection model and the contusion model are described here. **(A)** Composition of the respiratory pathway in the bulbospinal pathway. **(B)** CPP activated by the C2 hemisection model allows for recovery of the diaphragm on the side of the injury. **(C)** Activation of CPP in the cervical medullary contusion model resulted in mild damage to the diaphragm.

the C2 hemisection model, researchers have developed alternative models, including a cold block of the high cervical segment, C1 hemisection with the decerebrate brain, C2 hemisection with injury of the ventral lateral aspect, C4 hemisection, and contusion of the middle and high cervical segments, to replicate the plasticity of respiratory function observed in human SCI (Figure 3) (96). Recently, Vinit et al. demonstrated the presence of CPP by applying Transcranial Magnetic Stimulation (TMS) 1 h after the C2 injury, which resulted in evoked potentials in the diaphragm on the injured side (93).

3.3. Axonal regeneration

The regenerative capacity of axons is influenced by the distance between the injury site and the cell body. In the case of CSCI, the corticospinal tract has a lower potential for axonal regeneration compared to the bulbospinal tract (45). Axon resection in the bulbospinal pathway, resulting from C2 lateral spinal cord injury in rats, leads to degenerative changes. However, it can also trigger regenerative processes such as lateral sprouting or medial axonal remobilization (101). The recruitment of Spinal Interneurons (SpINs) at the C1 level was found to be increased when interacting with the bulbospinal pathway (101). Additionally, other substances have been discovered to promote axonal regeneration related to respiration. Phosphatase and tensin homologs promote substantial long-distance regeneration of rVRG axons after hemisection (102–104), but have less ability to restore diaphragm function. Chondroitinase ABC (ChABC) inhibits the up-regulation of chondroitin sulfate proteoglycans around phrenic motor neurons after spinal cord injury (24). When combined with autologous nerve grafts, ChABC restores functionality in paralyzed diaphragms (24). Consequently, the activation of SpINs and the use of axonal growth-promoting drugs are potential therapeutic strategies. However, the extent of axonal regeneration necessary for functional recovery remains largely unknown in most cases (105).

Further research is required to investigate supraspinal neurons and SpINs following CSCI, including studies on temporal alterations, impacts on diaphragm movement, and performance in various injury models.

4. Changes in respiratory function after CSCI

The coordination between the spinal cord, brainstem, and cerebral cortex is essential for the process of breathing. However, respiratory afferent and efferent pathways may be partially or completely disrupted following CSCI, leading to respiratory dysfunction. Figure 1 illustrates the altered respiratory function following CSCI.

4.1. Changes in breathing patterns

Following CSCI, patients may experience shallow and rapid breathing to maintain minute ventilation, but tidal volume tends to decrease under these circumstances (4, 100). Paralysis of the diaphragm due to SCI can result in defective breathing patterns such as paradoxical movements (106). During inspiration, the paralyzed diaphragm moves upward, while the abdomen moves inward as the accessory inspiratory muscles lift and the rib cage simultaneously expands, lowering intrathoracic pressure. This condition is more pronounced in the supine position.

4.2. Compensation of respiratory muscles

Damage to phrenic neurons after SCI can induce the expression of proteases and atrophy-related genes, leading to immediate atrophy of all types of diaphragm fibers (5). Moreover, early use of a ventilator can accelerate the atrophy of the diaphragm (107), and diaphragm contractility can decrease by up to 40% within 8 weeks after injury (108). Following SCI, compensatory hypertrophy of the diaphragm occurs due to a reduction in the diaphragmatic contraction rate (109). However, individuals of Chinese tend to exhibit less diaphragmatic hypertrophy than individuals of European or American descent (110). Accessory muscles such as the deltoid and trapezius play a crucial role in respiratory function following CSCI (14). In addition, the abdominal muscles are paralyzed and other muscles such as the latissimus dorsi and pectoralis major are activated during coughing (111). During respiratory muscle strength tests, the rhomboid muscle is more involved during the maximum inspiratory pressure test and the pectoralis major and latissimus dorsi are more involved during the maximum expiratory pressure test, compared to non-injured individuals (112).

4.3. Changes in pulmonary function

Pulmonary function often significantly improves within the initial 6-month period after injury and less so thereafter (113). Multiple factors, including the level, degree, and timing of injury, age, body position, and obesity, can influence changes in pulmonary function after CSCI (114, 115). Early improvements in respiratory function after SCI may be due to early edema subsidence, compensatory respiratory strategies, and altered respiratory muscle biomechanics. In contrast, for patients with chronic CSCI, age, persistent wheezing, and obesity are important factors affecting lung function. However, the degree and level of injury may not be one of the factors affecting pulmonary function in chronic spinal cord injury (116). A long-term follow-up found that age (>30 years) and BMI (>30 kg/m^2) as important factors affecting lung function after CSCI (117). A retrospective study of 339 patients with CSCI revealed that smoking, persistent wheezing, obesity, and MIP, as well as SCI levels and integrity, were significant determinants of lung function (118).

4.4. Increased frequency of sleep apnea

Although there are different criteria for evaluating sleep breathing disorders, the incidence of sleep apnea in patients with SCI was higher than in the healthy population, and the incidence of patients with tetraplegia was higher than in the paraplegic population (119, 120). The exact mechanism underlying sleep apnea after CSCI remains unclear, although some researchers have suggested associations with upper airway muscle inactivation, autonomic dysregulation, reduced lung volume, and modifications in brainstem plasticity or chemosensitivity (11, 121).

5. Magnetic resonance neuroimaging in respiratory structure and function after CSCI

In clinical practice, pulmonary function tests, chest computed tomography, chest fluoroscopy, chest radiography, diaphragmatic ultrasound, diaphragmatic electromyography, and phrenic nerve stimulation are used to evaluate the lung function of patients with CSCI (110, 122, 123). However, these methods only offer localized information on respiratory function and do not serve as a benchmark for changes in spinal cord and respiratory center structures and functions. In recent times, nuclear magnetic imaging methods such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and diffusion tensor imaging (DTI) have provided insights into the structure and function of the brain and spinal cord following SCI, enabling non-invasive visualization of the brainstem. These imaging techniques facilitate the evaluation of brain and spinal cord structure and function, prediction of neurological function, and assessment of treatment effectiveness (124, 125).

5.1. Structure MRI

Structural brain volume data can be obtained from T1-weighted images in MRI, and mathematical algorithms can be used to extract relevant brain features and perform statistical analysis of brain volume, morphology, and surface area (126). The reorganization of gray matter is caused by cell atrophy or apoptosis after axon transection, while the changes in white matter are caused by axon demyelination and deformation (127).

Following acute injury, the anatomy and organization of the spinal cord undergo significant changes. Several studies have shown that there is a reduction in the area and width of the cervical medulla, changes in the gray matter of the primary cortex and limbic system (50, 128), and a reduction in the dorsal pyramidal tract of the medulla oblongata and the white matter of the cerebellar peduncle (129) in the acute phase. These changes may result in clinical symptoms such as impairment of motor and sensory function.

In the subacute to chronic phase, atrophy and microstructural changes in the spinal cord proceed further. Progressive atrophy and microstructural changes occur in the thalamus, anterior cingulate gyrus, insula, pons, and secondary sensory cortex (130).

In the chronic phase after spinal cord injury, atrophy of the corticospinal tract and medial thalamic tract occurs, with reduced gray matter in the brainstem around the midbrain aqueduct, dorsal pons, and dorsal medulla oblongata myelin (131). A significant reduction in dorsal anterior spinal cord volume at the spinal medullary junction, is consistent with clinical histologic evidence (132). This may reflect the Wallerian degeneration of the associated axons after spinal cord injury. Extensive atrophy and microstructural changes are also observed in the cerebral tracts and sensory-motor cortical areas of the spinal cord at 2, 6, and 12 months after acute spinal cord injury (133). Furthermore, cortical gray and white matter volumes were reduced at the level of the medullary aqueducts compared to healthy controls at 12 months post-injury.

These findings suggest that structural changes in the spinal cord following acute spinal cord injury may be associated with respiratory dysfunction, particularly alterations in brainstem microstructure. However, further research is required to gain deeper insights into the mechanisms underlying these changes and their role in respiratory dysfunction.

5.2. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an imaging technique capable of quantifying atrophy, demyelination, and iron deposition within the spinal cord and cerebral cortex (134). It is widely used to assess spinal cord, brainstem, and brain alterations after CSCI (135–137). The diffusion of water molecules in neural tissues is mainly limited by cell membranes and myelin sheaths. When neurodegenerative lesions occur, the tissue produces more free water, leading to re-diffusion perpendicular to the white matter (124). Parameters commonly used in DTI include fractional anisotropy (FA), mean diffusivity (MD), and apparent diffusion coefficient (ADC). The definitions of these parameters can be found in more detail in the literature (124).

In the acute phase, a significant decrease in FA and an increase in MD at the level of injury can be observed after SCI, but changes in ADC are controversial (124, 138). Similarly, a decrease in FA values at the lesion level and in the upper cervical spinal cord can also be observed in the chronic phase (136, 139–142). A long-term follow-up study revealed worrisome results: gray matter below the C2/3 level decreased by 0.7% per month and white matter by 0.34% per month (143). At the level of the cerebral peduncle, individuals with cervical ASIA A/B SCI showed greater degrees of axonal damage and edema/tissue loss, but no statistical differences were found in whole-brain white matter compared to healthy individuals (144). Of concern is that spinal cord injuries also cause changes in the white matter of the brain. A DTI study found that chronic SCI has a wide range of neurodegenerative effects in the brain that are not limited to motor pathways (145). Meanwhile, patients with CSCI in the chronic phase continue to experience a slow decline in degenerative FA in the midbrain, pontine, and superior white matter of the medulla, while MD keeps increasing, probably because of cumulative cell membrane loss caused by delayed damage to glial cells or axons (146).

In addition, DTI can also be used to assess treatment efficacy. Gu et al. used DTI and immunohistochemistry to assess the efficacy of axonal regeneration, and DTI reflects the center of injury as well as the immediate condition of neural damage and the process of axonal regeneration (147). Zhang et al. used DTI to explore the efficacy of vocal therapy on respiratory function in patients with CSCI and found that neural networks related to respiration in the medulla and cortex became more active (148). To some extent, this reflects the treatment-facilitated recovery process in the brainstem and brain-related respiratory nerves. The combined application of DTI and fMRI enables central pathway monitoring and treatment evaluation (149).

In summary, scientific studies have provided valuable insights into the altered state of the spinal cord and brain following acute and chronic spinal cord injury. However, the understanding of these changes remains somewhat controversial, and further research is needed to explore the mechanisms and clinical implications in depth.

5.3. Functional MRI

The aforementioned techniques are primarily utilized to evaluate structural changes. It is equally crucial to assess the functional reorganization of the brain and spinal cord. While fMRI can detect alterations in blood oxygen level-dependent (BOLD) signals, the pattern of these changes is expected to be utilized in assessing the ability to reorganize function (125, 150).

Acute SCI patients have decreased functional connections between the bilateral primary sensory cortex and motor cortex, while functional connections increase between primary sensorimotor cortex, premotor cortex, supplementary motor area, thalamus, and cerebellum (151). Patients with advanced SCI may have changes in cognitive-related areas, such as increased functional connections between the dorsal anterior cingulate cortex and the motor cortex (152). Various studies have found that the classic somatosensory pathway degenerates (153) and reorganizes (154, 155) after SCI, meaning that the spinal thalamic tract or dorsal tract transmits sensory signals to the thalamus, which is transformed and projected to the primary sensory cortex. Others have found that sensory input in patients with incomplete CSCI may be mediated by alternative pathways, which may consist of the ipsilateral cerebellum, pons, and contralateral posterior central gyrus (127). In patients with incomplete spinal cord injury, the visual cortex supplements sensory and motor inputs (156). Many studies have found that the cerebellum is important for activation after SCI (157). The functional connections between the cerebellum and primary motor cortex, primary sensory cortex, and primary auditory cortex can be found in patients with complete injury (151, 152, 158). In patients with chronic CSCI, whole-brain network connectivity is reduced, and increased connectivity is observed in the subnetworks of the sensory-motor cortex and cerebellum (159). Although the cerebellum is not a region of respiration in the traditional sense, we speculate that the cerebellum may play an important role in respiratory sensory and motor function after SCI.

Respiration-related fMRI investigations primarily focus on the influence of subcortical structures. Studies have shown that respiratory control is connected to brainstem and subcortical activity, with many indicating the maintenance of connectivity between cortical and brainstem regions (53, 54, 160). Pattinson et al. identified regions of the brainstem and thalamus in healthy subjects that respond to CO_2 stimulation by fMRI and diffusion fiber tracing. They explored a link between the thalamus and higher cortical tracts, suggesting that the thalamus can play a role in respiratory control, but the relationship between structure and function was not explored in this study (161). The brainstem could be studied by BOLD fMRI to observe characteristics of the respiratory center at rest and its corresponding mechanisms (162). There are fewer fMRI studies on respiration in patients with SCI, likely due to the challenging nature of conducting respiratory center fMRI owing to the unique anatomy and small size of the brainstem. Relevant atlases are lacking, and physiological noise from cerebrospinal fluid and arteries obscures measurements near the brainstem (150, 163, 164). Nonetheless, researchers have explored several methods for brainstem fMRI data processing (55, 164, 165).

6. Concluding remarks

Traumatic spinal cord injury is a devastating and irreversible trauma. Despite the current advancements in clinical assessment, treatment, and medical management, such as rehabilitative care, patients still suffer significant neurological impairments. The focus of current research on cervical spinal cord injury is the restoration of respiratory function. From basic clinical studies, most of them have focused on respiratory plasticity at the spinal cord level, revealing the neuroplasticity of the respiratory network after cervical cord injury. However, the respiratory plasticity of structures above the spinal cord remains incompletely understood. In recent years, the use of MRI in traumatic spinal cord injury has shifted from clinical assessment to neuroimaging biomarkers (125). MRI can elucidate the injury mechanism, assess its extent, and serve as a surrogate endpoint for clinical trials. Previous studies have shown that brain reorganization following SCI primarily occurs through compensatory sensory connections in the auditory or visual cortex and cerebellar function. Zhang et al. also demonstrated that vocal breathing training improved respiratory function more in CSCI patients (148). Further research is needed to explore whether increasing sensory inputs in the visual, auditory, and other pathways during respiratory function training can enhance therapeutic outcomes (25). Additionally, the role of the cerebellum, which has been neglected in the past, should be considered. However, the study of respiratory function in cervical cord injury is still in its early and exploratory stages, with many pressing challenges to address in future research. Firstly, large-scale follow-up studies are lacking to provide comprehensive insight into disease progression. Secondly, SCI patients may experience long-term complications such as spasticity and neuropathic pain, which may cause changes in brain function, emphasizing the need to remain focused on injury severity, time after injury, recovery time, and the effects of drug intervention (166). Thirdly, smaller anatomical changes in the brainstem cannot be detected after SCI. Lastly, magnetic resonance neuroimaging shows that the brain undergoes reorganization after SCI, but it remains to be explored whether these changes are beneficial or harmful (167).

Magnetic resonance neuroimaging is expected to provide relevant evidence for respiratory plasticity and targeted treatment for CSCI, but this may require interdisciplinary research in neuroimaging, nuclear medicine, rehabilitation medicine, and other fields. The shortcomings of current magnetic resonance neuroimaging must be addressed while indicating new directions for the clinical treatment of respiratory issues in CSCI patients.

Author contributions

YX wrote the main manuscript text. LZ and RP completed extensive literature searches and reviews. The figures and tables were made by YX and SG. SG, HG, and MY did language modification. All authors contributed to the editorial process and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hao D, Du J, Yan L, He B, Qi X, Yu S, et al. Trends of epidemiological characteristics of traumatic spinal cord injury in China, 2009-2018. *Eur Spine J.* (2021) 30:3115–27. doi: 10.1007/s00586-021-06957-3

2. Eli I, Lerner DP, Ghogawala Z. Acute traumatic spinal cord injury. *Neurol Clin.* (2021) 39:471–88. doi: 10.1016/j.ncl.2021.02.004

3. Devivo MJ. Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord.* (2012) 50:365–72. doi: 10.1038/sc.2011.178

4. Goshgarian HG. The crossed phrenic phenomenon: a model for plasticity in the respiratory pathways following spinal cord injury. *J Appl Physiol.* (2003) 94:795–810. doi: 10.1152/japplphysiol.00847.2002

5. Gill LC, Ross HH, Lee KZ, Gonzalez-Rothi EJ, Dougherty BJ, Judge AR, et al. Rapid diaphragm atrophy following cervical spinal cord hemisection. *Respir Physiol Neurobiol.* (2014) 192:66–73. doi: 10.1016/j.resp.2013.12.006

6. Dicpinigaitis PV, Spungen AM, Bauman WA, Absgarten A, Almenoff PL. Bronchial hyperresponsiveness after cervical spinal cord injury. *Chest.* (1994) 105:1073–6. doi: 10.1378/chest.105.4.1073

7. Josefson C, Rekand T, Lundgren-Nilsson Å, Sunnerhagen KS. Respiratory complications during initial rehabilitation and survival following spinal cord injury in Sweden: a retrospective study. *Spinal Cord.* (2020) 59:659–64. doi: 10.1038/s41393-020-00549-6

8. Schilero GJ, Spungen AM, Bauman WA, Radulovic M, Lesser M. Pulmonary function and spinal cord injury. *Respir Physiol Neurobiol.* (2009) 166:129–41. doi: 10.1016/j.resp.2009.04.002

9. Zimmer MB, Nantwi K, Goshgarian HG. Effect of spinal cord injury on the respiratory system: basic research and current clinical treatment options. *J Spinal Cord Med.* (2007) 30:319–30. doi: 10.1080/10790268.2007.11753947

10. MacBean N, Ward E, Murdoch B, Cahill L, Solley M, Geraghty T. Characteristics of speech following cervical spinal cord injury. *J Med Speech Lang Pathol.* (2006) 14:167–85. Available online at: https://api.semanticscholar.org/CorpusID:73391237

11. Sankari A, Vaughan S, Bascom A, Martin JL, Badr MS. Sleep-disordered breathing and spinal cord injury: a state-of-the-art review. *Chest.* (2019) 155:438–45. doi: 10.1016/j.chest.2018.10.002

12. Sankari A, Bascom A, Oomman S, Badr MS. Sleep disordered breathing in chronic spinal cord injury. *J Clin Sleep Med.* (2014) 10:65–72. doi: 10.5664/jcsm.3362

13. Lane MA, Fuller DD, White TE, Reier PJ. Respiratory neuroplasticity and cervical spinal cord injury: translational perspectives. *Trends Neurosci.* (2008) 31:538–47. doi: 10.1016/j.tins.2008.07.002

14. Yang M, Tang L, Yang D, Chen L, Gong H, Li J. Correlation between residual strength of neck and shoulder muscles and respiratory function in patients with cervical spinal cord injury. *Chin J Rehabil Theory Pract.* (2017) 23:1308–12. doi: 10.3969/j.issn.1006-9771.2017.11.014

15. Bluechardt MH, Wiens M, Thomas SG, Plyley MJ. Repeated measurements of pulmonary function following spinal cord injury. *Paraplegia.* (1992) 30:768–74. doi: 10.1038/sc.1992.148

16. Locke KC, Randelman ML, Hoh DJ, Zholudeva LV, Lane MA. Respiratory plasticity following spinal cord injury: perspectives from mouse to man. *Neural Regen Res.* (2022) 17:2141–8. doi: 10.4103/1673-5374.335839

17. Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. *Annu Rev Neurosci.* (2003) 26:239–66. doi: 10.1146/annurev.neuro.26.041002.131103

18. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* (2003) 168:10–48. doi: 10.1164/rccm.2206020

19. Mitchell GS, Johnson SM. Neuroplasticity in respiratory motor control. *J Appl Physiol.* (2003) 94:358–74. doi: 10.1152/japplphysiol.00523.2002

20. Lane MA, Lee KZ, Fuller DD, Reier PJ. Spinal circuitry and respiratory recovery following spinal cord injury. *Respir Physiol Neurobiol.* (2009) 169:123–32. doi: 10.1016/j.resp.2009.08.007

21. Porter WT. The path of the respiratory impulse from the bulb to the phrenic nuclei. *J Physiol.* (1895) 17:455–85. doi: 10.1113/jphysiol.1895.sp000553

22. Nardone R, Höller Y, Brigo F, Seidl M, Christova M, Bergmann J, et al. Functional brain reorganization after spinal cord injury: systematic review of animal and human studies. *Brain Res.* (2013) 1504:58–73. doi: 10.1016/j.brainres.2012.12.034

23. Kokotilo KJ, Eng JJ, Curt A. Reorganization and preservation of motor control of the brain in spinal cord injury: a systematic review. *J Neurotrauma.* (2009) 26:2113–26. doi: 10.1089/neu.2008.0688

24. Alilain WJ, Horn KP, Hu H, Dick TE, Silver J. Functional regeneration of respiratory pathways after spinal cord injury. *Nature.* (2011) 475:196–200. doi: 10.1038/nature10199

25. Randelman M, Zholudeva LV, Vinit S, Lane MA. Respiratory training and plasticity after cervical spinal cord injury. *Front Cell Neurosci.* (2021) 15:700821. doi: 10.3389/fncel.2021.700821

26. David G, Mohammadi S, Martin AR, Cohen-Adad J, Weiskopf N, Thompson A, et al. Traumatic and nontraumatic spinal cord injury: pathological insights from neuroimaging. *Nat Rev Neurol.* (2019) 15:718–31. doi: 10.1038/s41582-019-0270-5

27. Betka S, Adler D, Similowski T, Blanke O. Breathing control, brain, and bodily self-consciousness: toward immersive digiceuticals to alleviate respiratory suffering. *Biol Psychol.* (2022) 171:108329. doi: 10.1016/j.biopsycho.2022.108329

28. Fogarty MJ, Mantilla CB, Sieck GC. Breathing: motor control of diaphragm muscle. *Physiology.* (2018) 33:113–26. doi: 10.1152/physiol.00002.2018

29. Schottelkotte KM, Crone SA. Forebrain control of breathing: anatomy and potential functions. *Front Neurol.* (2022) 13:1041887. doi: 10.3389/fneur.2022.1041887

30. Del Negro CA, Morgado-Valle C, Feldman JL. Respiratory rhythm: an emergent network property? *Neuron.* (2002) 34:821–30. doi: 10.1016/S0896-6273(02)00712-2

31. Eugenin J, Nicholls JG, Cohen LB, Muller KJ. Optical recording from respiratory pattern generator of fetal mouse brainstem reveals a distributed network. *Neuroscience.* (2006) 137:1221–7. doi: 10.1016/j.neuroscience.2005.10.053

32. Feldman JL, Del Negro CA. Looking for inspiration: new perspectives on respiratory rhythm. *Nat Rev Neurosci.* (2006) 7:232–42. doi: 10.1038/nrn1871

33. Mccrimmon DR, Monnier A, Hayashi F, Zuperku EJ. Pattern formation and rhythm generation in the ventral respiratory group. *Clin Exp Pharmacol Physiol.* (2000) 27:126–31. doi: 10.1046/j.1440-1681.2000.03193.x

34. Benarroch EE. Periaqueductal gray: an interface for behavioral control. *Neurology.* (2012) 78:210–7. doi: 10.1212/WNL.0b013e31823fcdee

35. Linnman C, Moulton EA, Barmettler G, Becerra L, Borsook D. Neuroimaging of the periaqueductal gray: state of the field. *Neuroimage.* (2012) 60:505–22. doi: 10.1016/j.neuroimage.2011.11.095

36. Browaldh N, Bautista TG, Dutschmann M, Berkowitz RG. The Kölliker-Fuse nucleus: a review of animal studies and the implications for cranial nerve function in humans. *Eur Arch Otorhinolaryngol.* (2016) 273:3505–10. doi: 10.1007/s00405-015-3861-9

37. Guyenet PG, Stornetta RL, Souza G, Abbott SBG, Shi Y, Bayliss DA. The retrotrapezoid nucleus: central chemoreceptor and regulator of breathing automaticity. *Trends Neurosci.* (2019) 42:807–24. doi: 10.1016/j.tins.2019.09.002

38. Zoccal DB, Furuya WI, Bassi M, Colombari DS, Colombari E. The nucleus of the solitary tract and the coordination of respiratory and sympathetic activities. *Front Physiol.* (2014) 5:238. doi: 10.3389/fphys.2014.00238

39. Smith JC, Abdala AP, Borgmann A, Rybak IA, Paton JF. Brainstem respiratory networks: building blocks and microcircuits. *Trends Neurosci.* (2013) 36:152–62. doi: 10.1016/j.tins.2012.11.004

40. Dutschmann M, Dick TE. Pontine mechanisms of respiratory control. *Compr Physiol.* (2012) 2:2443–69. doi: 10.1002/cphy.c100015

41. Nogués MA, Roncoroni AJ, Benarroch E. Breathing control in neurological diseases. *Clin Auton Res.* (2002) 12:440–9. doi: 10.1007/s10286-002-0067-1

42. Guyenet PG, Bayliss DA, Stornetta RL, Kanbar R, Shi Y, Holloway BB, et al. Interdependent feedback regulation of breathing by the carotid bodies and the retrotrapezoid nucleus. *J Physiol.* (2018) 596:3029–42. doi: 10.1113/JP274357

43. Smith JC. Respiratory rhythm and pattern generation: brainstem cellular and circuit mechanisms. *Handb Clin Neurol.* (2022) 188:1–35. doi: 10.1016/B978-0-323-91534-2.00004-7

44. Smith JC, Abdala AP, Koizumi H, Rybak IA, Paton JF. Spatial and functional architecture of the mammalian brain stem respiratory network: a hierarchy of three oscillatory mechanisms. *J Neurophysiol.* (2007) 98:3370–87. doi: 10.1152/jn.00985.2007

45. Kastner A, Matarazzo V. Neuroprotective and neurorestorative processes after spinal cord injury: the case of the bulbospinal respiratory neurons. *Neural Plast.* (2016) 2016:7692602. doi: 10.1155/2016/7692602

46. Ghali MGZ. Phrenic motoneurons: output elements of a highly organized intraspinal network. *J Neurophysiol.* (2018) 119:1057–70. doi: 10.1152/jn.00705.2015

47. Ikeda K, Kawakami K, Onimaru H, Okada Y, Yokota S, Koshiya N, et al. The respiratory control mechanisms in the brainstem and spinal cord: integrative views of the neuroanatomy and neurophysiology. *J Physiol Sci.* (2017) 67:45–62. doi: 10.1007/s12576-016-0475-y

48. Fukushi I, Yokota S, Okada Y. The role of the hypothalamus in modulation of respiration. *Respir Physiol Neurobiol.* (2019) 265:172–9. doi: 10.1016/j.resp.2018.07.003

49. Nuding SC, Segers LS, Baekey DM, Dick TE, Solomon IC, Shannon R, et al. Pontine-ventral respiratory column interactions through raphe circuits detected using multi-array spike train recordings. *J Neurophysiol.* (2009) 101:2943–60. doi: 10.1152/jn.91305.2008

50. Rushmore RJ, Wilson-Braun P, Papadimitriou G, Ng I, Rathi Y, Zhang F, et al. 3D exploration of the brainstem in 50-micron resolution MRI. *Front Neuroanat.* (2020) 14:40. doi: 10.3389/fnana.2020.00040

51. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. *J Physiol.* (2006) 570:407–20. doi: 10.1113/jphysiol.2005.098848

52. Ezure K, Tanaka I. Convergence of central respiratory and locomotor rhythms onto single neurons of the lateral reticular nucleus. *Exp Brain Res.* (1997) 113:230–42. doi: 10.1007/BF02450321

53. Mckay LC, Adams L, Frackowiak RS, Corfield DR. A bilateral cortico-bulbar network associated with breath holding in humans, determined by functional magnetic resonance imaging. *Neuroimage.* (2008) 40:1824–32. doi: 10.1016/j.neuroimage.2008.01.058

54. Mckay LC, Evans KC, Frackowiak RS, Corfield DR. Neural correlates of voluntary breathing in humans. *J Appl Physiol.* (2003) 95:1170–8. doi: 10.1152/japplphysiol.00641.2002

55. Ciumas C, Rheims S, Ryvlin P. fMRI studies evaluating central respiratory control in humans. *Front Neural Circ.* (2022) 16:982963. doi: 10.3389/fncir.2022.982963

56. Lipski J, Bektas A, Porter R. Short latency inputs to phrenic motoneurones from the sensorimotor cortex in the cat. *Exp Brain Res.* (1986) 61:280–90. doi: 10.1007/BF00239518

57. Gandevia SC, Rothwell JC. Activation of the human diaphragm from the motor cortex. *J Physiol.* (1987) 384:109–18. doi: 10.1113/jphysiol.1987.sp016445

58. Lissens MA, Vanderstraeten GG. Motor evoked potentials of the respiratory muscles in tetraplegic patients. *Spinal Cord.* (1996) 34:673–8. doi: 10.1038/sc.1996.122

59. Lissens MA. Motor evoked potentials of the human diaphragm elicited through magnetic transcranial brain stimulation. *J Neurol Sci.* (1994) 124:204–7. doi: 10.1016/0022-510X(94)90327-1

60. Khedr EM, Trakhan MN. Localization of diaphragm motor cortical representation and determination of corticodiaphragmatic latencies by using magnetic stimulation in normal adult human subjects. *Eur J Appl Physiol.* (2001) 85:560–6. doi: 10.1007/s004210100504

61. Colebatch JG, Adams L, Murphy K, Martin AJ, Lammertsma AA, Tochon-Danguy HJ, et al. Regional cerebral blood flow during volitional breathing in man. *J Physiol.* (1991) 443:91–103. doi: 10.1113/jphysiol.1991.sp018824

62. Sharshar T, Hopkinson NS, Jonville S, Prigent H, Carlier R, Dayer MJ, et al. Demonstration of a second rapidly conducting cortico-diaphragmatic pathway in humans. *J Physiol.* (2004) 560:897–908. doi: 10.1113/jphysiol.2004.061150

63. Tremoureux L, Raux M, Ranohavimparany A, Morélot-Panzini C, Pouget P, Similowski T. Electroencephalographic evidence for a respiratory-related cortical activity specific of the preparation of prephonatory breaths. *Respir Physiol Neurobiol.* (2014) 204:64–70. doi: 10.1016/j.resp.2014.06.018

64. Guyenet PG, Bayliss DA. Neural control of breathing and CO2 homeostasis. *Neuron.* (2015) 87:946–61. doi: 10.1016/j.neuron.2015.08.001

65. Mazzone SB, Undem BJ. Vagal afferent innervation of the airways in health and disease. *Physiol Rev.* (2016) 96:975–1024. doi: 10.1152/physrev.00039.2015

66. Ottaviani MM, Macefield VG. Structure and functions of the vagus nerve in mammals. *Compr Physiol.* (2022) 12:3989–4037. doi: 10.1002/cphy.c210042

67. Chan PY, Cheng CH, Hsu SC, Liu CY, Davenport PW, Von Leupoldt A. Respiratory sensory gating measured by respiratory-related evoked potentials in generalized anxiety disorder. *Front Psychol.* (2015) 6:957. doi: 10.3389/fpsyg.2015.00957

68. Farb NA, Segal ZV, Anderson AK. Attentional modulation of primary interoceptive and exteroceptive cortices. *Cereb Cortex.* (2013) 23:114–26. doi: 10.1093/cercor/bhr385

69. West JB, Luks AM. *West's Respiratory Physiology: The Essentials.* 10th ed. Philadelphia, PA: Wolters Kluwer.

70. Gainche L, Berlowitz DJ, Leguen M, Ruehland WR, O'donoghue FJ, Trinder J, et al. Nasal resistance is elevated in people with tetraplegia and is reduced by topical sympathomimetic administration. *J Clin Sleep Med.* (2016) 12:1487–92. doi: 10.5664/jcsm.6272

71. Miller AJ. The neurobiology of swallowing and dysphagia. *Dev Disabil Res Rev.* (2008) 14:77–86. doi: 10.1002/ddrr.12

72. De Troyer A, Boriek AM. Mechanics of the respiratory muscles. *Compr Physiol.* (2011) 1:1273–300. doi: 10.1002/cphy.c100009

73. Pilarski JQ, Leiter JC, Fregosi RF. Muscles of breathing: development, function, and patterns of activation. *Compr Physiol.* (2019) 9:1025–80. doi: 10.1002/cphy.c180008

74. Nicaise C, Putatunda R, Hala TJ, Regan KA, Frank DM, Brion JP, et al. Degeneration of phrenic motor neurons induces long-term diaphragm deficits following mid-cervical spinal contusion in mice. *J Neurotrauma.* (2012) 29:2748–60. doi: 10.1089/neu.2012.2467

75. Nicaise C, Frank DM, Hala TJ, Authelet M, Pochet R, Adriaens D, et al. Early phrenic motor neuron loss and transient respiratory abnormalities after unilateral cervical spinal cord contusion. *J Neurotrauma.* (2013) 30:1092–9. doi: 10.1089/neu.2012.2728

76. Lee KZ, Dougherty BJ, Sandhu MS, Lane MA, Reier PJ, Fuller DD. Phrenic motoneuron discharge patterns following chronic cervical spinal cord injury. *Exp Neurol.* (2013) 249:20–32. doi: 10.1016/j.expneurol.2013.08.003

77. Dougherty BJ, Lee KZ, Gonzalez-Rothi EJ, Lane MA, Reier PJ, Fuller DD. Recovery of inspiratory intercostal muscle activity following high cervical hemisection. *Respir Physiol Neurobiol.* (2012) 183:186–92. doi: 10.1016/j.resp.2012.06.006

78. Wen MH, Lee KZ. Diaphragm and intercostal muscle activity after mid-cervical spinal cord contusion in the rat. *J Neurotrauma.* (2018) 35:533–47. doi: 10.1089/neu.2017.5128

79. Zak I, Ghali MG, Britz G, Lee KZ. Pre-phrenic interneurons: characterization and role in phrenic pattern formation and respiratory recovery following spinal cord injury. *Respir Physiol Neurobiol.* (2019) 265:24–31. doi: 10.1016/j.resp.2018.09.005

80. Lipski J, Duffin J, Kruszewska B, Zhang X. Upper cervical inspiratory neurons in the rat: an electrophysiological and morphological study. *Exp Brain Res.* (1993) 95:477–87. doi: 10.1007/BF00227141

81. Lane MA, White TE, Coutts MA, Jones AL, Sandhu MS, Bloom DC, et al. Cervical prephrenic interneurons in the normal and lesioned spinal cord of the adult rat. *J Comp Neurol.* (2008) 511:692–709. doi: 10.1002/cne.21864

82. Ghali MG, Marchenko V. Dynamic changes in phrenic motor output following high cervical hemisection in the decerebrate rat. *Exp Neurol.* (2015) 271:379–89. doi: 10.1016/j.expneurol.2015.06.002

83. De Troyer A, Kirkwood PA, Wilson TA. Respiratory action of the intercostal muscles. *Physiol Rev.* (2005) 85:717–56. doi: 10.1152/physrev.00007.2004

84. Streeter KA, Sunshine MD, Patel SR, Gonzalez-Rothi EJ, Reier PJ, Baekey DM, et al. Mid-cervical interneuron networks following high cervical spinal cord injury. *Respir Physiol Neurobiol.* (2020) 271:103305. doi: 10.1016/j.resp.2019.103305

85. Streeter KA, Sunshine MD, Patel S, Gonzalez-Rothi EJ, Reier PJ, Baekey DM, et al. Intermittent hypoxia enhances functional connectivity of midcervical spinal interneurons. *J Neurosci.* (2017) 37:8349–62. doi: 10.1523/JNEUROSCI.0992-17.2017

86. Saywell SA, Ford TW, Meehan CF, Todd AJ, Kirkwood PA. Electrophysiological and morphological characterization of propriospinal interneurons in the thoracic spinal cord. *J Neurophysiol.* (2011) 105:806–26. doi: 10.1152/jn.00738.2010

87. Bareyre FM, Kerschensteiner M, Raineteau O, Mettenleiter TC, Weinmann O, Schwab ME. The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nat Neurosci.* (2004) 7:269–77. doi: 10.1038/nn1195

88. Ellenberger HH, Feldman JL. Brainstem connections of the rostral ventral respiratory group of the rat. *Brain Res.* (1990) 513:35–42. doi: 10.1016/0006-8993(90)91086-V

89. Bezdudnaya T, Marchenko V, Zholudeva LV, Spruance VM, Lane MA. Supraspinal respiratory plasticity following acute cervical spinal cord injury. *Exp Neurol.* (2017) 293:181–9. doi: 10.1016/j.expneurol.2017.04.003

90. Buttry JL, Goshgarian HG. Injection of WGA-Alexa 488 into the ipsilateral hemidiaphragm of acutely and chronically C2 hemisected rats reveals activity-dependent synaptic plasticity in the respiratory motor pathways. *Exp Neurol.* (2014) 261:440–50. doi: 10.1016/j.expneurol.2014.07.016

91. Filli L, Engmann AK, Zörner B, Weinmann O, Moraitis T, Gullo M, et al. Bridging the gap: a reticulo-propriospinal detour bypassing an incomplete spinal cord injury. *J Neurosci.* (2014) 34:13399–410. doi: 10.1523/JNEUROSCI.0701-14.2014

92. Vinit S, Keomani E, Deramaudt TB, Spruance VM, Bezdudnaya T, Lane MA, et al. Interdisciplinary approaches of transcranial magnetic stimulation applied to a respiratory neuronal circuitry model. *PLoS ONE.* (2014) 9:e113251. doi: 10.1371/journal.pone.0113251

93. Vinit S, Keomani E, Deramaudt TB, Bonay M, Petitjean M. Reorganization of respiratory descending pathways following cervical spinal partial section investigated by transcranial magnetic stimulation in the rat. *PLoS ONE.* (2016) 11:e0148180. doi: 10.1371/journal.pone.0148180

94. Kjell J, Olson L. Rat models of spinal cord injury: from pathology to potential therapies. *Dis Model Mech.* (2016) 9:1125–37. doi: 10.1242/dmm.025833

95. Awad BI, Warren PM, Steinmetz MP, Alilain WJ. The role of the crossed phrenic pathway after cervical contusion injury and a new model to evaluate therapeutic interventions. *Exp Neurol.* (2013) 248:398–405. doi: 10.1016/j.expneurol.2013.07.009

96. Ghali MGZ. The crossed phrenic phenomenon. *Neural Regen Res.* (2017) 12:845–64. doi: 10.4103/1673-5374.208539

97. Lewis LJ, Brookhart JM. Significance of the crossed phrenic phenomenon. *Am J Physiol.* (1951) 166:241–54. doi: 10.1152/ajplegacy.1951.166.2.241

98. Vinit S, Darlot F, Stamegna JC, Sanchez P, Gauthier P, Kastner A. Long-term reorganization of respiratory pathways after partial cervical spinal cord injury. *Eur J Neurosci.* (2008) 27:897–908. doi: 10.1111/j.1460-9568.2008.06072.x

99. Fuller DD, Sandhu MS, Doperalski NJ, Lane MA, White TE, Bishop MD, et al. Graded unilateral cervical spinal cord injury and respiratory motor recovery. *Respir Physiol Neurobiol.* (2009) 165:245–53. doi: 10.1016/j.resp.2008.12.010

100. Golder FJ, Mitchell GS. Spinal synaptic enhancement with acute intermittent hypoxia improves respiratory function after chronic cervical spinal cord injury. *J Neurosci.* (2005) 25:2925–32. doi: 10.1523/JNEUROSCI.0148-05.2005

101. Darlot F, Cayetanot F, Gauthier P, Matarazzo V, Kastner A. Extensive respiratory plasticity after cervical spinal cord injury in rats: axonal sprouting and rerouting of ventrolateral bulbospinal pathways. *Exp Neurol.* (2012) 236:88–102. doi: 10.1016/j.expneurol.2012.04.004

102. Cheng L, Sami A, Ghosh B, Goudsward HJ, Smith GM, Wright MC, et al. Respiratory axon regeneration in the chronically injured spinal cord. *Neurobiol Dis.* (2021) 155:105389. doi: 10.1016/j.nbd.2021.105389

103. Du K, Zheng S, Zhang Q, Li S, Gao X, Wang J, et al. Pten deletion promotes regrowth of corticospinal tract axons 1 year after spinal cord injury. *J Neurosci.* (2015) 35:9754–63. doi: 10.1523/JNEUROSCI.3637-14.2015

104. Urban MW, Ghosh B, Block CG, Strojny LR, Charsar BA, Goulão M, et al. Long-distance axon regeneration promotes recovery of diaphragmatic respiratory function after spinal cord injury. *eNeuro.* (2019) 6:ENEURO.0096-19.2019. doi: 10.1523/ENEURO.0096-19.2019

105. Bradbury EJ, Mcmahon SB. Spinal cord repair strategies: why do they work? *Nat Rev Neurosci.* (2006) 7:644–53. doi: 10.1038/nrn1964

106. McCMcCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Engl J Med.* (2012) 366:932–42. doi: 10.1056/NEJMra1007236

107. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* (2008) 358:1327–35. doi: 10.1056/NEJMoa070447

108. Mantilla CB, Greising SM, Zhan WZ, Seven YB, Sieck GC. Prolonged C2 spinal hemisection-induced inactivity reduces diaphragm muscle specific force with modest, selective atrophy of type IIx and/or IIb fibers. *J Appl Physiol.* (2013) 114:380–6. doi: 10.1152/japplphysiol.01122.2012

109. Malas FÜ, Köseoğlu F, Kara M, Ece H, Aytekin M, Öztürk GT, et al. Diaphragm ultrasonography and pulmonary function tests in patients with spinal cord injury. *Spinal Cord.* (2019) 57:679–83. doi: 10.1038/s41393-019-0275-3

110. Zhu Z, Li J, Yang D, Du L, Yang M. Ultrasonography of diaphragm can predict pulmonary function in spinal cord injury patients: a pilot case-control study. *Med Sci Monit.* (2019) 25:5369–74. doi: 10.12659/MSM.917992

111. Fujiwara T, Hara Y, Chino N. Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. *Am J Phys Med Rehabil.* (1999) 78:464–9. doi: 10.1097/00002060-199909000-00009

112. Terson de Paleville D, Lorenz D. Compensatory muscle activation during forced respiratory tasks in individuals with chronic spinal cord injury. *Respir Physiol Neurobiol.* (2015) 217:54–62. doi: 10.1016/j.resp.2015.07.001

113. Mueller G, De Groot S, Van Der Woude L, Hopman MT. Time-courses of lung function and respiratory muscle pressure generating capacity after spinal cord injury: a prospective cohort study. *J Rehabil Med.* (2008) 40:269–76. doi: 10.2340/16501977-0162

114. Postma K, Haisma JA, De Groot S, Hopman MT, Bergen MP, Stam HJ, et al. Changes in pulmonary function during the early years after inpatient rehabilitation in persons with spinal cord injury: a prospective cohort study. *Arch Phys Med Rehabil.* (2013) 94:1540–6. doi: 10.1016/j.apmr.2013.02.006

115. Raab AM, De Groot S, Berlowitz DJ, Post MWM, Adriaansen J, Hopman M, et al. Development and validation of models to predict respiratory function in persons with long-term spinal cord injury. *Spinal Cord.* (2019) 57:1064–75. doi: 10.1038/s41393-019-0313-1

116. Stolzmann KL, Gagnon DR, Brown R, Tun CG, Garshick E. Longitudinal change in FEV1 and FVC in chronic spinal cord injury. *Am J Respir Crit Care Med.* (2008) 177:781–6. doi: 10.1164/rccm.200709-1332OC

117. Van Silfhout L, Peters AE, Berlowitz DJ, Schembri R, Thijssen D, Graco M. Long-term change in respiratory function following spinal cord injury. *Spinal Cord.* (2016) 54:714–9. doi: 10.1038/sc.2015.233

118. Jain NB, Brown R, Tun CG, Gagnon D, Garshick E. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. *Arch Phys Med Rehabil.* (2006) 87:1327–33. doi: 10.1016/j.apmr.2006.06.015

119. Brown RE, Basheer R, Mckenna JT, Strecker RE, Mccarley RW. Control of sleep and wakefulness. *Physiol Rev.* (2012) 92:1087–187. doi: 10.1152/physrev.00032.2011

120. Chiodo AE, Sitrin RG, Bauman KA. Sleep disordered breathing in spinal cord injury: a systematic review. *J Spinal Cord Med.* (2016) 39:374–82. doi: 10.1080/10790268.2015.1126449

121. Fuller DD, Lee KZ, Tester NJ. The impact of spinal cord injury on breathing during sleep. *Respir Physiol Neurobiol.* (2013) 188:344–54. doi: 10.1016/j.resp.2013.06.009

122. Boon AJ, O'gorman C. Ultrasound in the assessment of respiration. *J Clin Neurophysiol.* (2016) 33:112–9. doi: 10.1097/WNP.0000000000000240

123. Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, Brown R. Spirometry testing standards in spinal cord injury. *Chest.* (2003) 123:725–30. doi: 10.1378/chest.123.3.725

124. Zaninovich OA, Avila MJ, Kay M, Becker JL, Hurlbert RJ, Martirosyan NL. The role of diffusion tensor imaging in the diagnosis, prognosis, and assessment of recovery and treatment of spinal cord injury: a systematic review. *Neurosurg Focus.* (2019) 46:E7. doi: 10.3171/2019.1.FOCUS18591

125. Freund P, Seif M, Weiskopf N, Friston K, Fehlings MG, Thompson AJ, et al. MRI in traumatic spinal cord injury: from clinical assessment to neuroimaging biomarkers. *Lancet Neurol.* (2019) 18:1123–35. doi: 10.1016/S1474-4422(19)30138-3

126. Ashburner J, Csernansky JG, Davatzikos C, Fox NC, Frisoni GB, Thompson PM. Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol.* (2003) 2:79–88. doi: 10.1016/S1474-4422(03)00304-1

127. Chen Q, Zheng W, Chen X, Li X, Wang L, Qin W, et al. Reorganization of the somatosensory pathway after subacute incomplete cervical cord injury. *Neuroimage Clin.* (2019) 21:101674. doi: 10.1016/j.nicl.2019.101674

128. Seif M, Curt A, Thompson AJ, Grabher P, Weiskopf N, Freund P. Quantitative MRI of rostral spinal cord and brain regions is predictive of functional recovery in acute spinal cord injury. *Neuroimage Clin.* (2018) 20:556–63. doi: 10.1016/j.nicl.2018.08.026

129. Freund P, Weiskopf N, Ward NS, Hutton C, Gall A, Ciccarelli O, et al. Disability, atrophy and cortical reorganization following spinal cord injury. *Brain.* (2011) 134:1610–22. doi: 10.1093/brain/awr093

130. Grabher P, Callaghan MF, Ashburner J, Weiskopf N, Thompson AJ, Curt A, et al. Tracking sensory system atrophy and outcome prediction in spinal cord injury. *Ann Neurol.* (2015) 78:751–61. doi: 10.1002/ana.24508

131. Grabher P, Blaiotta C, Ashburner J, Freund P. Relationship between brainstem neurodegeneration and clinical impairment in traumatic spinal cord injury. *Neuroimage Clin.* (2017) 15:494–501. doi: 10.1016/j.nicl.2017.05.026

132. Hug A, Bernini A, Wang H, Lutti A, Jende JME, Böttinger M, et al. In chronic complete spinal cord injury supraspinal changes detected by quantitative MRI are confined to volume reduction in the caudal brainstem. *Neuroimage Clin.* (2021) 31:102716. doi: 10.1016/j.nicl.2021.102716

133. Freund P, Weiskopf N, Ashburner J, Wolf K, Sutter R, Altmann DR, et al. MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. *Lancet Neurol.* (2013) 12:873–81. doi: 10.1016/S1474-4422(13)70146-7

134. Zakszewski E, Schmit B, Kurpad S, Budde MD. Diffusion imaging in the rat cervical spinal cord. *J Vis Exp.* (2015) 52390. doi: 10.3791/52390-v

135. Kim JH, Song SK. Diffusion tensor imaging of the mouse brainstem and cervical spinal cord. *Nat Protoc.* (2013) 8:409–17. doi: 10.1038/nprot.2013.012

136. Petersen JA, Wilm BJ, Von Meyenburg J, Schubert M, Seifert B, Najafi Y, et al. Chronic cervical spinal cord injury: DTI correlates with clinical and electrophysiological measures. *J Neurotrauma.* (2012) 29:1556–66. doi: 10.1089/neu.2011.2027

137. Shanmuganathan K, Zhuo J, Chen HH, Aarabi B, Adams J, Miller C, et al. Diffusion tensor imaging parameter obtained during acute blunt cervical spinal cord injury in predicting long-term outcome. *J Neurotrauma.* (2017) 34:2964–71. doi: 10.1089/neu.2016.4901

138. D'souza MM, Choudhary A, Poonia M, Kumar P, Khush S. Diffusion tensor MR imaging in spinal cord injury. *Injury.* (2017) 48:880–4. doi: 10.1016/j.injury.2017.02.016

139. Ellingson BM, Ulmer JL, Kurpad SN, Schmit BD. Diffusion tensor MR imaging in chronic spinal cord injury. *Am J Neuroradiol.* (2008) 29:1976–82. doi: 10.3174/ajnr.A1272

140. Koskinen E, Brander A, Hakulinen U, Luoto T, Helminen M, Ylinen A, et al. Assessing the state of chronic spinal cord injury using diffusion tensor imaging. *J Neurotrauma.* (2013) 30:1587–95. doi: 10.1089/neu.2013.2943

141. Chang Y, Jung TD, Yoo DS, Hyun JK. Diffusion tensor imaging and fiber tractography of patients with cervical spinal cord injury. *J Neurotrauma.* (2010) 27:2033–40. doi: 10.1089/neu.2009.1265

142. Cohen-Adad J, El Mendili MM, Lehéricy S, Pradat PF, Blancho S, Rossignol S, et al. Demyelination and degeneration in the injured human spinal cord detected with diffusion and magnetization transfer MRI. *Neuroimage.* (2011) 55:1024–33. doi: 10.1016/j.neuroimage.2010.11.089

143. David G, Pfyffer D, Vallotton K, Pfender N, Thompson A, Weiskopf N, et al. Longitudinal changes of spinal cord grey and white matter following spinal cord injury. *J Neurol Neurosurg Psychiatry.* (2021) 92:1222–30. doi: 10.1136/jnnp-2021-326337

144. Sun P, Murphy RK, Gamble P, George A, Song SK, Ray WZ. Diffusion assessment of cortical changes, induced by traumatic spinal cord injury. *Brain Sci.* (2017) 7:21. doi: 10.3390/brainsci7020021

145. Ilvesmäki T, Koskinen E, Brander A, Luoto T, Öhman J, Eskol A, et al. Spinal cord injury induces widespread chronic changes in cerebral white matter. *Hum Brain Mapp.* (2017) 38:3637–47. doi: 10.1002/hbm.23619

146. Guleria S, Gupta RK, Saksena S, Chandra A, Srivastava RN, Husain M, et al. Retrograde Wallerian degeneration of cranial corticospinal tracts in cervical spinal cord injury patients using diffusion tensor imaging. *J Neurosci Res.* (2008) 86:2271–80. doi: 10.1002/jnr.21664

147. Gu M, Gao Z, Li X, Guo L, Lu T, Li Y, et al. Conditioned medium of olfactory ensheathing cells promotes the functional recovery and axonal regeneration after contusive spinal cord injury. *Brain Res.* (2017) 1654:43–54. doi: 10.1016/j.brainres.2016.10.023

148. Zhang XY, Yu WY, Teng WJ, Song YC, Yang DG, Liu HW, et al. Effect of vocal respiratory training on respiratory function and respiratory neural plasticity in patients with cervical spinal cord injury: a randomized controlled trial. *Neural Regen Res.* (2022) 17:1065–71. doi: 10.4103/1673-5374.324856

149. Freund P, Wheeler-Kingshott CA, Nagy Z, Gorgoraptis N, Weiskopf N, Friston K, et al. Axonal integrity predicts cortical reorganisation following cervical injury. *J Neurol Neurosurg Psychiatry.* (2012) 83:629–37. doi: 10.1136/jnnp-2011-301875

150. Leitch JK, Figley CR, Stroman PW. Applying functional MRI to the spinal cord and brainstem. *Magn Reson Imaging.* (2010) 28:1225–33. doi: 10.1016/j.mri.2010.03.032

151. Hou JM, Sun TS, Xiang ZM, Zhang JZ, Zhang ZC, Zhao M, et al. Alterations of resting-state regional and network-level neural function after acute spinal cord injury. *Neuroscience.* (2014) 277:446–54. doi: 10.1016/j.neuroscience.2014.07.045

152. Guo Y, Ge Y, Li J, Dou W, Pan Y. Impact of injury duration on a sensorimotor functional network in complete spinal cord injury. *J Neurosci Res.* (2022) 100:1765–74. doi: 10.1002/jnr.25069

153. Wang W, Tang S, Li C, Chen J, Li H, Su Y, et al. Specific brain morphometric changes in spinal cord injury: a voxel-based meta-analysis of white and gray matter volume. *J Neurotrauma.* (2019) 36:2348–57. doi: 10.1089/neu.2018.6205

154. Wrigley PJ, Siddall PJ, Gustin SM. New evidence for preserved somatosensory pathways in complete spinal cord injury: a fMRI study. *Hum Brain Mapp.* (2018) 39:588–98. doi: 10.1002/hbm.23868

155. Karunakaran KD, Yuan R, He J, Zhao J, Cui JL, Zang YF, et al. Resting-state functional connectivity of the thalamus in complete spinal cord injury. *Neurorehabil Neural Repair.* (2020) 34:122–33. doi: 10.1177/1545968319893299

156. Chen Q, Zheng W, Chen X, Li X, Wang L, Qin W, et al. Whether visual-related structural and functional changes occur in brain of patients with acute incomplete cervical cord injury: a multimodal based MRI study. *Neuroscience.* (2018) 393:284–94. doi: 10.1016/j.neuroscience.2018.10.014

157. Wang W, Xie W, Zhang Q, Liu L, Liu J, Zhou S, et al. Reorganization of the brain in spinal cord injury: a meta-analysis of functional MRI studies. *Neuroradiology.* (2019) 61:1309–18. doi: 10.1007/s00234-019-02272-3

158. Hawasli AH, Rutlin J, Roland JL, Murphy RKJ, Song SK, Leuthardt EC, et al. Spinal cord injury disrupts resting-state networks in the human brain. *J Neurotrauma.* (2018) 35:864–73. doi: 10.1089/neu.2017.5212

159. Kaushal M, Oni-Orisan A, Chen G, Li W, Leschke J, Ward BD, et al. Evaluation of whole-brain resting-state functional connectivity in spinal cord injury: a large-scale network analysis using network-based statistic. *J Neurotrauma.* (2017) 34:1278–82. doi: 10.1089/neu.2016.4649

160. Peiffer C, Poline JB, Thivard L, Aubier M, Samson Y. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med.* (2001) 163:951–7. doi: 10.1164/ajrccm.163.4.2005057

161. Pattinson KT, Mitsis GD, Harvey AK, Jbabdi S, Dirckx S, Mayhew SD, et al. Determination of the human brainstem respiratory control network and its cortical connections in vivo using functional and structural imaging. *Neuroimage.* (2009) 44:295–305. doi: 10.1016/j.neuroimage.2008.09.007

162. Wei P, Li J, Gao F, Ye D, Zhong Q, Liu S. Resting state networks in human cervical spinal cord observed with fMRI. *Eur J Appl Physiol.* (2010) 108:265–71. doi: 10.1007/s00421-009-1205-4

163. Beissner F. Functional MRI of the brainstem: common problems and their solutions. *Clin Neuroradiol.* (2015) 25(Suppl. 2):251–7. doi: 10.1007/s00062-015-0404-0

164. Beissner F, Schumann A, Brunn F, Eisenträger D, Bär KJ. Advances in functional magnetic resonance imaging of the human brainstem. *Neuroimage.* (2014) 86:91–8. doi: 10.1016/j.neuroimage.2013.07.081

165. Harvey AK, Pattinson KT, Brooks JC, Mayhew SD, Jenkinson M, Wise RG. Brainstem functional magnetic resonance imaging: disentangling signal from physiological noise. *J Magn Reson Imaging.* (2008) 28:1337–44. doi: 10.1002/jmri.21623

166. Guo Y, Gao F, Guo H, Yu W, Chen Z, Yang M, et al. Cortical Morphometric changes associated with completeness, level, and duration of spinal cord injury in humans: a case-control study. *Brain Behav.* (2021) 11:e02037. doi: 10.1002/brb3.2037

167. Dunlop SA. Activity-dependent plasticity: implications for recovery after spinal cord injury. *Trends Neurosci.* (2008) 31:410–8. doi: 10.1016/j.tins.2008.05.004

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Effects of vestibular rehabilitation training combined with anti-vertigo drugs on vertigo and balance function in patients with vestibular neuronitis: a systematic review and meta-analysis

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Objective: To investigate the effects of vestibular rehabilitation training (VRT) combined with anti-vertigo drugs on vertigo and balance function in patients with vestibular neuronitis (VN).

Data sources: PubMed, EMBASE, The Cochrane Library, Web of Science, CNKI, Wan Fang Data, VIP, and CBM were searched until July 13, 2023.

Participants: Patients with vestibular neuronitis participated in the study.

Results: Twenty one studies including 1,415 patients were included in this review for meta-analysis. According to the Physiotherapy Evidence Database (PEDro) quality assessment, four studies received high quality (≥seven scores) and 17 studies received moderate quality (six scores). The meta-analysis showed that VRT combined with anti-vertigo drugs significantly reduced the Dizziness Handicap Inventory (DHI) score, the Vestibular Disorders Activities of Daily Living Scale (VADL) score and the Canal Paresis (CP) score, and improved the overall efficiency and the Berg Balance Scale (BBS) score, promoting vestibular evoked myogenic potentials (VEMPs) returned to normal in VN compared to simple anti-vertigo drugs or VRT alone.

Conclusion: The results of this meta-analysis demonstrate the efficacy and safety of VRT combined with anti-vertigo drugs in patients with VN. Combined therapy can alleviate vestibular dysfunction such as vertigo and vomiting in patients, improve daily activity ability and balance ability, in addition to VRT has fewer adverse reactions, so it is extremely safe. However, there are shortcomings such as lack of long-term follow-up and different frequency and duration of treatment. Therefore, future randomized controlled trials (RCTs) with larger sample sizes and longer-term observations are needed to verify the effectiveness of VRT in combination with anti-vertigo drugs for VN.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/

KEYWORDS

vestibular rehabilitation training, anti-vertigo drugs, vestibular neuronitis, systematic review, meta-analysis

1. Introduction

Vestibular neuritis (VN) is a common disease in otolaryngology. It is an acute unilateral vestibular dysfunction syndrome caused by inflammation of the surrounding vestibular organs (1). According to current reports, VN is the most common external vestibular disorder causing vertigo after benign paroxysmal positional vertigo (BPPV) and Meniere disease (MD) (2). The overall incidence of VN is 3.2 to 9% of all vertigo, and according to research statistics, the annual incidence of VN in Croatia is about 11.7 per 100,000 to 15.5 per 10,000 (3), mainly in middle-aged and elderly people, and the incidence of female is higher than that of male (4). The clinical manifestations of VN are acute onset, lasting more than 24 h, often accompanied by primary symptoms such as nausea, vomiting, vertigo, nystagmus, and postural instability, but without hearing impairment and central nervous system involvement (5–7), symptoms gradually resolve in most patients after a few weeks. Hypertension, diabetes, hyperlipidemia, hypothyroidism and other diseases are the common complications of VN (3). Acute symptoms such as primary vertigo and complications lead to increased physical symptoms in VN patients, negatively affecting their recovery and seriously reducing their quality of life (8).

At present, the diagnosis and treatment of VN lacks unified standards and norms, and most cases rely on exclusion methods for clinical diagnosis and treatment, which needs to be distinguished from BPPV, MD, and other diseases. And the etiology and pathogenesis of VN are unknown, but some studies have suggested that the pathogenesis may be related to the reactivation of herpes simplex virus type I in vestibular ganglia (9, 10). Some scholars have suggested that the cause of VN may be related to autoimmunity (11). Milionis' study (12) has showed that C-reactive protein, fibrinogen, interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) in VN patients were higher than those in healthy subjects. In addition, vascular occlusion ischemia and other cardiovascular factors may also be the cause of VN (13). Xiong et al. (14) has found that serum 25-(OH)D at physiological concentration is a protective factor for VN, but low levels of serum 25-(OH)D are associated with the onset of VN. It is worth mentioning that VN is mostly unilateral and involves the superior vestibular nerve, but rarely involves the inferior vestibular nerve alone, which may be related to its anatomical structure (15).

The treatment of VN is mainly divided into drug therapy and non-drug therapy. Medications, including steroids (methylprednisolone, prednisolone, dexamethasone), antihistamine drugs (promethazine), histamines (betahistine), endogenous coenzyme b12 (mecobalamin) and alkaline drugs (sodium bicarbonate), are the most commonly used. Currently, the mechanism of drug treatment of VN mainly includes: Firstly, anti-vertigo drugs can interact with inflammatory transcription factors, thereby inhibiting pro-inflammatory molecules, reducing the number of inflammatory cells (16), effectively reducing the inflammatory response of vestibular nerve, and promoting the recovery of vestibular nerve injury. Secondly, anti-vertigo drugs can accelerate the compensation of vestibular function by the central nervous system. It has been proved in animal experiments (17, 18) that glucocorticoids can effectively promote central compensation. However, drug treatment may have some adverse effects, such as indigestion, mood swings, high blood sugar and even stomach ulcers with bleeding (19). Therefore, we must find better methods to achieve better treatment results while reducing adverse reactions.

In 1972, McCabe first proposed that VRT could reduce recurrent and prolonged vertigo (20). VRT is an exercise-based treatment that promotes the emergence of vestibular compensation by repeatedly stimulating the vestibular system (21). In 2021, "Expert Consensus on Vestibular Rehabilitation" (22), as well as other related studies (23, 24), confirmed the effectiveness and reliability of VRT for VN through clinical trials. Studies have also shown that VRT combined with drug therapy for VN may be more effective than drug therapy (25) alone or simple VRT (26).

At present, there are many clinical studies on VRT combined with anti-vertigo drugs in the treatment of VN, but there are few systematic reviews (27, 28). Among them, Hidayati et al. (27) included four studies and compared steroid drugs combined with VRT with steroid drugs or VRT alone. However, the main content was the difference in efficacy between steroid drugs and VRT. The review finally concluded that there was no difference in long-term efficacy between the two. And whether to combine steroid drugs with VRT is an issue that needs to be considered. Most recently, Huang et al. (28) compared steroid drugs combined with VRT as an intervention method in the experimental group with steroid drugs in the control group, and the outcome indicators included DHI score, caloric lateralization and VEMPs. It was concluded that steroid drugs combined with VRT was more effective than steroid alone. However, there are few included studies and outcome indicators. There are many drugs currently used to treat VN, not just steroids. In addition, many clinical studies have shown that when VN patients feel vertigo, their balance ability and daily activities will also be greatly affected. We believe that this is the biggest worry and annoyance of VN patients, and it is also a priority problem for patients to solve during treatment. However, these two related meta-analyses only considered steroid medications and did not focus on relevant outcome measures such as balance and daily activities. Based on the above reviews, the goal of our meta-analysis was to analyze a large number of studies, so we developed inclusion criteria from different perspectives, expanded the sample size, and finally included 21 RCTs with a total of 1,425 subjects. In terms of outcome measurement, we included six outcome indicators, including DHI score, VADL score, CP score, BBS score, overall efficiency and VEMPs, to provide a more comprehensive analysis of results. The aim is to update and expand the efficacy and safety of VRT combined with anti-vertigo drugs in the treatment of VN, and to provide a more reliable basis for the follow-up clinical research.

2. Materials and methods

2.1. Search strategy

This review was reported in conformity to the Preferred Reporting Item for Systematic Review and Meta-analyses Statement. We searched PubMed, EMBASE, Web of science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Technology Periodical Database (VIP), Wan Fang Data, and China Biology Medicine (CBM) from the earliest available date until July 13, 2023. Chinese search keywords included "#1 vestibular neuronitis/vestibular nerve inflammation/acute peripheral vestibulopathy/episodic recurrent vertigo/vestibular neuropathy"; #2 "vestibular rehabilitation training/

vestibular rehabilitation/vestibular training/vestibular therapy/VRT/balance training." English search was conducted using keywords and their varies (Figure 1), including "vestibular neuronitis" and "vestibular rehabilitation training." The language was restricted to Chinese and English and the study type was only required to be a randomized controlled trial (RCT).

2.2. Inclusion criteria

After we reviewed relevant articles, eligibility criteria for this review based on PICOS frameworks (population, intervention, comparison, outcome, and study) were as follows: (1) Participants: RCTs of patients with VN which published in English or Chinese. Differences in sex, age, country, time, and race were not taken into account. (2) Intervention: VRT combined with anti-vertigo drugs (such as methylprednisolone, betahistine mesilate, dexamethasone sodium phosphate, promethazine, sodium bicarbonate, mecobalamin) administered to patients. (3) Comparison: Anti-vertigo drugs or VRT as a control intervention. (4) Outcome: At least one outcome index such as overall efficiency, Dizziness Handicap Inventory (DHI), Berg Balance Scale (BBS), Vestibular Evoked Myogenic Potentials (VEMPs), Vestibular Disorders Activities of Daily Living Scale (VADL), and Canal Paresis (CP) score.

2.3. Exclusion criteria

(1) Non-RCTs. (2) Test number ≤ 10 (Because fewer subjects may lead to inaccurate results. Here 10 represents 10 subjects in each group). (3) Unable to get full text or incomplete article data. (4) Both intervention methods were VRT.

2.4. Data extraction

Two authors (J.C. and Y.L.X.) screened studies according to inclusion and exclusion criteria and collected data independently. Information such as author name, year of publication, age of patients in the trial and control groups, sample size, intervention mode, treatment frequency, duration, and outcome were recorded. All studies are managed using Endnote X9. Differences are resolved by discussion or arbitration by a third reviewer (Z.X.L.).

2.5. Quality assessment

We assessed the quality of the literature using the Physicaltherapy Evidence Database (PEDro). The Pedro scale uses 11 criteria, each of which is rated "yes" or "no," with one point awarded for each response. The first item does not count toward the PEDro score, which is a total of 10 points. PEDro total score $\geq$ seven points is classified as high quality, five to six points is classified as medium quality, $\leq$ four points is classified as low quality. The scores were given independently by two reviewers (J.C. and Y.L.X.). If the results are inconsistent, they are discussed with a third reviewer (Z.X.L.).

Two reviewers (J.C. and Y.L.X.) also completed the risk of bias. The evaluation was based on the Cochrane Handbook for Systematic Review of Interventions, edition 5.3. Items include: (1) random sequence generation (selection bias). (2) allocation concealment (selection bias). (3) blinding of participants and personnel (performance bias). (4) blinding of outcome assessment (detection bias). (5) incomplete outcome data (attrition bias). (6) selective reporting (reporting bias). (7) other bias. The quality of the included studies was rated as low/unclear/high risk of bias (low risk of bias as "yes," high risk of bias as "no," otherwise was "unclear").

2.6. Statistical analysis

We developed inclusion/exclusion criteria for screening articles, followed by data extraction and quality assessment. We used StataMP 14.0 software to conduct meta-analysis and give the final results. For continuous data, mean difference (MD) and 95% confidence intervals (CI) were used when evaluating results using the same scale. Two statistical tests were used to assess inter-study heterogeneity. If $I^2 < 50\%$ or $p > 0.05$, it was considered low heterogeneity, and the fixed effects model was used to merge the data.

#1Vestibular Neuronitis[MeSH Terms]
#2(Vestibular Neuronitides[Title/Abstract]) OR (Neuritis, Vestibular[Title/Abstract]) OR (Vestibular Neuritides[Title/Abstract]) OR (Neuronitis, Vestibular[Title/Abstract]) OR (Vestibular Nerve Neuritis[Title/Abstract]) OR (Neuritides, Vestibular Nerve[Title/Abstract]) OR (Epidemic Neurolabyrinthitis[Title/Abstract]) OR (Epidemic Neurolabyrinthitides[Title/Abstract]) OR (Vestibular Nerve Inflammation[Title/Abstract]) OR (Inflammations, Vestibular Nerve[Title/Abstract]) OR (Subacute Vestibular Neuritis[Title/Abstract]) OR (Neuritides, Subacute Vestibular[Title/Abstract]) OR (Acute Peripheral Vestibulopathy[Title/Abstract]) OR (Acute Peripheral Vestibulopathies[Title/Abstract]) OR (Acute Vestibular Neuritis[Title/Abstract]) OR (Acute Vestibular Neuritides[Title/Abstract]) OR (Recurrent Vestibular Neuritis[Title/Abstract]) OR (Neuritides, Recurrent Vestibular[Title/Abstract]) OR (Vestibulopathy[Title/Abstract]) OR (Recurrent Vestibulopathy[Title/Abstract]) OR (Recurrent Vestibulopathies[Title/Abstract]) OR (Episodic Recurrent Vertigo[Title/Abstract]) OR (Episodic Recurrent Vertigos[Title/Abstract]) OR (Vestibular Neuropathy[Title/Abstract]) OR (Neuropathies, Vestibular[Title/Abstract])
#3 #1 OR #2
#4(Vestibular rehabilitation[Title/Abstract]) OR (Vestibular training[Title/Abstract]) OR (Vestibular rehabilitation training[Title/Abstract]) OR (Vestibular therapy[Title/Abstract]) OR (Vestibular rehabilitation therapy[Title/Abstract]) OR (VRT[Title/Abstract]) OR (Vestibular sense[Title/Abstract]) OR (Balance[Title/Abstract]) OR (Balance training [Title/Abstract]) OR (Equilibrium[Title/Abstract])
#5 #3 AND #4

FIGURE 1
Pubmed search history.

If $I^2 > 50\%$ or $p < 0.05$ implies high heterogeneity, a random effects model was used for meta-analysis and subgroup analysis or sensitivity analysis was considered to determine the source of heterogeneity. Overall efficiency was classified into two levels: (1) effective and (2) ineffective. Overall efficiency referred to the percentage of participants in the first two levels as a percentage of the total. Publication bias was studied by funnel plot and Egger's test was used to verify the bias of the funnel plot.

2.7. Trial sequential analysis

Meta-analyses often require multiple tests, and random errors can sometimes lead to false significance results when accumulating data, and the increased frequency of statistical tests in meta-analyses increases the likelihood of reporting such results. However, trial sequence analysis (TSA) overcomes the shortcomings of classical meta-analysis and corrects for the increase in type I errors.

Sequence analysis was performed using TSA.0.9.5.10 beta. If the Z-curve exceeds the traditional boundary, but does not cross the TSA boundary, it indicates a possible false positive error. If it intersects the TSA boundary, it indicates that the meta-analysis results are robust, even if RIS is not reached. The Z-curve does not intersect the traditional cutoff values and the TSA cutoff values, and a positive or negative conclusion cannot be drawn. The Z-curve intersects the zero line, indicating no significance. We set a 5% risk of type I error (α) and a 20% risk of type II error (β) to calculate the amount of information required, and reduced the relative risk (RRR) and control event rate by 20% based on the data from the meta-analysis.

3. Result

3.1. Selection and inclusion of studies

A total of 1,074 studies were initially screened (PubMed = 197, EMBASE = 121, The Cochrane Library = 92, Web of Science = 160, CNKI = 134, Wan Fang Data = 201, Vip = 125, CBM = 44). After primary searches from the databases, 700 articles were screened. After duplicates removed, reading the titles and abstracts, 648 articles were excluded. Full texts of 52 articles were retrieved, and 31 articles were excluded with reasons listed as the following: non-RCT ($n = 10$), test number ≤ 10 ($n = 3$), unavailable or faulty data ($n = 13$) and both intervention methods were VRT ($n = 5$). In the end, 21 RCTs were included. Three were written in English, 18 of which were written in Chinese. The detailed screening process was shown in Figure 2.

3.2. Characteristics of included studies

A total of 21 studies (25, 26, 29–47) involving 8 datasets were included. All of the studies were published between 2014 and 2023 in English or Chinese. The sample size ranged from 29 to 200. All experimental groups received VRT combined with anti-vertigo drugs. Among them, anti-vertigo drugs included methylprednisolone, dexamethasone, betahistine, sodium bicarbonate, mecobalamin, promethazine. The control groups underwent VRT or antivertigo therapy as did the experimental group. The primary outcomes included the overall efficiency, DHI score and BBS. The secondary outcomes included VEMPs, CP score, and VADL score. Characteristics of these studies are shown in Table 1. There was no significant difference in baseline data between the two groups.

3.3. Methodological quality of included studies

The quality of the included studies was evaluated according to the PEDro quality assessment scale, most of all had methodological deficiencies in the blinding of subjects, therapists, and assessors. Four studies obtained high quality and 17 studies obtained moderate quality, as detailed in Table 2.

3.4. Risk of bias in studies

The plot of the risk of bias for each included study are shown in Figure 3, whole trials are at low risk. All of 21 studies reported random sequence generation and were assessed as low risk. Eighteen studies were assessed as unclear risk, and 3 were assessed as low risk in the aspect of allocation concealment. In blinding of participants and personnel, total studies were assessed as unclear risk because of no report. What is more, 18 studies were assessed as unclear risk and 3 studies were assessed as low risk in the blinding of the outcome assessment. Of all these 21 studies were judged to be low risk in incomplete outcome data and selective reporting. Finally, 21 studies were assessed as unclear risk in other bias.

3.5. Publication bias

We used StataMP 14 to conduct publication bias analysis of Egger's test for DHI scores with RCTs >10. The Egger' test result showed $p < 0.05$, which might lead to publication bias, so it was corrected by the trim and fill analysis. The correction result is shown in Figure 4. There was no significant difference between the corrected result and the pre-corrected result, which proved that the funnel plot was basically symmetric and the results of this meta-analysis were stable without publication bias. In addition, most of the studies in this meta-analysis are from China, and although most of them have good correlation and reliability, it may still lead to national publication bias, which is a problem worthy of attention and needs to be solved in the future.

3.6. Trial sequential analysis

Ten RCTs (26, 32, 34, 35, 37, 38, 41, 42, 44, 46) reported the overall efficiency of the binary variable, which were analyzed sequentially, with a type I error of 5% and a statistical power of 80%. The information axis was set as the cumulative sample size, and the sample size was used as the expected information value (RIS). Figure 5 shows that the Z-curve crosses the conventional boundary value and the TSA boundary value, indicating that the results obtained from this meta-analysis are robust and the efficacy of VRT combined with anti-vertigo drugs in the treatment of VN is positive. Meantime, the penalty curve

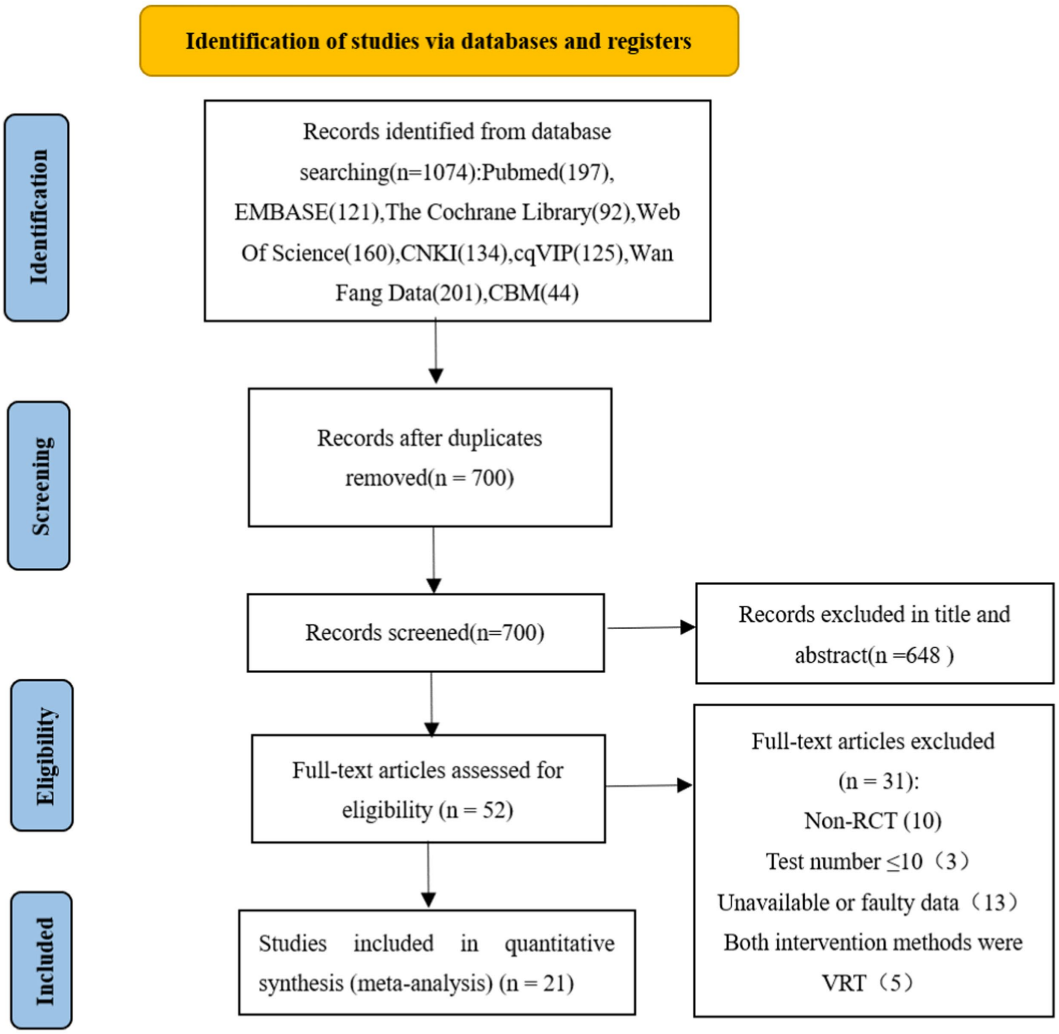

FIGURE 2
Flowchart of the selection process.

also exceeded the traditional boundary value and reached the RIS value, which made the meta-analysis result more stable.

3.7. Meta-analysis results

3.7.1. Primary outcomes

3.7.1.1. Result of the overall efficiency

A total of 10 studies (26, 32, 34, 35, 37, 38, 41, 42, 44, 46) evaluated 853 participants and reported overall efficiency. Data were pooled using a fixed effect model ($I^2 = 0\%$, $p = 0.978 > 0.05$) (Figure 6), and the result showed that VRT combined with anti-vertigo drugs was adequate for the treatment of VN compared with the control group [RR = 1.25, 95% CI (1.18, 1.32)].

3.7.1.2. Result of the DHI score

A total of 18 RCTs (25, 29–40, 42, 43, 46, 47), including 981 patients, reported DHI scores. The DHI scores of 18 studies were analyzed, showing statistical heterogeneity among the studies ($I^2 = 98.4\%$, $p < 0.0001$). The random effect model was used for meta-analysis. The results showed that the treatment effect of the experimental group was better than the control group [MD = −6.70, 95% CI (−8.49, −4.90)] (Figure 7A), which could prove that VRT combined with anti-vertigo drugs had a positive effect on relieving the degree of vertigo in VN patients. Because of the significant heterogeneity of DHI score, a subgroup analysis of initial DHI score (<15 points or ≥15 points) of VN patients showed that heterogeneity was reduced in both groups. We found that 7 RCTs with a total of 347 VN patients had an initial DHI score of <15 points, and VRT combined with anti-vertigo drugs significantly reduced DHI score compared with the control group[MD = −1.38, 95% CI (−1.71, −1.05), $I^2 = 41.6\%$, $p = 0.114 > 0.05$]. The initial DHI score of 634 VN patients in 11 RCTs was ≥15 points, and the results also showed that the combined group could better relieve the vertigo state of VN patients and reduce the DHI score [MD = −10.67, 95% CI (−11.25, −10.10), $I^2 = 8.8\%$, $p = 0.360 > 0.05$]. The results of subgroup analysis proved that VRT combined with anti-vertigo drugs had positive significance in improving the symptoms of patients. In addition, we can infer from the results that the higher the initial DHI score,

TABLE 1 Characteristics summary of included studies.

Study	Country	Experimental group				Control group				Drug dose and number of days	duration	Outcomes	Positive/ negative
		Age	Sample size	Intervention	Frequency	Age	Sample size	Intervention	Frequency				
Chen (40)	China	42.49 ± 1.25	19	VRT+ Methylprednisolone, Betahistine mesilate	2/day	42.52 ± 1.21	19	Methylprednisolone, Betahistine mesilate	1/day	20–80 mg/d, 36 mg/d, 9 days	9 days	B + E	+
Fan et al. (39)	China	37.2 ± 13.1	30	VRT + Prednisolone, Betahistine	3/day	36.6 ± 11.9	30	Prednisolone, Betahistine	3/day	1 mg/kg, 12 mg/d, NR	24 weeks	B + F	+
Goudakos et al. (25)	Greece	53.95	20	VRT+ Dexamethasone sodium phosphate	1/day	51.75	20	Dexamethasone sodium phosphate	1/day	24 mg/d, 14 days	2 weeks	B + D	+
Ismail et al. (29)	Egypt	49.1 ± 12.8	20	VRT + Methylprednisolone	1/day	47.9 ± 13.9	20	Methylprednisolone	3/day	60 mg/d, 2 weeks	6 weeks	B + D	+
Ismail et al. (29)	Egypt	49.1 ± 12.8	20	VRT + Methylprednisolone	1/day	49.3 ± 11.6	20	VRT	1/day	60 mg/d, 2 weeks	6 weeks	B + D	+
Li et al. (26)	China	41.36 ± 5.92	35	VRT + Prednisone	3/day	42.01 ± 5.64	35	VRT	2/day	30 mg/d, 4 weeks	4 weeks	A + C	+
Li (43)	China	40.48 ± 2.05	43	VRT+ Sodium Bicarbonate	2/day	41.03 ± 3.28	43	Sodium Bicarbonate	1-2/day	40 mL/d, 3–5 days	3–5 days	B + C	+
Liao et al. (47)	China	42.53 ± 10.15	15	VRT + Promethazine, Betahistine	2/day	43.6 ± 10.75	15	Promethazine, Betahistine	3/day	30 mg/d, 36 mg/d, NR	4 weeks	B	+
Liu et al. (42)	China	41.30 ± 5.11	25	VRT+ Betahistine, Methylprednisolone	1/day	40.18 ± 5.03	25	Betahistine, Methylprednisolone	3/day	36 mg/d, 20–80 mg/d, 2 weeks	NR	A + B + E	+
Lu et al. (38)	China	56.2 ± 0.8	25	VRT+ Betahistine, Methylprednisolone	1/day	55.6 ± 0.5	25	Betahistine, Methylprednisolone	3/day	36 mg/d, 20–80 mg/d, 2 weeks	2 weeks	A + B + E	+
Shen et al. (41)	China	45.2 ± 3.6	100	VRT+ Dexamethasone, Prednisone, mecobalamin	≥3/day	43.5 ± 2.7	100	Dexamethasone, Prednisone, mecobalamin	3/day	NR	NR	A	+
Wang et al. (45)	China	19–73	26	VRT+ Methylprednisolone	≥2/day	19–73	24	Methylprednisolone	3/day	20–80 mg/d, 9 days	4 weeks	D + F	+
Wang et al. (31)	China	41.30 ± 6.25	35	VRT+ Betahistine, Prednisone	3/day	41.26 ± 6.38	35	Betahistine, Prednisone	3/day, 1/day	36 mg/d, 30 mg/d, 5 days	4 weeks	B + F	+
Wu (33)	China	39.17 ± 4.25	32	VRT+ Betahistine, Prednisone	NR	38.46 ± 3.79	32	Betahistine, Prednisone	3/day	18 mg/d, 1 mg/kg, NR	NR	B + C + E	+
Xu et al. (32)	China	47.3 ± 3.4	50	VRT+ Methylprednisolone	2-3/day	48.5 ± 3.5	50	Methylprednisolone	NR	20-80 mg/d, 9 days	4 weeks	A + B + E	+
Yan et al. (46)	China	47.8 ± 2.0	28	VRT+ Betahistine, Prednisone	3/day	49.2 ± 1.6	20	Betahistine, Prednisone	3/day	36 mg/d, 1 mg/kg, NR	2 weeks	A + B	+
Yan et al. (44)	China	46.58 ± 9.71	72	VRT+ mecobalamin, etc	3/day	46.58 ± 9.71	72	mecobalamin, etc.	3/day	1.5 mg/d, 10 days	10 days	A	+
Yoo et al. (30)	Korea	54.1 ± 12.5	15	VRT+ Methylprednisolone+ *Ginkgo biloba* extract	≤10/day	59.6 ± 11.8	14	*Ginkgo biloba* extract	2/day	80 mg/d, 14 days	4 weeks	B	+

(Continued)

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TABLE 1 (Continued)

Study	Country	Experimental group				Control group				Drug dose and number of days	duration	Outcomes	Positive/ negative
		Age	Sample size	Intervention	Frequency	Age	Sample size	Intervention	Frequency				
Zhang et al. (34)	China	35.6 ± 10.1	29	VRT + Promethazine, Betahistine	2/day	35.8 ± 10.2	29	Promethazine, Betahistine	3/day	30 mg/d, 36 mg/d, 4 weeks	4 weeks	A + B + E	+
Zhao et al. (37)	China	39.72 ± 9.41	40	VRT+ Betahistine, Dexamethasone	3/day	39.43 ± 9.50	40	Betahistine, Dexamethasone	3/day, 1/day	48 mg/d, 10–20 mg/d, 7 days	12 weeks	A + B + C	+
Zhao (35)	China	40.35 ± 3.18	27	VRT+ Betahistine, Dexamethasone	3/day	40.25 ± 3.21	26	Betahistine, Dexamethasone	3/day, 1/day	48 mg/d, 10–20 mg/d, 7 days	12 weeks	A + B + C	+
Zhao et al. (36)	China	47.49 ± 8.92	23	VRT+ Betahistine, Dexamethasone, Promethazine	2/day	47.95 ± 9.04	22	Betahistine, Dexamethasone, Promethazine	3/day	36 mg/d, 2 mg/d,25 mg/d, 2 weeks	4 weeks	B	+

A, Overall efficiency; B, DHI, Dizziness Handicap Inventory; C, BBS, Berg Balance Scale; D, VEMPs, Vestibular Evoked Myogenic Potentials (VEMPs); E, VADL, Vestibular Disorders Activities of Daily Living Scale; F, CP score, Canal Paresis score; VRT, vestibular rehabilitation training; NR: Not Reported.

the more significant the reduction of vertigo after treatment (Figure 7B).

3.7.1.3. Result of the BBS score

A total of 5 studies (26, 33, 35, 37, 43) assessed 398 participants who reported BBS scores. We used a fixed-effect model ($I^2 = 38.3\%$, $p = 0.116 > 0.05$) to aggregate the data (Figure 8), and the results showed that VRT combined with anti-vertigo drugs could better enhance the balance function of VN patients compared with the control group [MD = 6.84, 95%CI (6.08, 7.60)].

3.7.2. The secondary outcomes

3.7.2.1. Result of the VEMPs

A total of 3 studies (one three-arm study) (25, 29, 45) measured VEMPS in 154 patients. The fixed effect model showed statistical significance compared with the control group ($I^2 = 0\%$, $p = 0.959 > 0.05$), indicating that VRT combined with anti-vertigo drugs can improve vestibular muscle and nerve function in VN patients [RR = 0.63, 95% CI (0.40, 0.97)] (Figure 9).

3.7.2.2. Result of the CP score

A total of 3 RCTs (31, 39, 45) measured CP score values in 180 patients. The fixed-effect model showed statistical significance compared with the control group ($I^2 = 30.8\%$, $p = 0.236 > 0.05$), indicating that VRT combined with anti-vertigo drugs could significantly reduce canal paresis in VN patients [MD = −6.11, 95%CI (−8.02, −4.21)] (Figure 10).

3.7.2.3. Result of the VADL score

A meta-analysis of the VADL scores of 360 VN patients from 6 studies (32–34, 38, 40, 42) was performed using a random-effects model. The VADL score of VRT combined with anti-vertigo drugs was significantly lower than that of control group [MD = −8.95, 95%CI (−12.39, −5.52), $I^2 = 98.0\%$, $p < 0.001$] (Figure 11A). Due to the significant heterogeneity, we performed a subgroup stratified analysis on the age of VN patients (<40 years, 40–50 years old, >50 years) to reduce heterogeneity. Using the random effects model, the results showed the first group [MD = −14.95, 95%CI (−17.30, −12.61), $I^2 = 74.5\%$, $p = 0.047$], the second group [MD = −6.63, 95%CI (−7.25, −6.01), $I^2 = 0\%$, $p = 0.674 > 0.05$], and the third group [MD = −4.60, 95%CI (−5.67, −3.53), $p < 0.05$]. This suggested that VRT combined with anti-vertigo drugs could significantly reduce VADL scores in VN patients, thereby improving their daily activities and vestibular function (Figure 11B).

3.8. Sensitivity analysis

We used StataMP 14. for sensitivity analysis of the results. Firstly, the overall efficiency results are shown in Figure 12A. The meta-analysis included 10 studies, and the pooled results found that removing any of the articles did not have a strong effect on the results. The results were consistent with the meta-analysis [RR = 1.25, 95% CI (1.18, 1.32)], which proved that the meta-results were stable. The second was the sensitivity analysis of DHI, with a total of 18 RCTs, which was also found to be consistent with the meta-analysis [MD = −6.70, 95% CI (−8.49, −4.90)], indicating that the meta-results were stable (Figure 12B).

TABLE 2 Evaluation of the quality of the included documents through PEDro.

Study	1	2	3	4	5	6	7	8	9	10	11	Total score	Level
Chen (40)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Fan et al. (39)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Goudakos et al. (25)	√	√	√	√	×	×	√	√	√	√	√	8	High
Ismail et al. (29)	√	√	×	√	×	×	√	√	√	√	√	7	High
Li et al. (26)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Li (43)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Liao et al. (47)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Liu et al. (42)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Lu et al. (38)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Shen et al. (41)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Wang et al. (45)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Wang et al. (31)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Wu (33)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Xu et al. (32)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Yan et al. (46)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Yan et al. (44)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Yoo et al. (30)	√	√	√	√	×	×	×	√	√	√	√	7	High
Zhang et al. (34)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Zhao et al. (37)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Zhao (35)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Zhao et al. (36)	√	√	√	√	×	×	×	√	√	√	√	7	High

1 = inclusion exclusion criteria; 2 = randomized group; 3 = allocation concealment; 4 = similar baseline; 5 = subject blinding; 6 = therapist blinding; 7 = assessor blinding; 8 = more than 85% of patient measures; 9 = intention to treat; 10 = between-group analysis; 11 = at least one point measure (√: yes, no risk; ×: no, risky).

3.9. Meta-regression results

Due to the significant heterogeneity in the meta-analysis results of DHI data ($I^2 = 98.4\%$), based on the included RCTs, we performed meta regression on the age of VN patients, country, initial DHI score and type of anti-vertigo drugs to find the source of heterogeneity. The results showed that the age of VN patients ($p = 0.031 < 0.05$) and DHI initial score ($p < 0.001$) were the sources of heterogeneity (Table 3), while the country ($p = 0.895 > 0.05$) and the type of anti-vertigo drugs ($p = 0.411 > 0.05$) were not the source of heterogeneity. Similarly, there was significant heterogeneity in the meta-analysis of VADL ($I^2 = 98.0\%$). We performed meta regression on the age of VN patients and the type of anti-vertigo drugs, and found that the age of VN patients ($p = 0.027 < 0.05$) was the source of heterogeneity, while the type of anti-vertigo drugs ($p = 0.638 > 0.05$) was not the source of heterogeneity (Table 3).

4. Discussion

This meta-analysis included 21 studies with 1,425 VN patients. The experimental groups were treated with VRT combined with anti-vertigo drugs (such as methylprednisolone, betahistine mesilate, dexamethasone sodium phosphate, promethazine, sodium bicarbonate, mecobalamin) and the control groups received the same antivertigo drug or VRT (Table 1). To assess the quality of the included studies, we used the PEDro scale, which assessed 4 of 21 studies as high quality and 17 of medium quality. For the assessment of the risk of bias, 21 studies all described randomization methods and reported primary outcome measures. However, because other bias assessment risks were not reported in the studies, the risk assessment for bias was not known, and ultimately, the risk assessment for bias was evaluated as low. Egger' test was adopted to analyze the publication bias of DHI score, and the result showed that DHI score may lead to publication bias ($p < 0.05$). We further corrected it by trim and fill analysis, and the result showed that no new literature was added on the funnel plot. This proved that there was no significant difference from the results before correction, and the funnel plot was basically symmetric, that is, the results of this meta-analysis were stable without publication bias. In addition, we also used TSA to conduct stability tests on the results of the overall efficiency, and the results showed that the meta-analysis of the overall response rate was robust.

Meta-analysis results demonstrated that VRT combined with anti-vertigo drugs could reduce DHI score in VN patients compared with the control group [MD = −6.70, 95% CI (−8.49, −4.90), $I^2 = 98.4\%$, $p < 0.0001$]. Obviously, there was significant heterogeneity in this meta-analysis. To identify the source of heterogeneity, we performed meta regression according to the age of VN patients, initial DHI score and type of anti-vertigo drugs. Subgroup analysis based on initial DHI score (<15 points or ≥15 points) showed that [MD = −1.38, 95% CI

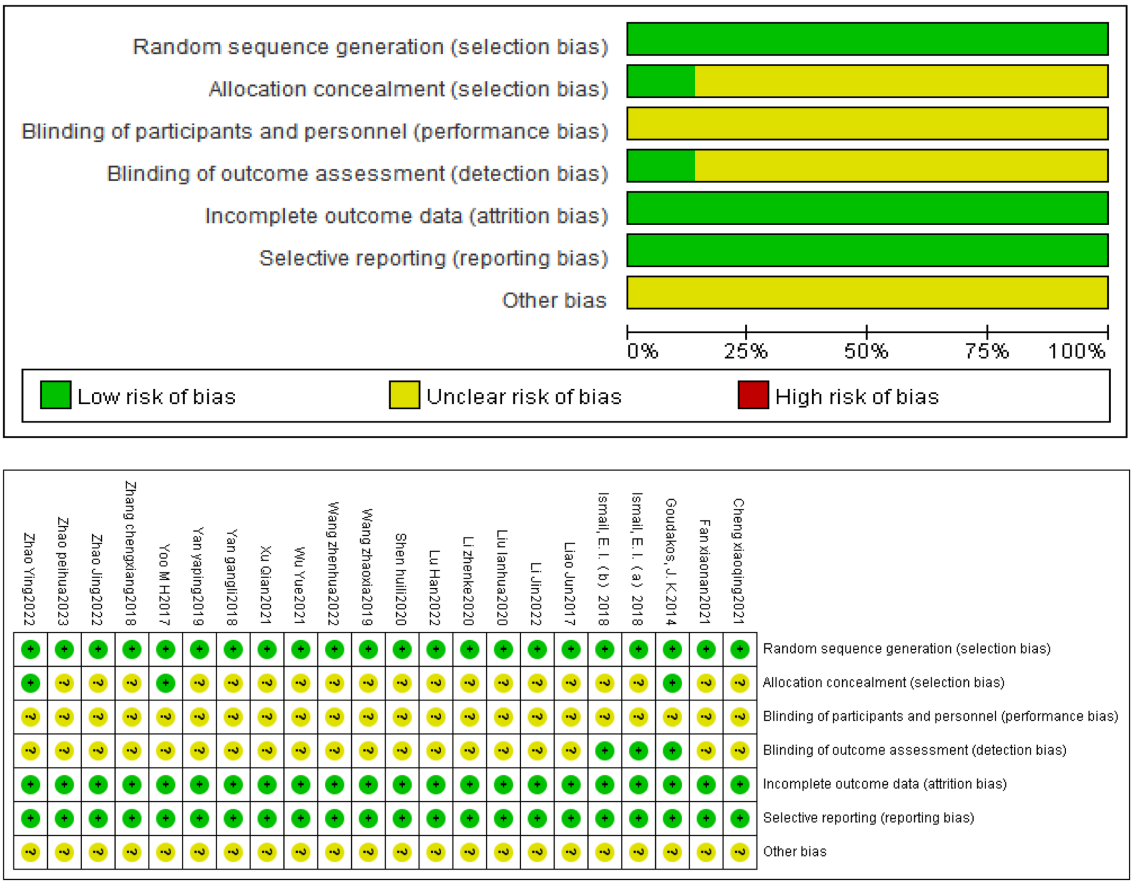

FIGURE 3
Risk of bias of included studies.

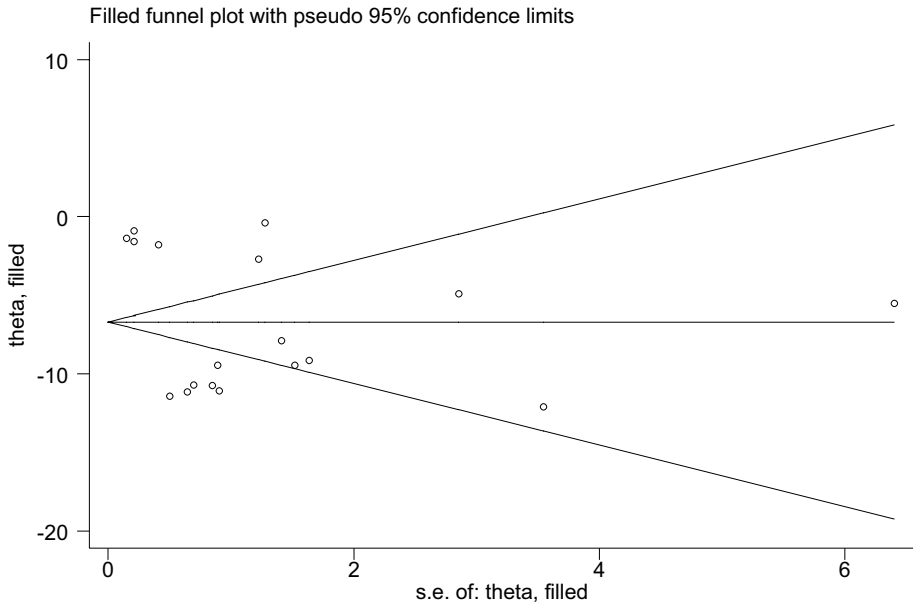

FIGURE 4
Trim and fill analysis of publication bias by DHI score.

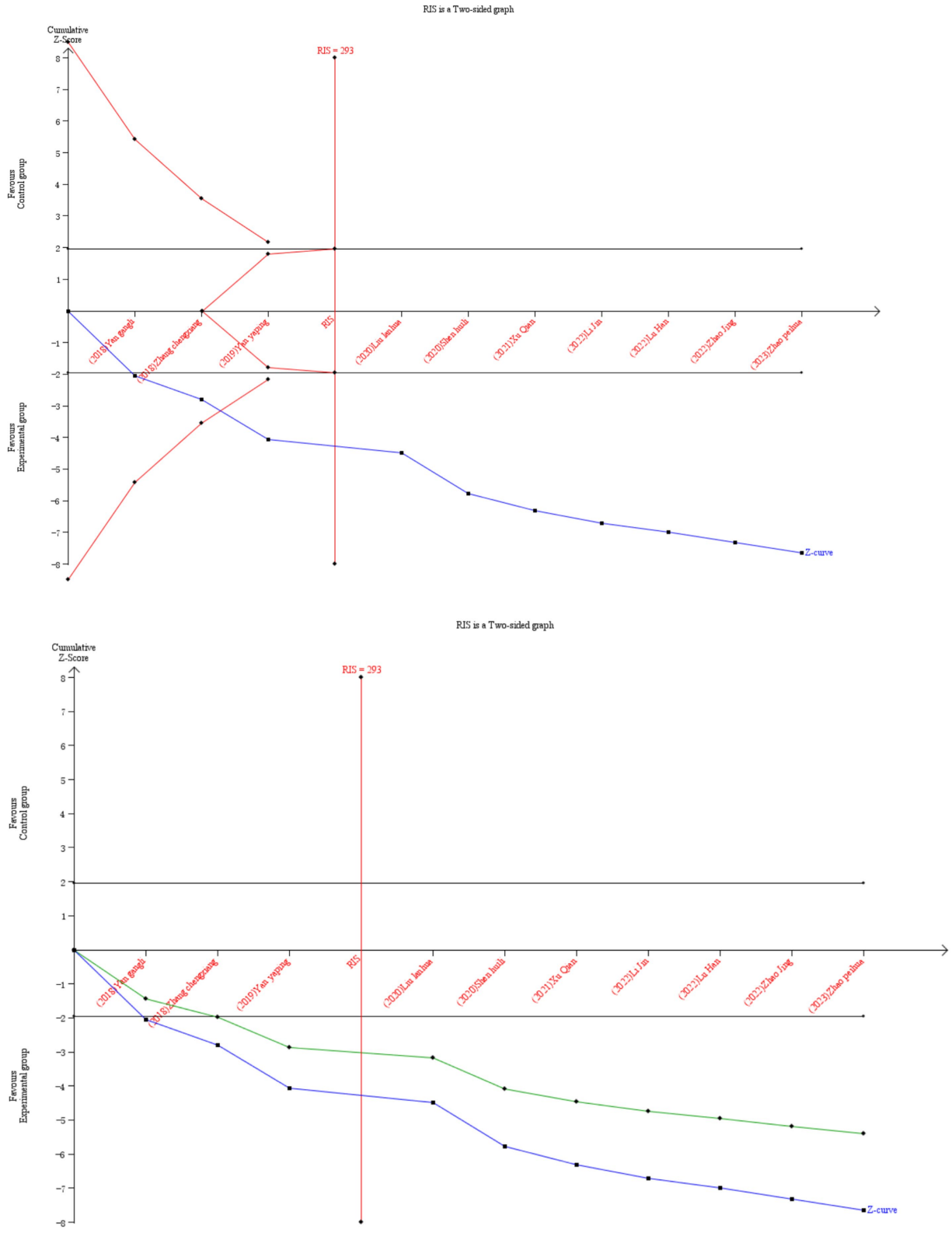

FIGURE 5
Comparison of overall efficiency of VRT combined with antivertigo drugs in the treatment of VN. The black line represents the conventional statistical boundary at $p = 0.05$. The blue line represents the cumulative Z-score of the meta-analysis. Red lines indicate TSA boundaries. The green line shows the Z-curve after penalty statistics. RIS represents the amount of information required.

(−1.71, −1.05), $I^2 = 41.6\%$, $p = 0.114 > 0.05$] (initial DHI score < 15 points) and [MD = −10.67, 95% CI (−11.25, −10.10), $I^2 = 8.8\%$, $p = 0.360 > 0.05$] (initial DHI score ≥ 15 points). The reason why we are making sub-group analysis for initial DHI score is because in the process of data entry, two reviewers have found that there is a wide difference in initial DHI score for different articles, which is highly

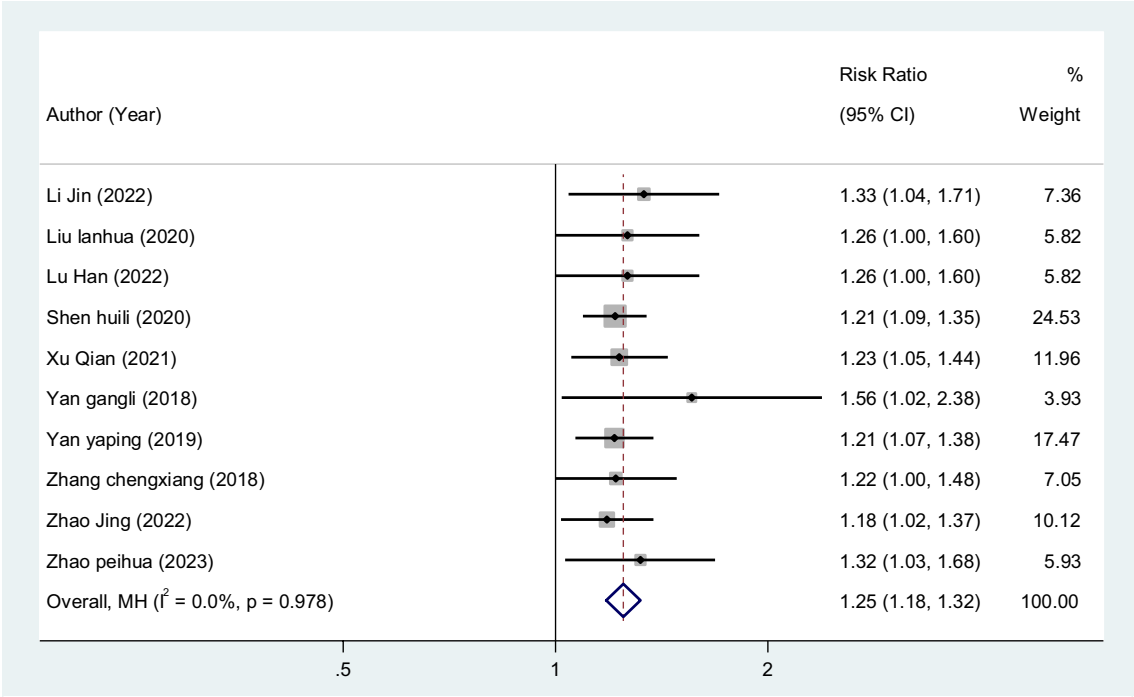

FIGURE 6
Forest plot of overall efficiency.

likely to lead to significant heterogeneity. The results showed that VRT combined with antivertigo had positive effect on improving vertigo state in VN patients. In order to further verify the stability of the meta results, we conducted a sensitivity analysis and found that no single article had a strong impact on the results, which was consistent with the original combined results [MD = −6.70, 95% CI (−8.49, −4.90)], and the results were stable. We adopted the same analysis method for VADL with significant heterogeneity [MD = −8.95, 95%CI (−12.39, −5.52), $I^2 = 98.0\%$, $p < 0.001$]. We performed meta regression according to the age of VN patients and type of anti-vertigo drugs. Subgroup analysis based on the age of VN patients (<40 years old, 40–50 years old, >50 years old) showed that [MD = −14.95, 95%CI (−17.30, −12.61), $I^2 = 74.5\%$, $p = 0.047$] (age < 40 years old), [MD = 6.63, 95% CI (7.25, 6.01), $I^2 = 0\%$, $p = 0.674 > 0.05$] (40–50 years old) and [MD = −4.60, 95%CI (−5.67, −3.53), $p < 0.05$] (age > 50 years old). The results showed that VRT combined with antivertigo could improve daily activities and vestibular function in VN patients. Similarly, sensitivity analysis was used to verify the stability of the meta-analysis, and the results showed that no matter which study was excluded, the combined results of the other studies were not statistically significant [MD = −8.95, 95%CI (−12.39, −5.52)], and the results were stable.

At present, the diagnosis of VN mainly relies on vestibular evoked myogenic potentials (VEMPs) and involved semicircular canal paresis (CP). VEMPs are myoelectric responses from the vestibular labyrinth induced by sound, vibration, or electrical stimulation, and are often used to measure otolith dysfunction (25). Some studies have suggested that the recovery of vestibular nerve injury in VN patients can be judged by observing the dynamic changes of VEMPs (48), and the abnormal number of VEMPs will decrease with the improvement of VN. The results of meta-analysis showed that VRT combined with antivertigo drugs could reduce the abnormal rate of VEMPs [RR = 0.63, 95%CI (0.40, 0.97), $I^2 = 0\%$, $p = 0.959 > 0.05$] and promote the recovery of vestibular function. The semicircular canal is a sensory device in the inner ear associated with maintaining posture and balance. Semicircular canal paresis is caused by nervous system damage, often accompanied by ataxia, balance dysfunction (49), Ceng believes that CP score can objectively evaluate semicircular canal function. The results of meta-analysis showed that VRT combined with anti-vertigo drugs could improve the BBS score of VN patients [MD = 6.84, 95%CI (6.08, 7.60), $I^2 = 38.3\%$, $p = 0.166 > 0.05$]. CP score was decreased [MD = −6.11, 95%CI (−8.02, −4.21), $I^2 = 30.8\%$, $p = 0.236 > 0.05$], and balance ability and vestibular function of patients were improved to a certain extent.

The etiology and pathogenesis of VN are not fully understood, but previous studies have shown that a variety of factors may be related to its pathogenesis. Firstly, viral infection leading to vestibular neurodegeneration is considered one of the most common causes of VN. There are two main types of viral infection: one is respiratory pathogen, which is seasonal and clustered (50), and the other is dormant HSV-1 virus, which is activated and exists in latent form in the vestibular ganglion of human, eventually leading to vestibular inflammation, and then causing vertigo and other symptoms (6). Studies have shown that vaccinating mice with herpes simplex virus induces vestibular ganglion cells in mice to become infected with VN after vestibular dysfunction. Secondly, the pathological mechanism of VN may be related to the inflammatory process caused by infection. Inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) are highly expressed in the body with human herpes virus, which is also related to the herpes virus infection mechanism of VN (51). Thirdly, VN may be caused by vascular lesions of the nerves. Multiple causes of

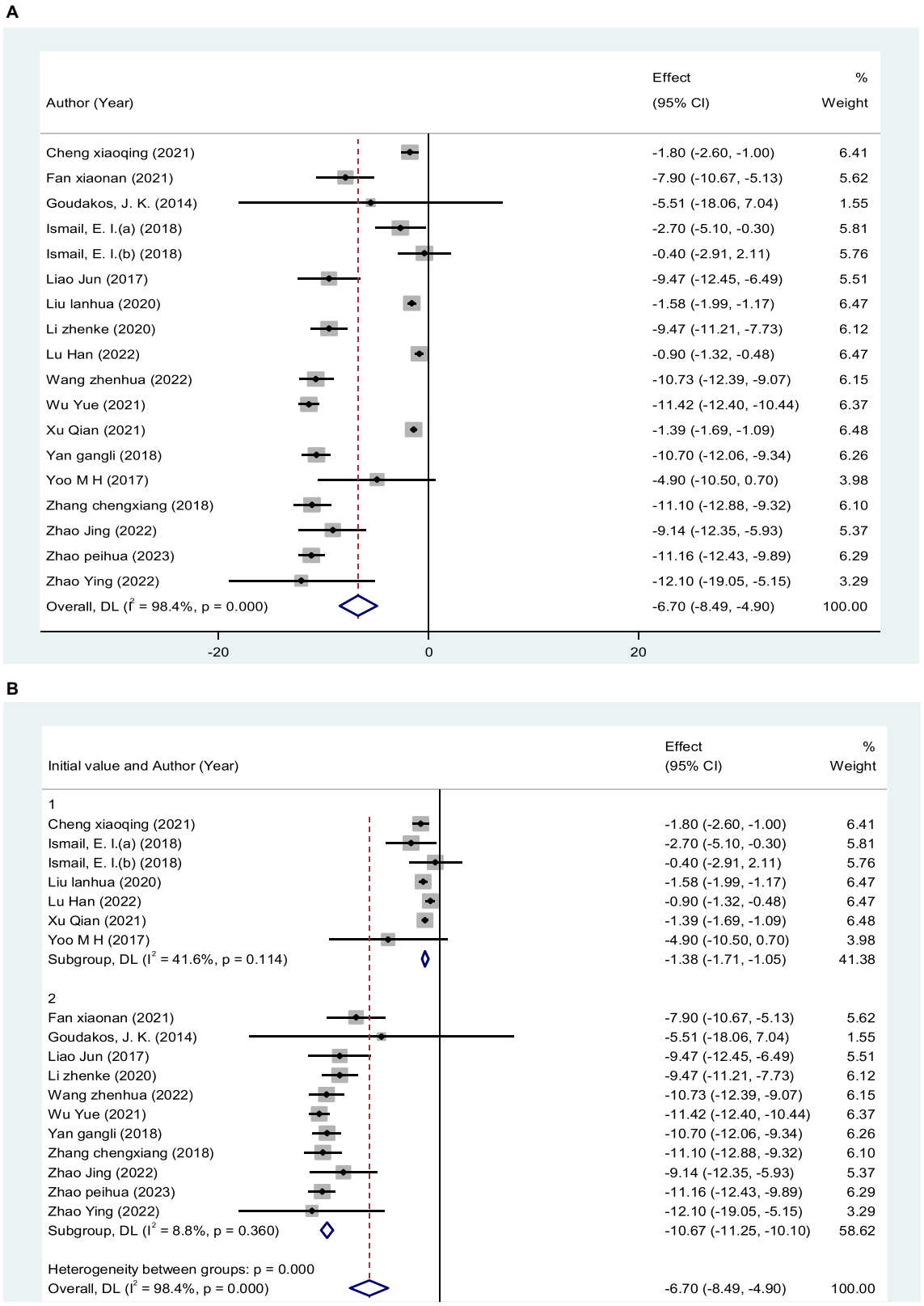

FIGURE 7
Forest plot of DHI score. **(A)** All studies. **(B)** After subgroup analysis (15 points indicates the initial DHI score).

labyrinthine artery stenosis or obstruction occlusion, ischemia and hypoxia of perivestibular organs, leading to rapid unilateral vestibular dysfunction (52). Fourthly, autoimmunity also mediates the occurrence of VN. The marker CD40 in monocytes/macrophages plays an important role in inflammation, vascular processes and immunity in VN (53). The immune imbalance between T-helper and

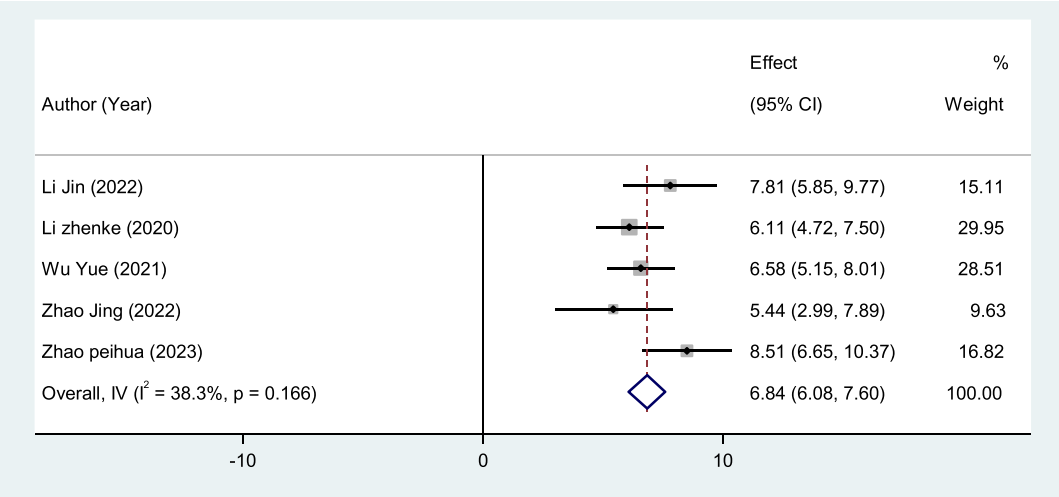

FIGURE 8
Forest plot of BBS.

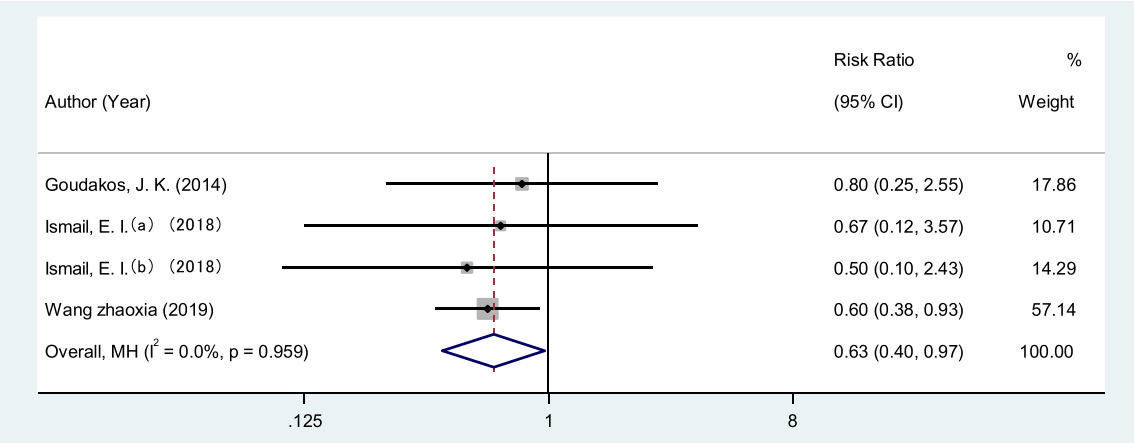

FIGURE 9
Forest plot of VEMPs.

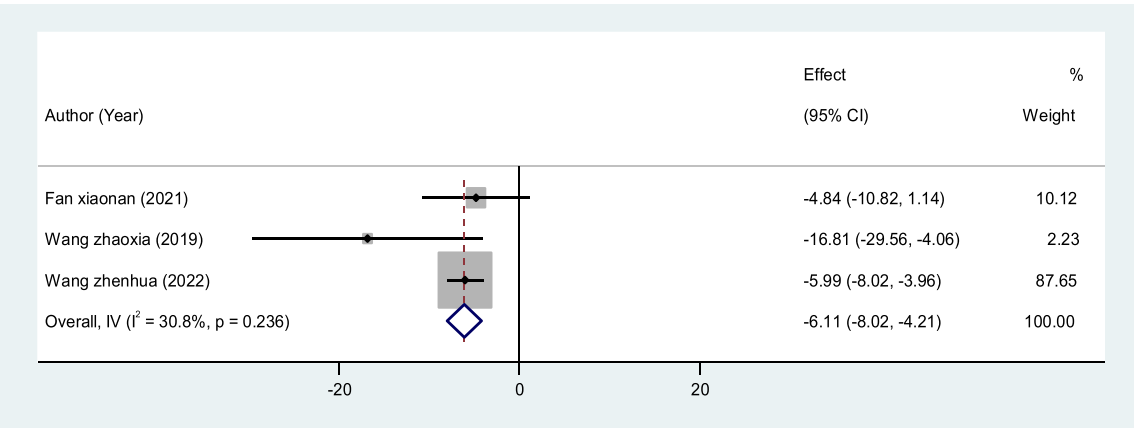

FIGURE 10
Forest plot of CP score.

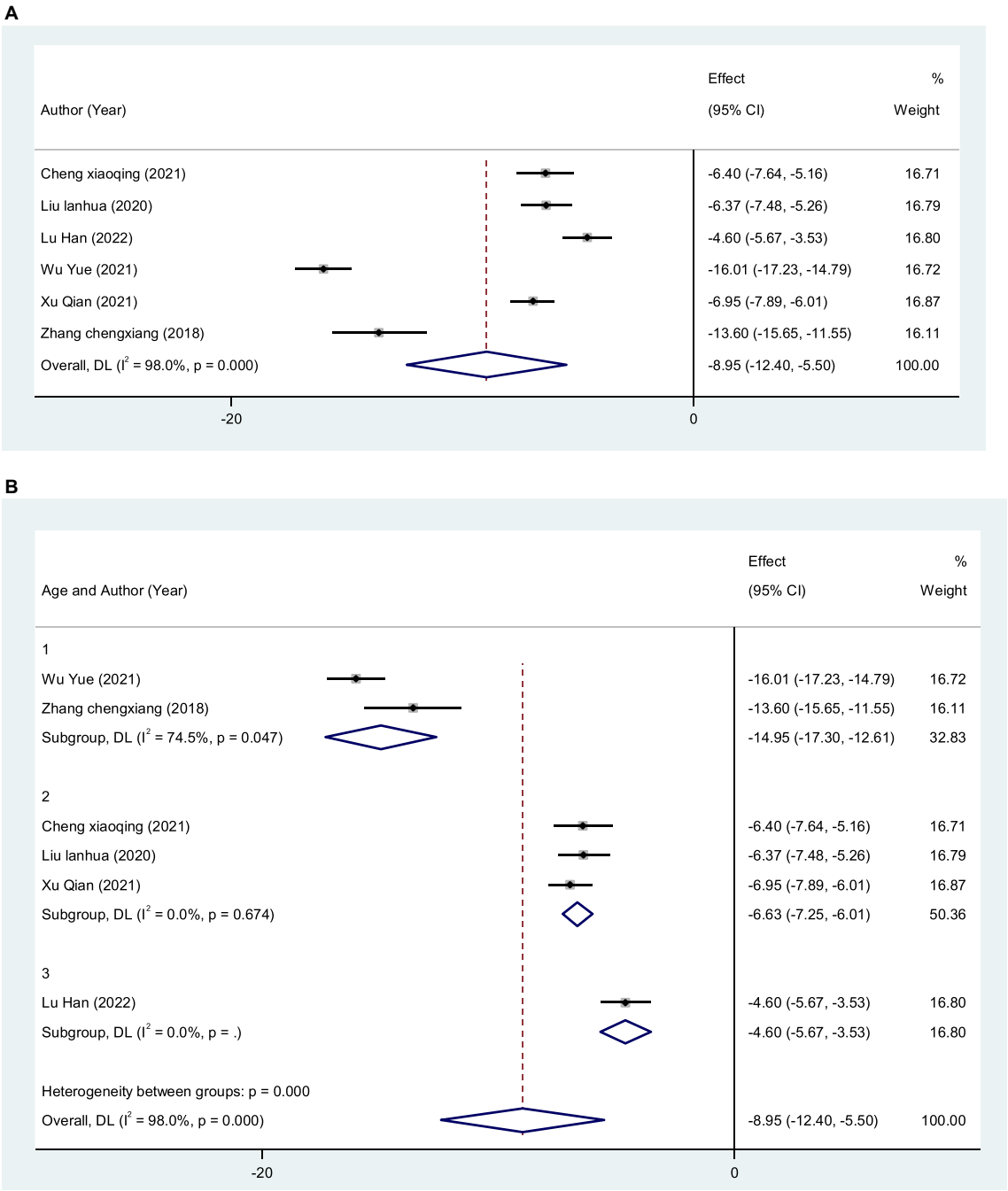

FIGURE 11
Forest plot of VADL score. **(A)** All studies. **(B)** After subgroup analysis.

T-suppressor cells is also closely related to VN (54). In addition, other factors such as vitamin D deficiency (55) and metabolic diseases such as diabetes may also contribute to the development of VN (56).

At present, the treatment of VN is mainly based on autonomic symptoms such as vomiting and vertigo and the severity of the disease. The therapeutic mechanism is to improve cerebral blood circulation, through vestibular inhibitors, neuroprotective agents or vestibular rehabilitation training and surgical procedures to improve central compensation (50, 57, 58). Antivertigo drugs are used for vertigo accompanied with nausea and vomiting in patients with acute VN stage. As the mechanism of action of such drugs is to delay the establishment of central compensation and affect the prognosis of VN, they cannot be used for a long time (57). VRT is a kind of non-invasive physical therapy. Its principle of action is realized through the plasticity and compensatory capacity of the vestibular nervous system. The mechanism of action is to readjust eye movement, proprioception and postural control through the reorganization of brain stem and cerebellar pathways, and then achieve the effect of treating vestibular vertigo (59–61). However, single drug therapy or VRT is always difficult to achieve the expected effect, and some studies have found that VRT combined drug therapy can better promote the rehabilitation of VN patients (62). As an important method for the treatment of VN,

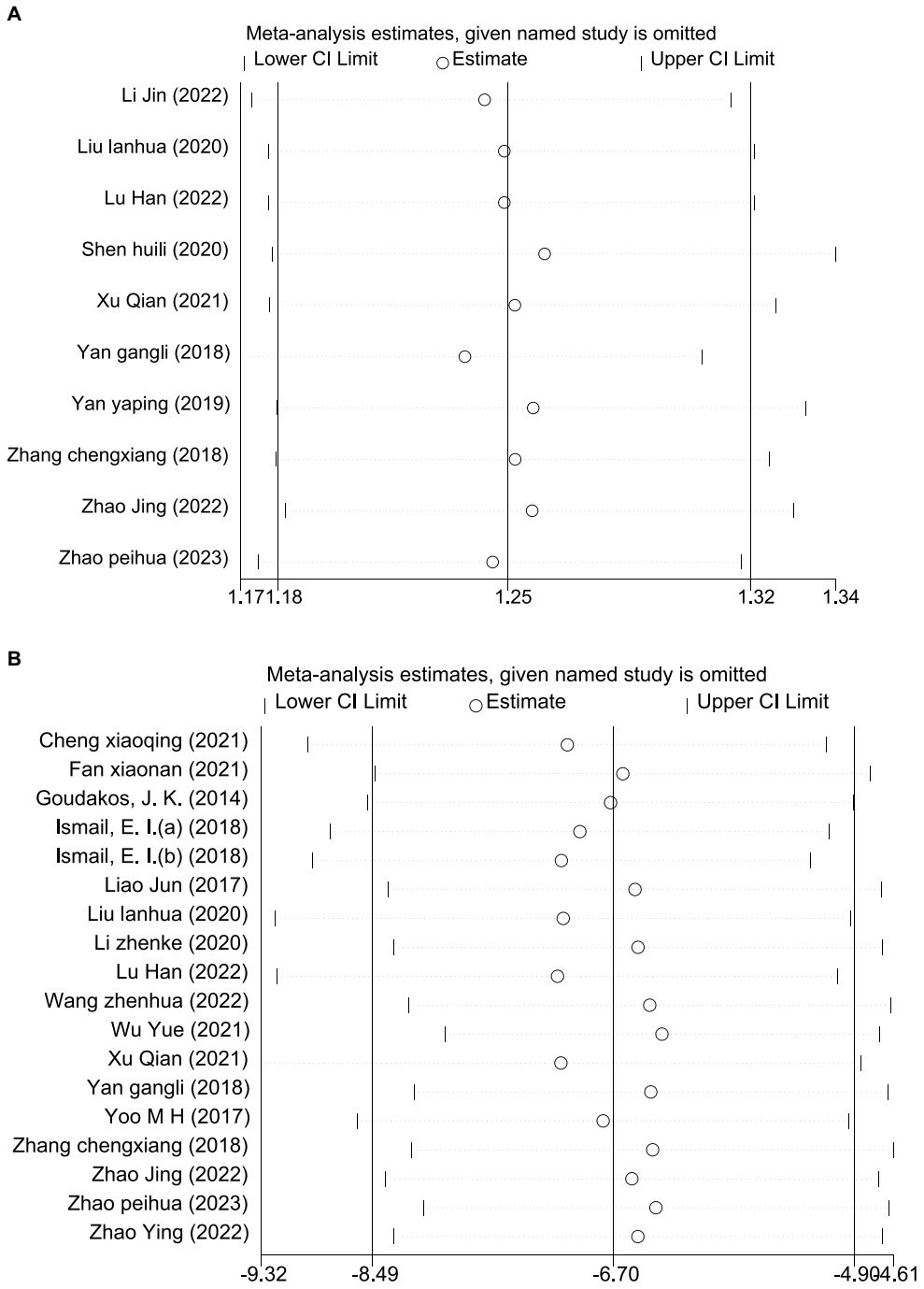

FIGURE 12
Result of sensitivity analysis. **(A)** overall efficiency. **(B)** DHI.

VRT has the advantages of simplicity, economy, non-invasive, strong compliance, etc. VRT should be used in combination with drug therapy with strong symptomatic and rapid effect, and be widely promoted in clinical practice.

A total of 3 RCTs in the included study reported adverse effects. One study (30) reported mild and transient discomfort, such as indigestion, facial swelling, and mood swings. In Goudakos' antivertigo trial (25), one patient using hypoglycemic drugs to control diabetes developed disease instability and hyperglycemia, and blood sugar returned to normal levels after dose adjustment. Xu's study (32) reported 4 cases of general fatigue, 5 cases of insomnia, and 1 case of dryness-heat.

This meta-analysis was conducted by developing strict inclusion/exclusion criteria and controlling for methodological quality, however some limitations remain. Firstly, this meta-analysis strictly followed the inclusion and exclusion criteria for literature screening, but most of the included studies were from China and there were few English studies, which may lead to the existence of country bias. So new

TABLE 3 Meta-regression results of DHI and VADL.

Outcome	_ES	Coef.	Std. Err.	*t*	*p*>|*t*|	[95% Conf. Interval]	
DHI	Age	0.6378277	0.2643176	2.41	0.031	0.0668042	1.208851
	Country	−0.1262971	0.9419664	−0.13	0.895	−2.161292	1.908698
	Initial score	−8.874486	0.3828021	−23.18	0.000	−9.70148	−8.047493
	Drug type	−0.0516424	0.0607738	−0.85	0.411	−0.1829361	0.0796514
	_cons	6.385251	1.264856	5.05	0.000	3.652696	9.117806
VADL	Age	5.827061	1.427994	4.08	0.027	1.282548	10.37157
	Drug type	−0.3031553	0.5816561	−0.52	0.638	−2.154245	1.547934
	_cons	−18.50436	3.1693	−5.84	0.010	−28.59049	−8.418235

meta-analyses are needed after more English studies are published in the future to ensure the comprehensiveness and impartiality of the studies. Secondly, some of the studies in our review have methodological flaws. The most common methodological flaw was a lack of blindness to participants, therapists, and evaluators. Thirdly, some studies have small sample size, short intervention time, and lack of follow-up, so larger and high-quality randomized controlled trials are needed. Finally, according to the inclusion criteria, only five RCTs used BBS as an outcome indicator. Although our conclusion is positive, confirming that VRT combined with antivertigo does promote the restoration of balance function in VN patients, more high-quality studies are needed to verify this conclusion in the future.

5. Conclusion

VRT combined with antivertigo drugs can improve vertigo and balance function in VN patients. At the same time, combined therapy can also enhance vestibular nerve and muscle function of VN patients, promote the recovery of otolith dysfunction, reduce the impact of vertigo on daily activities, and improve the quality of life of patients. In addition, the combination treatment had fewer adverse effects, demonstrating safety. However, there are shortcomings such as small sample size, short intervention time, and lack of long-term follow-up. In the future, larger sample size and higher quality randomized controlled trials are needed to further verify the effectiveness of VRT combined with anti-vertigo drugs on VN. A new meta-analysis could determine which class of drugs VRT in combination is more effective in treating VN.

Author contributions

JC: Writing – original draft, Writing – review & editing. ZXL: Writing – review & editing. YLX: Writing – review & editing. SJ: Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Geng Z, Jing Z, Changbao N, Huifang Z. Research progress in the diagnosis and treatment of vestibular neuronitis. *J Audiol Speech Disord*. (2019) 27:681–5. doi: 10.3969/j.issn.1006-7299.2019.06.024

2. Strupp M, Magnusson M. Acute unilateral vestibulopathy. *Neurol Clin*. (2015) 33:669–85. doi: 10.1016/j.ncl.2015.04.012

3. Adamec I, Krbot Skorić M, Handžić J, Habek M. Incidence, seasonality and comorbidity in vestibular neuritis. *Neurol Sci*. (2015) 36:91–5. doi: 10.1007/s10072-014-1912-4

4. Hülse R, Biesdorf A, Hörmann K, Stuck B, Erhart M, Hülse M, et al. Peripheral vestibular disorders: an epidemiologic survey in 70 million individuals. *Otol Neurotol*. (2019) 40:88–95. doi: 10.1097/MAO.0000000000002013

5. Weiwei H, Qiongfeng G, Zhenyi F, Xu G, Yunqin W. Correlation between vestibular neuritis and arteriosclerosis. *J Stroke Neurol Dis*. (2018) 35:1115–7. doi: 10.19845/j.cnki.zfysjjbzz.2018.12.015

6. Yacovino DA, Zanotti E, Cherchi M. The spectrum of acute vestibular neuropathy through modern vestibular testing: A descriptive analysis. *Clin Neurophysiol Pract*. (2021) 6:137–45. doi: 10.1016/j.cnp.2021.02.008

7. Zhuang JH. Clinical characteristics and management strategies of vestibular neuritis in different periods. *Chinese J Int Med*. (2023) 62:743–7. doi: 10.3760/cma.j.cn112138-20230207-00063

8. Adamec I, Krbot Skorić M, Gabelić T, Barun B, Ljevak J, Bujan Kovač A, et al. Intravenous dexamethasone in acute management of vestibular neuritis: a randomized, placebo-controlled, single-blind trial. *Eur J Emerg Med*. (2016) 23:363–9. doi: 10.1097/MEJ.0000000000000275

9. Le TN, Westerberg BD, Lea J. Vestibular neuritis: recent advances in etiology, diagnostic evaluation, and treatment. *Adv Otorhinolaryngol*. (2019) 82:87–92. doi: 10.1159/000490275

10. Himmelein S, Lindemann A, Sinicina I, Horn AKE, Brandt T, Strupp M, et al. Differential involvement during latent herpes simplex virus 1 infection of the superior and inferior divisions of the vestibular ganglia: implications for vestibular neuritis. *J Virol*. (2017) 91:e00331-17. doi: 10.1128/JVI.00331-17

11. Kassner SS, Schöttler S, Bonaterra GA, Stern-Straeter J, Hormann K, Kinscherf R, et al. Proinflammatory activation of peripheral blood mononuclear cells in patients with vestibular neuritis. *Audiol Neurootol*. (2011) 16:242–7. doi: 10.1159/000320839

12. Milionis HJ, Mittari V, Exarchakos G, Kalaitzidis R, Skevas AT, Elisaf MS. Lipoprotein (a) and acute-phase response in patients with vestibular neuronitis. *Eur J Clin Investig*. (2003) 33:1045–50. doi: 10.1111/j.1365-2362.2003.01275.x

13. Oron Y, Shemesh S, Shushan S, Cinamon U, Goldfarb A, Dabby R, et al. Cardiovascular risk factors among patients with vestibular neuritis. *Ann Otol Rhinol Laryngol*. (2017) 126:597–601. doi: 10.1177/0003489417718846

14. Shuiling X, Ganggang C, Ying C, Ting X, Liyuan Z, Haili Z, et al. Expression of serum 25-hydroxyvitamin D and its correlation in patients with vestibular neuritis. *J Clin Otolaryngol Head Neck Surg*. (2022) 36:607–12. doi: 10.13201/j.issn.2096-7993.2022.08.008

15. Yuqing J, Hui L. Research progress in the diagnosis and treatment of vestibular neuritis In: *Proceedings of the 25th Annual Conference of Otolaryngology Branch of Chinese Association of Traditional Chinese Medicine and the 11th Annual Conference of Otolaryngology Professional Committee of World Union*. Jinan: (2019)

16. Xin L, Weiwei X. Meta-analysis of the efficacy of corticosteroids in the treatment of vestibular neuritis. *J Audiol Speech Disord*. (2022) 30:297–303. doi: 10.3969/j.issn.1006-7299.2022.03.014

17. Karlberg ML, Magnusson M. Treatment of acute vestibular neuronitis with glucocorticoids. *Otol Neurotol*. (2011) 32:1140–3. doi: 10.1097/MAO.0b013e3182267e24

18. Yamanaka T, Him A, Cameron SA, Dutia MB. Rapid compensatory changes in GABA receptor efficacy in rat vestibular neurones after unilateral labyrinthectomy. *J Physiol*. (2000) 523:413–24. doi: 10.1111/j.1469-7793.2000.t01-1-00413.x

19. Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, et al. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. *N Engl J Med*. (2004) 351:354–61. doi: 10.1056/NEJMoa033280

20. Mengshuang M. *Vestibular function examination and vestibular rehabilitation of vertigo* [D]. Henan: Zhengzhou University (2019).

21. van Vugt VA, van der Wouden JC, Essery R, Yardley L, Twisk JWR, van der Horst HE, et al. Internet based vestibular rehabilitation with and without physiotherapy support for adults aged 50 and older with a chronic vestibular syndrome in general practice: three armed randomised controlled trial. *BMJ*. (2019) 367:l5922. doi: 10.1136/bmj.l5922

22. Fanglu C, Jing W, Xu Y, Liyi W, Sulin Z, Expert consensus on vestibular rehabilitation. Otolaryngology Expert Committee of Capacity Building and Continuing Education Center of National Health Commission, Otolaryngology Professional Committee of Chinese Association of Integrated Traditional and Western Medicine, Vertigo Medicine Branch of China Association for Promotion of International Exchanges in Healthcare. Chinese Association of Traditional Chinese Medicine Encephalopathy Professional Committee vertigo group, Chinese Medical Association otolaryngology Head and neck Surgery Branch otolaryngology vertigo coordination group. *Chin Med J*. (2021) 101:2037–43 doi: 10.3760/cma.j.cn112137-20210318-00685

23. Alsalaheen BA, Mucha A, Morris LO, Whitney SL, Furman JM, Camiolo-Reddy CE, et al. Vestibular rehabilitation for dizziness and balance disorders after concussion. *J Neurol Phys Ther*. (2010) 34:87–93. doi: 10.1097/NPT.0b013e3181dde568

24. Mengsha J, Xi K. Research progress of vestibular rehabilitation in the treatment of peripheral vertigo. *J Clin Otolaryngol Head Neck Surg*. (2022) 36:582–587. doi: 10.13201/j.issn.2096-7993.2022.08.003

25. Goudakos JK, Markou KD, Psillas G, Vital V, Tsaligopoulos M. Corticosteroids and vestibular exercises in vestibular neuritis. Single-blind randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. (2014) 140:434–40. doi: 10.1001/jamaoto.2014.48

26. Jin L, Xingju Z. Effects of glucocorticoid combined with vestibular function training on balance function, inflammatory factors and oxidative stress levels in patients with vestibular neuritis. *Med Clin Res*. (2022) 39:1712–4. doi: 10.3969/ji.ssn.1671-7171.2022.11.032

27. Hidayati HB, Imania HAN, Octaviana DS, Kurniawan RB, Wungu CDK, Rida Ariarini NN, et al. Vestibular rehabilitation therapy and corticosteroids for vestibular neuritis: a systematic review and meta-analysis of randomized controlled trials. *Medicina (Kaunas)*. (2022) 58:1221. doi: 10.3390/medicina58091221

28. Huang HH, Chen CC, Lee HH, Chen HC, Lee TY, Tam KW, et al. Efficacy of vestibular rehabilitation in vestibular neuritis: a systematic review and meta-analysis. *Am J Phys Med Rehabil*. (2023). doi: 10.1097/PHM.0000000000002301

29. Ismail EI, Morgan AE, Abdel Rahman AM. Corticosteroids versus vestibular rehabilitation in long-term outcomes in vestibular neuritis. *J Vestib Res*. (2018) 28:417–24. doi: 10.3233/VES-180645

30. Yoo MH, Yang CJ, Kim SA, Park MJ, Ahn JH, Chung JW, et al. Efficacy of steroid therapy based on symptomatic and functional improvement in patients with vestibular neuritis: a prospective randomized controlled trial. *Eur Arch Otorhinolaryngol*. (2017) 274:2443–51. doi: 10.1007/s00405-017-4556-1

31. Zhenhua W, Xinjun M, Yiwen L, Haie X, Jiangang J, Linfang J, et al. The clinical effect of gazing stability vestibular rehabilitation training on patients with acute vestibular neuritis. *Reflexol Rehabil Med*. (2022) 3:141–4.

32. Qian X, Yuan W. Clinical effect analysis of hormone combined vestibular rehabilitation therapy and simple hormone therapy for vestibular neuritis. *Health Home*. (2021) 15:108–9.

33. Yue W. The application value of vestibular rehabilitation in the treatment of vestibular neuritis patients. *Special Health*. (2021) 27:44.

34. Chengxiang Z, Zongrui Y, Guiru Z. Clinical study of adjuvant vestibular rehabilitation training in patients with acute vestibular neuritis. China. *Health Nutr*. (2018) 28:31. doi: 10.3969/j.issn.1004-7484.2018.04.038

35. Peihua Z. Effect of vestibular rehabilitation on acute vestibular neuritis. *Marriage Parenthood Health*. (2023) 29:136–8. doi: 10.3969/j.issn.1006-9488.2023.02.046

36. Ying Z, Lijun W, Wei L, Yijun S. The value of semicircular canal high-intensity stimulation training in the treatment of vestibular neuritis with SRAM IV vertigo diagnosis and treatment system. *J Clin Otolaryngol Head Neck Surg*. (2022) 36:925–9. doi: 10.13201/j.issn.2096-7993.2022.12.007

37. Jing Z, Yongyi Z, Minglu H, Rong F. Effect of vestibular rehabilitation on acute vestibular neuritis. *Chinese J Otol*. (2022) 20:684–8. doi: 10.3969/j.issn.1672-2922.2022.04.028

38. Han L, Hao Z, Yimei L. Clinical effect of vestibular rehabilitation training combined with methylprednisolone on vestibular neuritis and its effect on sleep quality. *World J Sleep Med*. (2022) 9:2276–7. doi: 10.3969/j.issn.2095-7130.2022.12.014

39. Xiaonan F, Yong Z, Mingze C, Gejuan Z, Juan M, Shilin L, et al. Effect evaluation of vestibular rehabilitation in the treatment of vestibular neuritis. Chinese Modern. *Doctor*. (2021) 59:38–40+5.

40. Xiaoqing C. Clinical study of methylprednisolone combined with peripheral vestibular rehabilitation training in the treatment of vestibular neuritis. *Smart Health*. (2021) 7:129–31. doi: 10.19335/j.cnki.2096-1219.2021.10.044

41. Huili S, Weiying Q. Effect of SRM-IV vertigo diagnosis and treatment system on vertigo induced by vestibular neuritis. *Shanxi J Med*. (2020) 49:292–4. doi: 10.3969/j.issn.0253-9926.2020.03.020

42. Lan-Hua L, Wei-jie C, Shulin H. Clinical effect of vestibular rehabilitation training combined with methylprednone on vestibular neuritis. *J Clin Rational Drug Use*. (2020) 13:78–9. doi: 10.15887/j.cnki.13-1389/r.2020.22.034

43. Zhenke L. Effects of sodium bicarbonate injection combined with vestibular rehabilitation training on vertigo degree and balance function in patients with vestibular neuritis. *Henan Med Res*. (2020) 29:3510–1. doi: 10.3969/j.issn.1004-437X.2020.19.023

44. Yaping Y, Chengmin C, Ping L, Shuxiang Z. Effect of SRM-IV vertigo diagnosis and treatment system on vertigo induced by vestibular neuritis. *Chinese J Armed Police Med*. (2019) 30:669–71. doi: 10.3969/j.issn.1004-3594.2019.08.007

45. Zhaoxia W, Xian-Rong X, Yuan-Jun L, Jinye L. Clinical effect of hormone combined vestibular rehabilitation therapy and single hormone therapy for vestibular neuritis. *J Clin Otolaryngol Head Neck Surg*. (2019) 33:493–7. doi: 10.13201/j.issn.1001-1781.2019.06.004

46. Gangli Y, Chaowu L, Hailing N, Zhiwei T, Jun X, Fengguang L, et al. Evaluation of therapeutic effect of peripheral vestibular rehabilitation on vestibular neuronitis. *Nerve Injury Funct Reconstruct*. (2018) 13:472–3. doi: 10.16780/j.cnki.sjssgncj.2018.09.012

47. Jun L, Zhimin Z, Wanyu W, Jie H. Effect of vestibular rehabilitation training combined with drug therapy on vestibular neuritis. *Sichuan Med J*. (2017) 38:332–4. doi: 10.16252/j.cnki.issn1004-0501-2017.03.024

48. Murofushi T, Iwasaki S, Ushio M. Recovery of vestibular evoked myogenic potentials after a vertigo attack due to vestibular neuritis. *Acta Otolaryngol*. (2006) 126:364–7. doi: 10.1080/00016480500417189

49. Jintian C, Shuqi Z, Tao Y, Yinfei L, Xiangli Z. Preliminary study on evaluation of semicircular canal function by video head pulse test combined with cold and thermal test. *Chinese J Otol*. (2018) 16:267–71. doi: 10.3969/j.issn.1672-2922.2018.03.002

50. Yong Y, Jingjing Z, Liang Z, Jingmin L, Hui W, Qi Z, et al. Overview of pathogenesis and treatment of vertigo in Chinese and Western medicine. *Chinese Med Rev*. (2023) 20:40–4. doi: 10.20047/j.issn1673-7210.2023.19.08

51. Weschke DP, Leisenring WM, Lawler RL, Stevens-Ayers T, Huang ML, Jerome KR, et al. Inflammatory cytokine profile in individuals with inherited chromosomally integrated human herpesvirus 6. *Biol Blood Marrow Transplant*. (2020) 26:254–61. doi: 10.1016/j.bbmt.2019.10.023

52. Wei W, Zhen H, Jingqing W. Overview of pathogenesis of vestibular neuritis of traditional Chinese and Western medicine. *J Cardio-Cerebrovasc Dis Integr Trad Chinese Western Med*. (2022) 20:78–82. doi: 10.12102/j.issn.1672-1349.2022.01.014

53. Henn V, Slupsky JR, Gräfe M, Anagnostopoulos I, Förster R, Müller-Berghaus G, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. *Nature*. (1998) 391:591–4. doi: 10.1038/35393

54. Greco A, Macri GF, Gallo A, Fusconi M, de Virgilio A, Pagliuca G, et al. Is vestibular neuritis an immune related vestibular neuropathy inducing vertigo? *J Immunol Res*. (2014) 2014:459048:1–8. doi: 10.1155/2014/459048

55. Büki B, Jünger H, Zhang Y, Lundberg YW. The price of immune responses and the role of vitamin D in the inner ear. *Otol Neurotol*. (2019) 40:701–9. doi: 10.1097/MAO.0000000000002258

56. Ying C, Ting P, Haili Z. Correlation between serum 25-hydroxyvitamin D level and vestibular neuritis. *Chinese J Otolaryngol Basilar Skull Surg*. (2020) 26:594–8. doi: 10.11798/j.issn.1007-1520.202005026

57. Jeong SH, Kim HJ, Kim JS. Vestibular neuritis. *Semin Neurol*. (2013) 33:185–94. doi: 10.1055/s-0033-1354598

58. Nelson MD, Akin FW, Riska KM, Andresen K, Mondelli SS. Vestibular assessment and rehabilitation: ten-year survey trends of audiologists' opinions and practice. *J Am Acad Audiol*. (2016) 27:126–40. doi: 10.3766/jaaa.15035

59. Sitong G, Jing Z, Huifang Z. Research progress of vestibular rehabilitation therapy. *J Audiol Speech Disord*. (2019) 27:561–5. doi: 10.3969/j.issn.1006-7299.2019.05.022

60. Xiaoyuan Q, Ning S, Ping G, Xu Y. Research progress of vestibular rehabilitation mechanism and treatment. *Chinese J Gen Med*. (2022) 25:1399–405. doi: 10.12114/j.issn.1007-9572.2021.01.104

61. Yuanjun L, Xianrong X. Research progress of vestibular neuritis. *Chinese J Otol*. (2016) 14:515–20. doi: 10.3969/j.issn.1672-2922.2016.04.017

62. Mi W, Wei L. Effect of vestibular rehabilitation on patients with balance disorder. *J Audiol Speech Disord*. (2015) 23:230–3. doi: 10.3969/j.issn.1006-7299.2015.03.004

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The effect of the Lokomat® robotic-orthosis system on lower extremity rehabilitation in patients with stroke: a systematic review and meta-analysis

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Background: The Lokomat® is a device utilized for gait training in post-stroke patients. Through a systematic review, the objective was to determine whether robot-assisted gait training with the Lokomat® is more effective in enhancing lower extremity rehabilitation in patients with stroke in comparison to conventional physical therapy (CPT).

Methods: In this study, a systematic search was conducted in various databases, including CINAHL, MEDLINE, PubMed, Embase, Cochrane Library, Scopus, Web of Science, and Physiotherapy Evidence Database (PEDro), as well as bibliographies of previous meta-analyses, to identify all randomized controlled trials that investigated the use of Lokomat® devices in adult stroke patients. The study aimed to derive pooled estimates of standardized mean differences for six outcomes, namely, Fugl–Meyer Assessment lower-extremity subscale (FMA-LE), Berg Balance Scale (BBS), gait speed, functional ambulation category scale (FAC), timed up and go (TUG), and functional independence measure (FIM), through random effects meta-analyses.

Results: The review analyzed 21 studies with a total of 709 participants and found that the use of Lokomat® in stroke patients resulted in favorable outcomes for the recovery of balance as measured by the BBS (mean difference = 2.71, 95% CI 1.39 to 4.03; $p < 0.0001$). However, the FAC showed that Lokomat® was less effective than the CPT group (mean difference = −0.28, 95% CI −0.45 to 0.11, $P = 0.001$). There were no significant differences in FMA-LE (mean difference = 1.27, 95% CI −0.88 to 3.42, $P = 0.25$), gait speed (mean difference = 0.02, 95% CI −0.03 to 0.07, $P = 0.44$), TUG (mean difference = −0.12, 95% CI −0.71 to 0.46, $P = 0.68$), or FIM (mean difference = 2.12, 95% CI −2.92 to 7.16, $P = 0.41$) between the Lokomat® and CPT groups for stroke patients.

Conclusion: Our results indicate that, with the exception of more notable improvements in balance, robot-assisted gait training utilizing the Lokomat® was not superior to CPT based on the current literature. Considering its ability to reduce therapists' work intensity and burden, the way in which Lokomat® is applied should be strengthened, or future randomized controlled trial studies should use more sensitive assessment criteria.

KEYWORDS

Lokomat®, stroke, lower extremity function, rehabilitation, meta-analysis

Introduction

Stroke is a highly prevalent medical condition that often leads to permanent disability (1). Post-stroke impairment can have a significant impact on various aspects of physical function, including joint mobility and stability, muscular strength, tone, reflexes, muscle endurance, movement control, and gait pattern functions. These deficits can pose significant challenges to activities such as transferring, maintaining body posture, movement, balance, and walking (2). According to estimates, a considerable proportion of individuals who have suffered stroke, up to 65%, experience lower limb complications in the post-stroke phase (3). The ability to walk and achieve independence in activities of daily living (ADL) holds significant importance in various domains, including enhancing psychological wellbeing (4), mitigating the risk of cognitive decline (5), and promoting physical activity (6). The restoration of gait, both in terms of quantity and quality, is regarded as a primary objective (7).

Rehabilitation robotics is an emerging clinical intervention aimed at re-establishing functional movement of the limb by stimulating and restoring the nervous system that controls limb movement. This goal is achieved through multiple movements powered by robotic devices (8). Studies have shown that robot-assisted gait training triggers unique neurophysiological modulations (9). In addition, robot-assisted gait training enables patients to perform intense rehabilitation exercises in a safe manner while reducing the time and physical burden on physical therapists (10). Numerous empirical studies have supported the significant efficacy of robot-assisted interventions in the treatment of lower limb injuries after stroke (11). Stationary robot-assisted training can better improve the walking ability of subacute stroke survivors compared to traditional training methods. In addition, end-effector robots are superior to exoskeleton robots in improving step speed (12). However, some scholars have questioned the widespread use of body weight-supported running training (BWSTT) and robot-assisted gait training (RAST) in clinical practice through retrospective studies, arguing that physical therapists should remain cautious in adopting these strategies in the absence of sufficient evidence to support them (13).

Lokomat® (Hocoma AG, Volketswil, Switzerland) is a globally utilized exoskeleton equipped with linear drives on the hip and knee joints designed to aid in locomotion on a treadmill by directing the participant's legs along a predetermined path (14). Prior research endeavors aimed at assessing the efficacy of Lokomat® have predominantly amalgamated the lower-extremity robot, comprising both the end-effector and exoskeleton, and have scarcely scrutinized individual devices. Furthermore, the outcomes of such studies have primarily centered on gait kinematic parameters (15–17). Recent research has primarily examined the effects of Lokomat® intervention on balance function in patients, with limited literature available to provide a comprehensive assessment of the restoration of lower limb function (18). It is essential to identify and employ the techniques that have been shown to produce the most significant results in order to lower the cost and improve the effectiveness of post-stroke rehabilitation. Hence, the aim of this study was to determine the effects of robot-assisted gait training with Lokomat® in stroke patients on lower extremity function. In this study, FMA-LE was used as the primary outcome indicator, and BBS, gait speed, FAC, TUG, and FIM were used as secondary outcome indicators.

Methods

In this study, we adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in order to accurately report our findings from the systematic review (Figure 1) (19). The Cochrane handbook's published guidelines were strictly followed throughout the study (20). In addition, in this study, to ensure that the inclusion metrics were high-quality studies relevant to the study topic, we used predefined outcome measures to select studies. The protocol for this review is registered on PROSPERO (no. CRD42023438449).

Search strategy

For relevant English-language literature, we searched the following electronic databases: CINAHL, MEDLINE, PubMed, Embase, Cochrane Library, Scopus, Web of Science, and Physiotherapy Evidence Database (PEDro). These databases define the search time to be from 1 January 2000 to 31 May 2023. The words stroke, cerebrovascular accident, CVA, Lokomat, robotic device, exoskeleton, robotic-assisted gait training, RAGT, gait, lower extremity function, and motion control were used in the literature search. Additionally, the PICOS framework (population, intervention, comparison, outcome, and study setting/design) was used in the design of this study.

Study selection

Two authors (LW and GX) evaluated the title and summary of the studies that were found and then analyzed the complete reports of all studies that could be relevant based on predetermined criteria. Any discrepancies in the selection of studies were resolved through discussion with a third author (QW).

This study aimed to identify randomized controlled trials (RCTs) that compared the effectiveness of robotic-assisted gait training using Lokomat® with CPT in improving lower limb function among stroke patients. The inclusion criteria for the RCTs were as follows: patients of both genders aged over 18 years with lower-extremity hemiparesis, outcome measures focused on motor function and limited walking ability after ischemic or hemorrhagic stroke, and sufficient cognitive abilities to comprehend the exercises involved in the interventions. Trials that utilized electromechanical devices other than Lokomat® were excluded from the analysis.

Data extraction

Two authors (LW and GX) conducted an independent extraction of information from each study included in the analysis. The extracted information included title, authors, country, year of publication, journal of publication, participants (number, mean age, and gender), study design, rehabilitative intervention

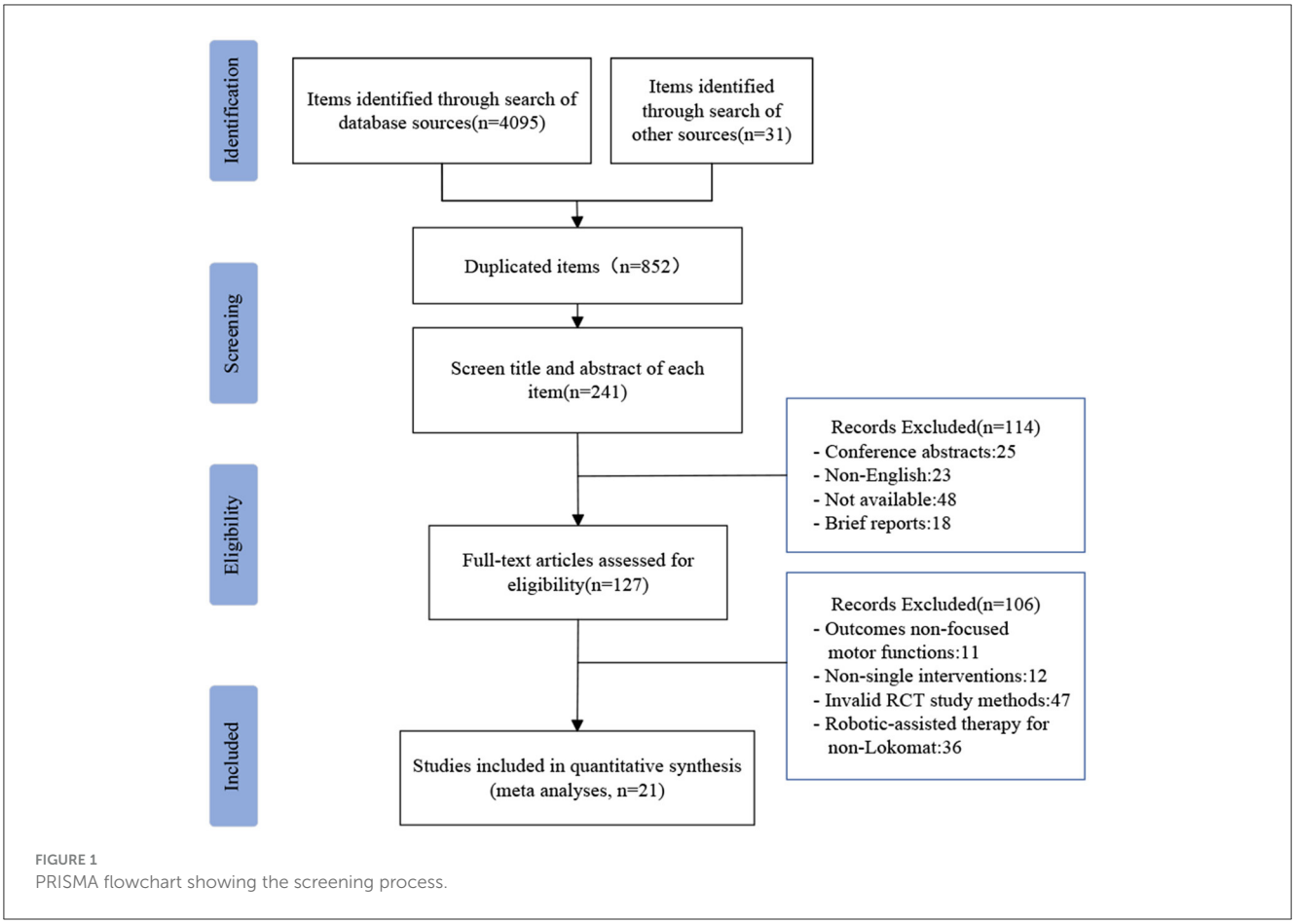

FIGURE 1
PRISMA flowchart showing the screening process.

details (frequency and duration of the sessions, Lokomat® parameters such as weight support and speed), outcome measures, results, follow-up, attrition rates, and safety. Any discrepancies in the extracted data were resolved through discussion with another author (QW). In the context of reporting data on scale, the utilization of medians and interquartile ranges was accompanied by a reference to the methods proposed by Hozo et al. (21). These methods involve the application of basic inequalities and approximations to estimate the sample mean and standard deviation (SD), thereby facilitating subsequent analysis. In instances where it was deemed necessary, we initiated communication with the authors to obtain supplementary data.

Risk of bias in included studies

Of the specific methods described for randomization, 20 out of 21 studies mentioned randomization, of which 12 specifically described randomization methods, 6 studies used computer-generated, 5 used random number table generation, and 1 used hidden envelope generation. In contrast, one study did not mention randomization. Allocation concealment to conceal enrollment identities, studies in 12 articles mentioned distribution concealment, with 7 detailing the use of opaque envelopes, 3 studies using a specific scale, and 2 only mentioning it without specifying how it was implemented. The remaining 9 did not report whether concealment was performed. Blinding of participants and staff: Due to the nature of the intervention, it was not possible to blind participants and research staff. Therefore, all studies were judged to be high risk. However, 15 of the included studies made reference to blinding the assessor. Incomplete outcome data: the field is unbiased.

Assessment of the quality and methodology of literature inclusion

The evaluation of the methodological quality of the studies included in the research was carried out independently by two authors (LW and GX). The assessment was conducted using the PEDro scale (22), a validated and reliable tool for measuring methodological quality (23). The PEDro scale consists of 11 items, including eligibility criteria, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, follow-up of at least 85% for one key outcome, intention-to-treat analysis, between-group statistical comparison for one key outcome, and point and variability measures for one key outcome. The score of the first entry does not count toward the final overall score. If criteria are not specified, they are considered not met. The achieved criteria can be summed to obtain a score ranging from 0 (minimum) to 10 (maximum),

TABLE 1 Evaluation of the study's methodological quality using the PEDro criteria.

Included studies	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subject	Blind therapist	Blind assessor	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	Total score (0–10)	Methodological quality
Bang et al. (25)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Belas et al. (26)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4	Poor
Bergmann et al. (27)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
Chang et al. (28)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Choi et al. (29)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5	Acceptable
Ucar et al. (30)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4	Poor
Han et al. (31)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5	Acceptable
Hidler et al. (32)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
Hornby et al. (33)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5	Acceptable
Husemann et al. (34)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Kelley et al. (35)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
Kim et al. (36)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Manuli et al. (37)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
Mustafaoglu et al. (38)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Park et al. (39)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5	Acceptable
Schwartz et al. (40)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
Taveggia et al. (41)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	7	Good
Uivarosan et al. (42)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	3	Poor

(Continued)

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TABLE 1 (Continued)

Included studies	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subject	Blind therapist	Blind assessor	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	Total score (0–10)	Methodological quality
Van Nunen et al. (43)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5	Acceptable
Westlake et al. (44)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good
YUN et al. (45)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	6	Good

Eligibility criteria item does not contribute to total score.

indicating the overall methodological quality of the study (≤4 poor, 4–5 acceptable, 6–8 good, 9–10 excellent), (Table 1).

Data analysis

The analysis in this study was conducted using the Review Manager (RevMan) software (computer program, version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). In the case of each study that was incorporated and presented with continuous data, the between-group effect sizes were computed by contrasting the means between groups post-intervention. Furthermore, in instances where the outcome was evaluated by more than two RCTs, the pooled effects were determined using mean differences (MDs) with 95% confidence interval (CI) through random effects models that accounted for the differences in the use of instruments. The present study utilized pooled analyses, which were reported with 95% CI. The assessment of heterogeneity through the utilization of I^2 statistics was interpreted in the following manner: when $I^2 = \%$, there is an absence of heterogeneity; when $I^2 > 0\%$ but $< 25\%$, there is minimal heterogeneity; when I^2 is $\geq 25\%$ but $< 50\%$, there is mild heterogeneity; when $I^2 \geq 50\%$ but $< 75\%$, there is moderate heterogeneity; and when $I^2 \geq 75\%$, there is strong heterogeneity (24).

Results

Literature search

A total of 4126 references were identified through various databases and additional sources. These included 200 references from CINAHL, 748 from PubMed, 408 from MEDLINE, 1024 from Embase, 74 from Cochrane Library, 869 from Scupos, 21 from PEDro, 751 from Web of Science, and 31 from other sources. Among these references, 3274 were duplicates, and 611 were excluded based on a review of their titles and abstracts. Further exclusions were made for 114 articles, which were deemed unsuitable due to reasons such as being conference abstracts, non-English publications, unavailability, or brief reports. Ultimately, a total of 127 articles were selected for full-text review. After careful examination, articles were excluded if they did not focus on motor function, did not involve single intervention factors, did not employ effective RCT study methods, or did not pertain to robotic treatment using the Lokomat®. As a result, 21 articles met the inclusion criteria and were included in the final analysis.

Included studies

Table 2 displays the methodological characteristics and main results of the aforementioned studies.

TABLE 2 Methodological characteristics and main results of the included studies.

Study (country)	Study design	Population (1 = RAGT; 2 = CPT)	Intervention (Lokomat® characteristics)	Comparison	Outcomes	Follow-up
Bang et al. (25) (Korea)	RCT	1. $n = 9$ (4F/5M; mean age 53.56 ± 3.94); 2. $n = 9$ (5F/4M; mean age 53.67 ± 2. 83)	Parameters: BWS (40%), speed (0.45 m/s); Frequency: 5 (1 h/session) for 4 weeks	Treadmill training without body support	BBS; Gait Speed; ABC	None
Belas et al. (26) (Brazil)	RCT	1. $n = 7$ (2F/5M; mean age 44.4 ± 12. 7); 2. $n = 9$ (2F/6M; mean age 56.4 ± 11. 8)	Parameters: BWS (50%), speed (1.5 km/h); Frequency: 3 (1 h/session/week) for 5 months	Therapist-assisted gait training + conventional treatment	BBS; TUG; FIMSARA	None
Bergmann et al. (27) (Germany)	RCT	1. $n = 15$ (5F/10M; mean age 72 ± 9); 2. $n = 15$ (8F/7M; mean age 71 ± 10)	Parameters: BWS (50%), speed (2 km/h); Frequency: 5 (1 h/session/week) for 2 weeks	Conventional treatment (consisted of active and dynamic exercises)	FAC; SCP; BLS; SVV	2-weeks/FAC
Chang et al. (28) (Korea)	RCT	1. $n = 20$ (7F/13M; mean age 55.5 ± 12. 0); 2. $n = 17$ (7F/10M; mean age 59.7 ± 12. 1)	Parameters: BWS (from 40% to 0%), guidance force (from 100% to 10%), speed (from 1.2 to 2.6km/h); Frequency: 10 (40 min/session/week) for 2 weeks	Conventional treatment (based on NDT developed Bobath)	FMA-LE; FAC; MI-L	None
Choi et al. (29) (Korea)	RCT	1. $n = 6$ (4F/2M; mean age 54.7 ± 12. 3); 2. $n = 6$ (3F/3M; mean age 61. 4 ± 9.7)	Parameters: BWS (50%); Frequency: 5 (1 h/session/week) for 6 weeks	Conventional physical therapy + gait training with treadmill + NDT	BBS; TUG	None
Ucar et al. (30) (Turkey)	RCT	1. $n = 11$ (0F/11M; mean age 56.2); 2. $n = 11$ (0F/11M; mean age 61. 5)	Parameters: BWS (50%), speed 1.5 km/h; Frequency: 5 (30 min/session/week) for 2 weeks	Conventional treatment (focused on gait)	TUG	8-weeks/TUG
Han et al. (31) (Korea)	RCT	1. $n = 30$ (13F/17M; mean age 67.89 ± 14.96); 2. $n = 26$ (11F/15M; mean age 63.2 ± 10.62)	Parameters: BWS (from 50% to 0%), guidance force (from 100% to 40%), speed (from 1.2 to 2.6km/h); Frequency: 5 (30 min/session/week) for 4 weeks	Conventional treatment (NDT)	FMA-LE; BBS; FAC	None
Hidler et al. (32) (United States)	RCT	1. $n = 33$ (12F/21M; mean age 59.5 ± 11. 3); 2. $n = 30$ (12F/18M; mean age 54.6 ± 9.4)	Parameters: BWS (40%), guidance force (100%), speed (1.5 km/h); Frequency: 3 (1.5 h/session/week) for 8∼10 weeks	Conventional treatment (gait training)	FAC;	3-months/FAC
Hornby et al. (33) (United States)	RCT	1. $n = 24$ (9F/15M; mean age 57 ± 10); 2. $n = 24$ (9F/15M; mean age 57 ± 11)	Parameters: BWS (40%), speed (2∼3 km/h); Frequency: 12 (30-min) sessions	Treadmill with BWS assisted by therapist	BBS; Gait Speed	None
Husemann et al. (34) (Germany)	RCT	1. $n = 16$ (5F/11M; mean age 60 ± 13); 2. $n = 14$ (4F/10M; mean age 57 ± 11)	Parameters: BWS (30%); Frequency: 20 (1 h) sessions	Conventional physiotherapy (gait training)	FAC; Gait Speed; MI-L; BI	None

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TABLE 2 (Continued)

Study (country)	Study design	Population (1 = RAGT; 2 = CPT)	Intervention (Lokomat® characteristics)	Comparison	Outcomes	Follow-up
Kelley et al. (35) (United States)	RCT	1. $n = 11$ (4F/7M; mean age 66.91 ± 8.50); 2. $n = 19$ (3F/6M; mean age 64.33 ± 10.91)	Parameters: BWS (40%), guidance force (100%), speed (0.42∼0.89 m/s); Frequency: 5 (1 h/session/week) for 8 weeks	Conventional physiotherapy (endurance, velocity, safety, and gait deviations)	Gait Speed	3-months/ Gait Speed
Kim et al. (36) (Korea)	RCT	1. $n = 10$ (1F/9M; mean age 48.70 ± 7.01); 2. $n = 9$ (2F/7M; mean age 46.00 ± 15.64)	Parameters: BWS (from 80% to 50%), guidance force (from 100% to 20%), speed (1.0∼3.0 km/h); Frequency: 5 (session/week) for 4 weeks	Conventional physiotherapy (static and dynamic balance)	FMA-LE; Gait Speed; FAC; TIS; SARA	None
Manuli et al. (37) (Italy)	RCT	1. $n = 30$ (26F/4M; mean age 40.1 ± 10.7); 2. $n = 30$ (16F/14M; mean age 43.1 ± 9.7)	Parameters: BWS (from 70% to 20%); Frequency: 5 (1 h/session/week) for 8 weeks	Conventional treatment (NDT)	FIM	None
Mustafaoglu et al. (38) (Turkey)	RCT	1. $n = 15$ (4F/11M; mean age 53.7 ± 11. 6); 2. $n = 15$ (4F/11M; mean age 52. 6 ± 14.7)	Parameters: BWS (40%), speed (1.2∼2.6 km/h); Frequency: 2 times/week for 4 weeks	Conventional treatment (trunk stabilization, weight transfer)	BBS; TUG; RMI	None
Park et al. (39) (Turkey)	RCT	1. $n = 12$ (5F/7M; mean age 55.58 ± 10.42); 2. $n = 16$ (7F/9M; mean age 57.50 ± 9.90)	Parameters: BWS (30%), guidance force (100%), speed (1.5∼2.0 km/h); Frequency: 3 (45 min/session/week) for 6 weeks	Gait training with treadmill	BBS; TUG; BI; FMA	None
Schwartz et al. (40) (Israel)	RCT	1. $n = 37$ (21F/16M; mean age 62 ± 85); 2. $n = 30$ (20F/10M; mean age 65 ± 75)	Parameters: BWS (from 50% to 10%); Frequency: 5 (30 min/session/week) for 6 weeks	Conventional physiotherapy (gait training)	Gait Speed; TUG; FIM	None
Taveggia et al. (41) (Italy)	RCT	1. $n = 13$ (6F/7M; mean age 71 ± 5); 2. $n = 15$ (5F/10M; mean age 73 ± 7)	Parameters: BWS (50%), speed (0.4 m/s); Frequency: 5 (session/week) for 5 weeks	Conventional physiotherapy (gait training)	Gait Speed; FIM	17-weeks/ Gait Speed; FIM
Uivarosan et al. (42) (Romania)	RCT	1. $n = 18$ (3F/15M; mean age 63.67 ± 6.63); 2. $n = 30$ (14F/16M; mean age 64.12 ± 7.25)	Parameters: speed (maximum that patients tolerate); Frequency: 14 (30 min/session/day) per 6 months	Recovery therapy (kinetotherapy + hydrokinetotherapy + masotherapy + electrotherapy et al.)	BI; FIM	None
Van Nunen et al. (43) (Netherlands)	RCT	1. $n = 16$ (6F/10M; mean age 50.0 ± 9.6); 2. $n = 14$ (8F/5M; mean age 56.0 ± 8.7)	Parameters: BWS (up to 10%), guidance force (up to 20%), speed (1.5 km/h, up to 2.5 km/h); Frequency: 2 h/week for 8 weeks	Overground assisted therapy	BBS; TUG; Gait Speed; FAC; RMI	36-weeks/ BBS; TUG; Gait Speed; FAC; RMI
Westlake et al. (44) (United States)	RCT	1. $n = 8$ (2F/6M; mean age 58.6 ± 16.9); 2. $n = 8$ (1F/7M; mean age 55.1 ± 13.6)	Parameters: BWS (35%), speed (2.5km/h); Frequency: 3 (30 min/session/week) for 4 weeks	Conventional physiotherapy (treated by skilled physical therapists/trainers)	FMA-LE; BBS; Gait Speed	None

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TABLE 2 (Continued)

Study (country)	Study design	Population (1 = RAGT; 2 = CPT)	Intervention (Lokomat® characteristics)	Comparison	Outcomes	Follow-up
Yun et al. (45) (Korea)	RCT	1. $n = 18$ (8F/10M; mean age 63.6 ± 8.3); 2. $n = 18$ (9F/9M; mean age 64.3 ± 8.4)	Parameters: BWS (50%), guidance force (100%), speed (1.1 km/h); Frequency: 5 (30 min/session/week) for 3 weeks	Conventional treatment (NDT)	FMA-LE; FMA; BBS;	4-weeks/ FMA-LE; FMA; BBS

RCT, randomized controlled trial; RAGT, robot-assisted gait training; CPT, conventional physical therapy; F, female; M, male; BWS, body-weight support; BBS, Berg Balance Scale; ABC, activities-specific balance confidence; TUG, Timed Up and Go; SARA, Scale for the Assessment and Rating of Ataxia; FIM, Functional Independence Measure; SCP, Scale for Contraversive Pushing; BLS, Burke Lateropulsion Scale; SVV, Subjective Visual Vertical; FAC, functional ambulation category scale; MI-L, leg score of Motricity Index; FMA-LE, Fugl-Meyer Assessment lower-extremity subscale; BI, Barthel Index; TIS, Trunk impairment scale; FES, Falls Efficacy Scale; RMI, Rivermead Mobility Index; FMA, Fugl–Meyer Assessment; NDT, neurodevelopmental technique.

Design and participants

Stroke patients were recruited from stroke units or in-hospital rehabilitation centers in nine countries across Europe, Asia, and America. A total of 709 patients were included in the study, with 436 (59%) being male subjects. The average age of the participants was 58.43 years, ranging from 40 to 73 years. The average time from stroke onset to inclusion in the study was 13.7 months, with a range of 16.1 days to 10.5 years. Out of the 21 RCTs included in the analysis, seven studies conducted follow-up assessments at an average of 13 weeks after the completion of treatment, ranging from 2 to 36 weeks. The remaining 14 studies only reported post-treatment assessments.

Characteristics of robot-assisted gait training with Lokomat®

The Lokomat system, manufactured by Hocoma in Volketswil, Switzerland, was the robotic device utilized in this research. The Lokomat® device is employed alongside a body weight support (BWS) system, which assists in offsetting a portion of the individual's weight.

All 20 studies provided specific experimental parameters, except for one study that did not include machine setup parameters (42). These parameters included body support weight, guiding force, step speed, and treatment frequency time. The majority of studies reported body support weights ranging from 30% to 50%, with some studies noting that 30% was the most commonly used weight (46). Guidance force varied from 20% to 100%, and the initial training pace was approximately 1 km/h, gradually increasing to 3 km/h over the training period. The minimum number of training sessions in a treatment cycle was 8, the maximum was 60, and the median was 20 (26, 38, 41, 43). For a single session, the minimum duration was 30 min, the maximum was 2 h, and the median was 45 min (30, 31, 33, 40, 42, 44, 45).

The details of the Lokomat® setup parameters and treatment frequency can be found in Table 2.

Characteristics of CPT

In the studies analyzed, the CPT group received treatment of similar duration and frequency as the experimental group. The included studies encompassed four that utilized neurodevelopmental therapy (NDT)-based rehabilitation methods, four that incorporated treadmill training, and the remaining CPT interventions consisted of gait training, dynamic and static exercises, trunk control, and balance training (25, 28, 29, 31, 33, 37, 39, 45).

Evaluation of the study's methodological quality with the PEDro criteria

Based on the evaluation using the PEDro scale, it was determined that out of the total number of studies assessed, 3 were

classified as poor (26, 30, 42), 5 as acceptable (29, 31, 33, 39, 43), and 13 as good (25, 27, 28, 32, 34–38, 40, 41, 44, 45), indicating a generally high quality of literature. It is worth noting that only two studies reviewed did not make mention of randomization (26, 42), while eight studies reported allocation concealment (25, 27, 28, 33, 34, 36, 44, 45). Furthermore, 14 studies were found to have employed blinding techniques to the assessor (25–28, 30, 31, 34–41), with three of them extending this blinding the statistical analysts (25, 37, 41). Due to the inherent characteristics of the intervention, it was not feasible to implement blinding for both participants and researchers. Consequently, none of the studies were scored in either of these two aspects.

Adverse events

Only one study mentioned the occurrence of an adverse event, specifically: 12 skin changes (redness or breakage of the skin due to pressure or friction on the shoulder strap or cuff) in 5 Lokomat® participants (35).

Meta-analysis results

Primary outcome

FMA-LE

A total of five studies were included in the assessment of the Functional Mobility Assessment of the Lower Extremities (FMA-LE), involving a total of 164 patients. The studies exhibited minimal heterogeneity ($I^2 = 18\%$, $P = 0.30$). A meta-analysis was conducted using a random effects model, which revealed no significant difference in the combined effect [MD = 1.27, $P = 0.25$, 95% (CI −0.88, 3.42)]. This suggests that there is no statistically significant distinction between Lokomat® robot-assisted gait training and CPT in terms of their impact on lower limb functional training (Figure 2).

Secondary outcome

BBS

A comprehensive analysis was conducted on a total of nine studies involving 273 patients to evaluate the effectiveness of Lokomat® robot-assisted gait training compared to CPT in improving balance function. The study groups exhibited mild heterogeneity ($I^2 = 37\%$, $P = 0.12$), and a random-effects model was employed for the meta-analysis. The results revealed a significant difference in the combined effect [MD = 2.71, $P < 0.01$, 95% CI (1.39, 4.03)], indicating that Lokomat® robot-assisted gait training was more efficacious in enhancing balance function when compared to CPT (See Figure 3).

Gait speed

Gait speed was chosen as an outcome measure in a total of nine studies involving 272 patients. The study groups exhibited moderate heterogeneity (I2 = 54%, $P = 0.03$), and a meta-analysis was conducted using a random-effects model. The results showed no significant difference in the combined effect [MD = 0.02, $P = 0.44$, 95% CI (−0.03, 0.07)], indicating that Lokomat® robot-assisted gait training does not offer a significant advantage over CPT in terms of improving walking speed (Figure 4).

FAC

A comprehensive analysis was conducted on a total of seven studies involving 275 patients to evaluate the effectiveness of Lokomat® robotic-assisted gait training compared to CPT in improving functional walking. The study groups exhibited a slight degree of heterogeneity ($I^2 = 15\%$, $P = 0.31$). A meta-analysis was performed using a random-effects model, revealing a significant difference in the combined effect [MD = −0.28, $P < 0.01$, 95% CI (−0.45, −0.11)]. This indicates that Lokomat® robotic-assisted gait training did not demonstrate superiority over CPT in enhancing functional walking (Figure 5).

TUG

A systematic review was conducted to assess the effectiveness of Lokomat® robot-assisted gait training compared to CPT in improving the time to complete the TUG. A total of seven studies involving 204 patients were included in the analysis. The study groups exhibited moderate heterogeneity ($I^2 = 70\%$, $P < 0.01$). A meta-analysis was performed using a random-effects model, which revealed no significant difference in the combined effect [MD = −0.12, $P = 0.68$, 95% CI (−0.71, 0.46)]. These findings suggest that Lokomat® robot-assisted gait training is not significantly superior to CPT in terms of enhancing TUG performance (Figure 6).

FIM

A selection of five studies involving a total of 218 patients was utilized to assess the Functional Independence Measure (FIM). The study groups exhibited a moderate level of heterogeneity (I2 = 54%, $P = 0.07$). A meta-analysis was conducted using a random-effects model, which revealed no significant difference in the combined effect (MD = 2.12, $P = 0.41$, 95% CI [−2.92, 7.16]). This suggests that there is no substantial disparity in the improvement of functional independence between Lokomat® robot-assisted gait training and CPT (Figure 7).

Discussion

The existing studies lack a comprehensive evaluation of the effectiveness of robot-assisted gait training using the Lokomat® compared to CPT for lower extremity rehabilitation. Therefore, the purpose of this systematic review is to fill this gap. The literature examined in this review demonstrates a commendable level of quality, with the majority of studies being deemed acceptable and good. As a result, our conclusions can be considered informative.

In a meta-analysis conducted by Baronchelli et al. (18), the authors examined the recovery of balance function in stroke patients using three different balance scales in comparison to traditional physical therapy. The findings indicated that Lokomat® robot-assisted walking training was more effective in improving the TUG test and the Rivermead Mobility Index, while the results for BBS were inconclusive. The inconsistency in the BBS results can be attributed to the fact that Baronchelli et al. calculated the difference between pre- and post-treatment outcome measures, whereas our study combined the results after treatment, leading

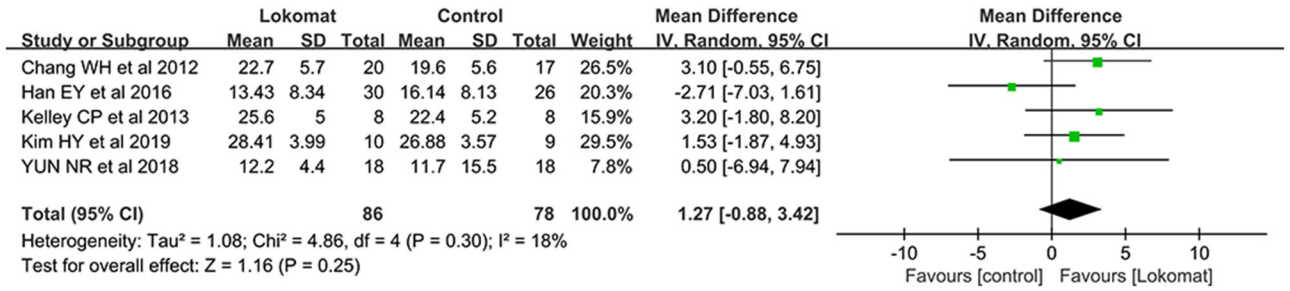

FIGURE 2
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on FMA-LE at post-treatment.

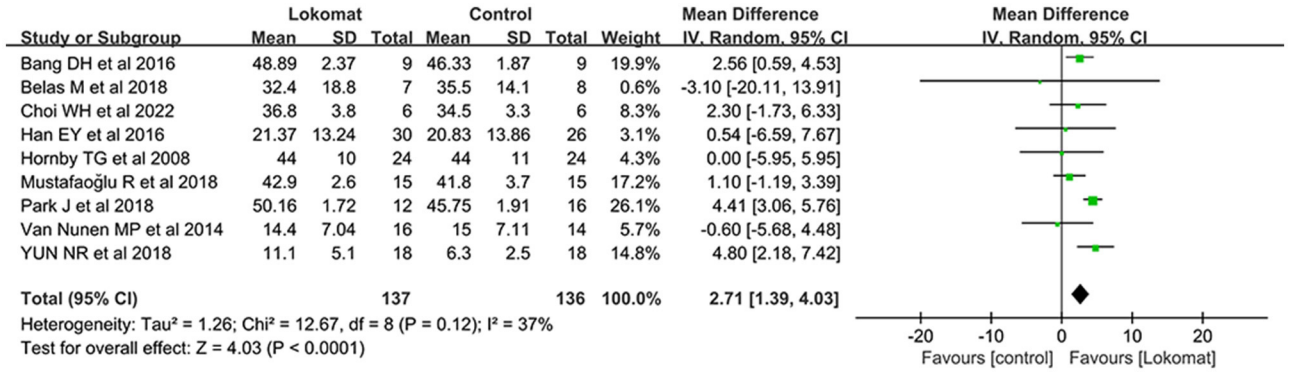

FIGURE 3
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on BBS at post-treatment.

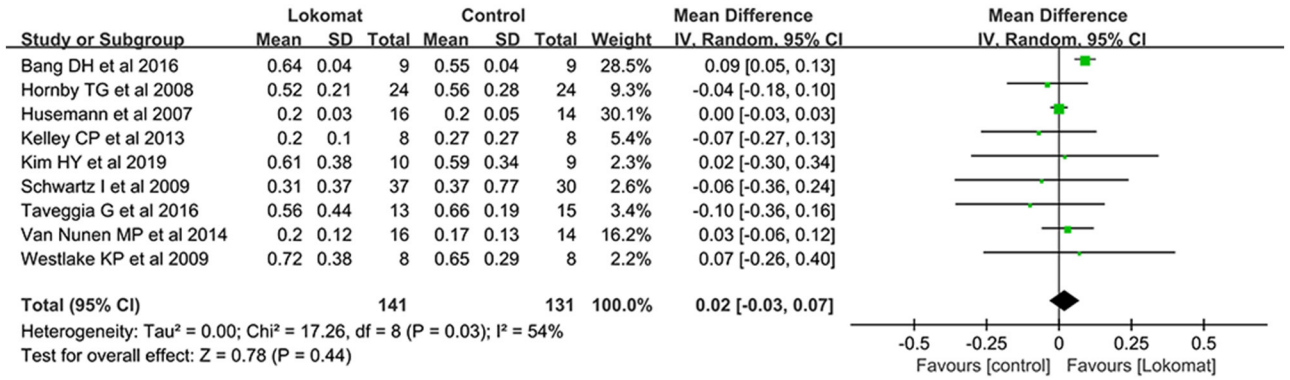

FIGURE 4
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on gait speed at post-treatment.

to inconsistent findings. We argue that our approach aligns with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. In terms of motor function, our analysis of the functional ambulation category (FAC) yielded consistent results with a study conducted by Calafiore et al. (16), showing no significant difference between the two interventions. It is worth noting that the wide range of grading in the FAC scale may make it challenging to detect treatment differences within a short intervention period. Additionally, other studies have reported that the robot did not outperform traditional therapy in areas such as daily life function and walking speed (47, 48). The early design of the robot also restricted trunk and pelvic movements, which negatively affected pelvic movements during gait training (32). This limitation may explain the lack of observed improvement in gait in some studies.

The findings of the present study indicate that the development of robotic devices has aimed to alleviate the physical strain associated with repetitive manual-assistance tasks and enhance the

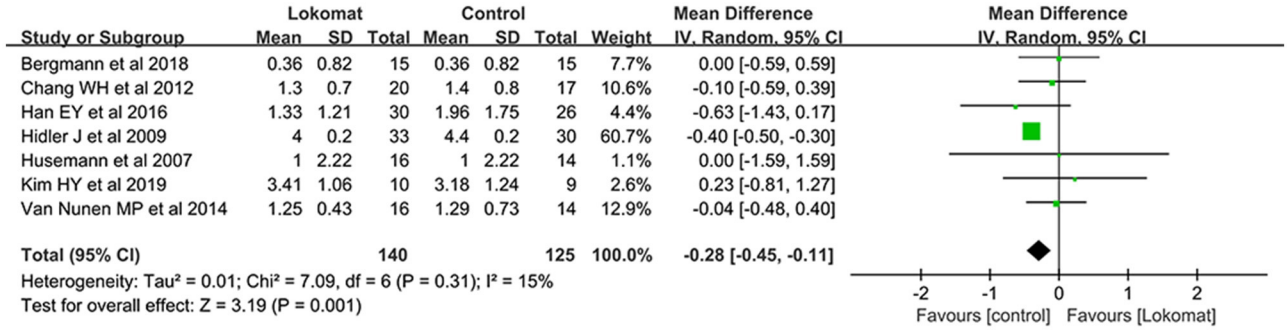

FIGURE 5
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on FAC at post-treatment.

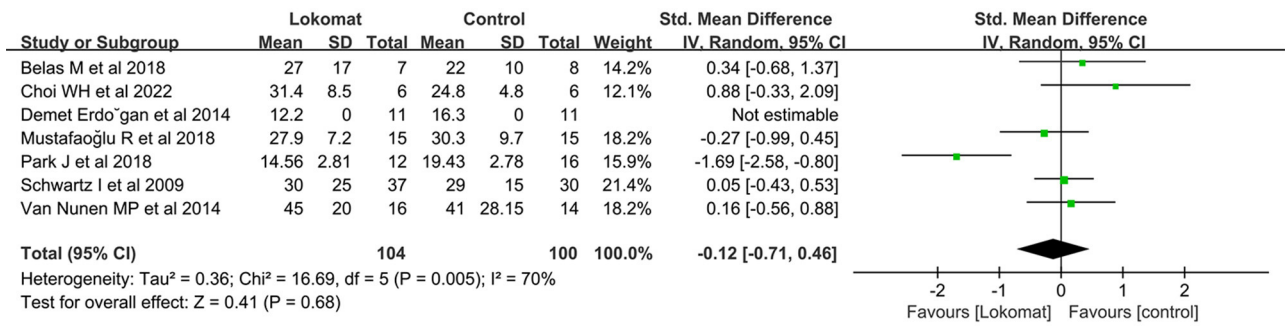

FIGURE 6
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on TUG at post-treatment.

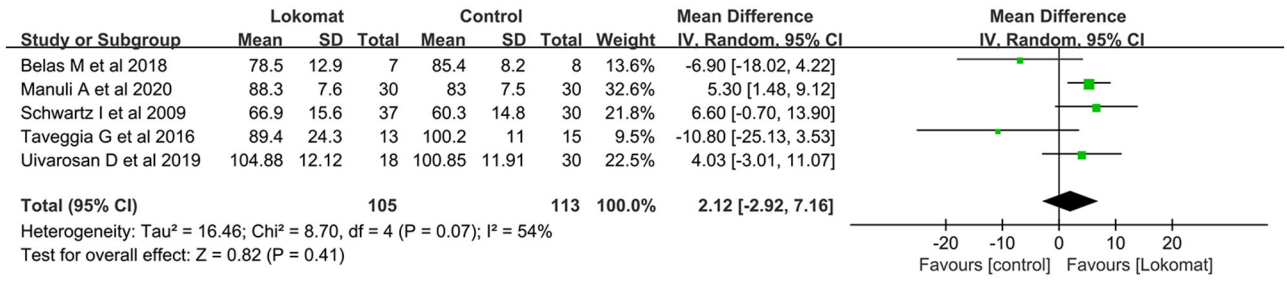

FIGURE 7
Forest plot: comparison of the effect of robot-assisted gait training with the Lokomat® and CPT on FIM at post-treatment.

quality of gait performance and to provide assistance to therapists and patients throughout different phases of neurorehabilitation. While there is scientific and clinical evidence supporting the efficacy, safety, and tolerability of gait training with robotic devices, there is a scarcity of documentation regarding their comparative advantages over conventional therapies. Currently, there is a focus on enhancing the assisted gait patterns by utilizing sensors and control algorithms in order to improve their quality (49). Recent studies have demonstrated that the utilization of robot-assisted treadmill training led to a more balanced distribution of muscle activity in individuals with paresis as opposed to the conventional treatment methods (50). Another aspect of interest is that Lokomat® robot-assisted walking training can reduce the burden on the therapist when the training is more intense and longer in duration (51). Although no such data were obtained in this study, this is an important reason for us to recommend the promotion and use of Lokomat® even after drawing this conclusion. With the exception of Kelley et al. (35), who documented study-related adverse events (AEs) such as skin redness or breakage caused by pressure or friction from the straps or cuffs, no other studies reported any adverse events. Consequently, the utilization of the Lokomat® robot is generally considered to be safe.

It is conceivable that the diverse outcome measures employed in the literature reviewed may obscure the potential benefits

derived from the Lokomat®. In essence, the outcome measures utilized in the articles may not accurately reflect the true effects of the treatment. Consequently, there is a necessity for more refined and objective scales to comprehensively assess the clinical outcomes, enabling a more accurate understanding of the treatment's efficacy. Furthermore, the utilization of the Lokomat® in gait training heavily relies on the therapist's personal experience and familiarity with the device. While efforts are continuously made to refine standard rehabilitation protocols, it is evident that the use of the robot necessitates individualized treatment. It is imperative to perceive it as a tool rather than a ready-made solution, thus necessitating further investigation into treatment duration, support weights, walking parameters, and other relevant factors to optimize its utility for physiotherapists.

Potential discrepancies in the findings of this study may have arisen from various factors, including the quality and language of the literature incorporated. First, with regard to the quality of the literature, it is worth noting that while all the included trials were RCTs, the adequacy of blinding and randomization procedures in individual studies was not consistently well executed. Second, the restriction to English language literature may have resulted in the exclusion of relevant studies published in other languages. Unavailability due to non-publication or non-appearance in publicly available databases introduces a certain amount of uncertainty when analyzing the results. This may result in our results not being comprehensive enough to capture the true effect across the field. Therefore, a certain amount of caution is introduced when interpreting our results and presenting conclusions. In addition, we recommend that future studies consider reporting their findings more comprehensively and make them as accessible as possible so that further meta-analysis can better reveal the true picture of the effect of the Lokomat® on motor function rehabilitation after stroke. Although the assessment of literature quality adhered to basic criteria across the board, it is important to acknowledge the presence of heterogeneity in the results, indicating a potential lack of reliability.

In general, the system is easily configured, minimizes the requirement for physical therapy labor, and aligns with human expectations of robotic assistance. Nevertheless, the findings of the present investigation indicate suboptimal clinical outcomes in lower extremity rehabilitation, particularly in relation to exercise. Consequently, additional improvements in the implementation and assessment approaches are necessary.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Richards LG, Cramer SC. Therapies targeting stroke recovery. *Stroke.* (2023) 54:265–9. doi: 10.1161/STROKEAHA.122.041729

2. Eng JJ, Tang PF. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. *Expert Rev Neurother.* (2007) 7:1417–36. doi: 10.1586/14737175.7.10.1417

3. Wist S, Clivaz J, Sattelmayer M. Muscle strengthening for hemiparesis after stroke: a meta-analysis. *Ann Phys Rehabil Med.* (2016) 59:114–24. doi: 10.1016/j.rehab.2016.02.001

4. Trompetto C, Marinelli L, Mori L, Cossu E, Zilioli R, Simonini M, et al. Postactivation depression changes after robotic-assisted gait training in hemiplegic stroke patients. *Gait Posture.* (2013) 38:729–33. doi: 10.1016/j.gaitpost.2013.03.011

5. Chou MY, Nishita Y, Nakagawa T, Tange C, Tomida M, Shimokata H, et al. Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. *BMC Geriatr.* (2019) 19:186. doi: 10.1186/s12877-019-1199-7

6. Kramer SF, Hung SH, Brodtmann A. The impact of physical activity before and after stroke on stroke risk and recovery: a narrative review. *Curr Neurol Neurosci Rep.* (2019) 19:28. doi: 10.1007/s11910-019-0949-4

7. Negrini F, Gasperini G, Guanziroli E, Vitale JA, Banfi G, Molteni F. Using an accelerometer-based step counter in post-stroke patients: validation of a low-cost tool. *Int J Environ Res Public Health.* (2020) 17:3177. doi: 10.3390/ijerph17093177

8. Hobbs B, Artemiadis P. A review of robot-assisted lower-limb stroke therapy: unexplored paths and future directions in gait rehabilitation. *Front Neurorobot.* (2020) 14:19. doi: 10.3389/fnbot.2020.00019

9. Calabro RS, Naro A, Russo M, Bramanti P, Carioti L, Balletta T, et al. Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial. *J Neuroeng Rehabil.* (2018) 15:35. doi: 10.1186/s12984-018-0377-8

10. Molteni F, Gasperini G, Cannaviello G, Guanziroli E. Exoskeleton and end-effector robots for upper and lower limbs rehabilitation: narrative review. *PM R.* (2018) 10:S174–88. doi: 10.1016/j.pmrj.2018.06.005

11. Morone G, Paolucci S, Cherubini A, De Angelis D, Venturiero V, Coiro P, et al. Robot-assisted gait training for stroke patients: current state of the art and perspectives of robotics. *Neuropsychiatr Dis Treat.* (2017) 13:1303–11. doi: 10.2147/NDT.S114102

12. Pournajaf S, Calabro RS, Naro A, Goffredo M, Aprile I, Tamburella F, et al. Robotic versus conventional overground gait training in subacute stroke survivors: a multicenter controlled clinical trial. *J Clin Med.* (2023) 12:439. doi: 10.3390/jcm12020439

13. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? *Neurorehabil Neural Repair.* (2012) 26:308–17. doi: 10.1177/1545968312439687

14. Zhang X, Yue Z, Wang J. Robotics in Lower-Limb Rehabilitation after Stroke. *Behav Neurol.* (2017) 2017:3731802. doi: 10.1155/2017/3731802

15. Bruni MF, Melegari C, De Cola MC, Bramanti A, Bramanti P, Calabro RS. What does best evidence tell us about robotic gait rehabilitation in stroke patients: a systematic review and meta-analysis. *J Clin Neurosci.* (2018) 48:11–7. doi: 10.1016/j.jocn.2017.10.048

16. Calafiore D, Negrini F, Tottoli N, Ferraro F, Ozyemisci-Taskiran O, de Sire A. Efficacy of robotic exoskeleton for gait rehabilitation in patients with subacute stroke : a systematic review. *Eur J Phys Rehabil Med.* (2022) 58:1–8. doi: 10.23736/S1973-9087.21.06846-5

17. Tedla JS, Dixit S, Gular K, Abohashrh M. Robotic-assisted gait training effect on function and gait speed in subacute and chronic stroke population: a systematic review and meta-analysis of randomized controlled trials. *Eur Neurol.* (2019) 81:103–11. doi: 10.1159/000500747

18. Baronchelli F, Zucchella C, Serrao M, Intiso D, Bartolo M. The effect of robotic assisted gait training with lokomat(R) on balance control after stroke: systematic review and meta-analysis. *Front Neurol.* (2021) 12:661815. doi: 10.3389/fneur.2021.661815

19. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* (2021) 372:n160. doi: 10.1136/bmj.n160

20. Cumpston MS, McKenzie JE, Welch VA, Brennan SE. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. *J Public Health (Oxf).* (2022) 44:e588–92. doi: 10.1093/pubmed/fdac036

21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* (2005) 5:13. doi: 10.1186/1471-2288-5-13

22. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther.* (2003) 83:713–21. doi: 10.1093/ptj/83.8.713

23. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother.* (2009) 55:129–33. doi: 10.1016/S0004-9514(09)70043-1

24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

25. Bang DH, Shin WS. Effects of robot-assisted gait training on spatiotemporal gait parameters and balance in patients with chronic stroke: A randomized controlled pilot trial. *NeuroRehabilitation.* (2016) 38:343–9. doi: 10.3233/NRE-161325

26. Belas Dos Santos M, Barros de Oliveira C, Dos Santos A, Garabello Pires C, Dylewski V, Arida RM. A comparative study of conventional physiotherapy versus robot-assisted gait training associated to physiotherapy in individuals with ataxia after stroke. *Behav Neurol.* (2018) 2018:2892065. doi: 10.1155/2018/2892065

27. Bergmann J, Krewer C, Jahn K, Muller F. Robot-assisted gait training to reduce pusher behavior: a randomized controlled trial. *Neurology.* (2018) 91:e1319–27. doi: 10.1212/WNL.0000000000006276

28. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. *Neurorehabil Neural Repair.* (2012) 26:318–24. doi: 10.1177/1545968311408916

29. Choi W. Effects of robot-assisted gait training with body weight support on gait and balance in stroke patients. *Int J Environ Res Public Health.* (2022) 19:5814. doi: 10.3390/ijerph19105814

30. Ucar DE, Paker N, Bugdayci D. Lokomat: a therapeutic chance for patients with chronic hemiplegia. *NeuroRehabilitation.* (2014) 34:447–53. doi: 10.3233/NRE-141054

31. Han EY, Im SH, Kim BR, Seo MJ, Kim MO. Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial. *Medicine.* (2016) 95:e5078. doi: 10.1097/MD.0000000000005078

32. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. *Neurorehabil Neural Repair.* (2009) 23:5–13. doi: 10.1177/1545968308326632

33. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. *Stroke.* (2008) 39:1786–92. doi: 10.1161/STROKEAHA.107.504779

34. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. *Stroke.* (2007) 38:349–54. doi: 10.1161/01.STR.0000254607.48765.cb

35. Kelley CP, Childress J, Boake C, Noser EA. Over-ground and robotic-assisted locomotor training in adults with chronic stroke: a blinded randomized clinical trial. *Disabil Rehabil Assist Technol.* (2013) 8:161–8. doi: 10.3109/17483107.2012.714052

36. Kim HY, Shin JH, Yang SP, Shin MA, Lee SH. Robot-assisted gait training for balance and lower extremity function in patients with infratentorial stroke: a single-blinded randomized controlled trial. *J Neuroeng Rehabil.* (2019) 16:99. doi: 10.1186/s12984-019-0553-5

37. Manuli A, Maggio MG, Latella D, Cannavo A, Balletta T, De Luca R, et al. Can robotic gait rehabilitation plus Virtual Reality affect cognitive and behavioural outcomes in patients with chronic stroke? A randomized controlled trial involving three different protocols. *J Stroke Cerebrovasc Dis.* (2020) 29:104994. doi: 10.1016/j.jstrokecerebrovasdis.2020.104994

38. Mustafaoglu R, Erhan B, Yeldan I, Ersoz Huseyinsinoglu B, Gunduz B, Razak Ozdincler A. The effects of body weight-supported treadmill training on static and dynamic balance in stroke patients: a pilot, single-blind, randomized trial. *Turk J Phys Med Rehabil.* (2018) 64:344–52. doi: 10.5606/tftrd.2018.2672

39. Park J, Chung Y. The effects of robot-assisted gait training using virtual reality and auditory stimulation on balance and gait abilities in persons with stroke. *NeuroRehabilitation.* (2018) 43:227–35. doi: 10.3233/NRE-172415

40. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, et al. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial. *PM R.* (2009) 1:516–23. doi: 10.1016/j.pmrj.2009.03.009

41. Taveggia G, Borboni A, Mule C, Villafane JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. *Int J Rehabil Res.* (2016) 39:29–35. doi: 10.1097/MRR.0000000000000137

42. Uivarosan D, Tit DM, Iovan C, Nistor-Cseppento DC, Endres L, Lazar L, et al. Effects of combining modern recovery techniques with neurotrophic medication and standard treatment in stroke patients. *Sci Total Environ.* (2019) 679:80–7. doi: 10.1016/j.scitotenv.2019.05.070

43. van Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, de Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. *Disabil Rehabil Assist Technol.* (2015) 10:141–8. doi: 10.3109/17483107.2013.873489

44. Westlake KP, Patten C. Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. *J Neuroeng Rehabil.* (2009) 6:18. doi: 10.1186/1743-0003-6-18

45. Yun N, Joo MC, Kim SC, Kim MS. Robot-assisted gait training effectively improved lateropulsion in subacute stroke patients: a single-blinded randomized controlled trial. *Eur J Phys Rehabil Med.* (2018) 54:827–36. doi: 10.23736/S1973-9087.18.05077-3

46. Swinnen E, Beckwee D, Pinte D, Meeusen R, Baeyens JP, Kerckhofs E. Treadmill training in multiple sclerosis: can body weight support or robot assistance provide added value? A systematic review. *Mult Scler Int.* (2012) 2012:240274. doi: 10.1155/2012/240274

47. Cho JE, Yoo JS, Kim KE, Cho ST, Jang WS, Cho KH, et al. Systematic review of appropriate robotic intervention for gait function in subacute stroke patients. *Biomed Res Int.* (2018) 2018:4085298. doi: 10.1155/2018/4085298

48. Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. *JBI Database System Rev Implement Rep.* (2017) 15:3049–91. doi: 10.11124/JBISRIR-2017-003456

49. Chen Q, Cheng H, Yue C, Huang R, Guo H. Dynamic balance gait for walking assistance exoskeleton. *Appl Bionics Biomech.* (2018) 2018:7847014. doi: 10.1155/2018/7847014

50. Krishnan C, Kotsapouikis D, Dhaher YY, Rymer WZ. Reducing robotic guidance during robot-assisted gait training improves gait function: a case report on a stroke survivor. *Arch Phys Med Rehabil.* (2013) 94:1202–6. doi: 10.1016/j.apmr.2012.11.016

51. Stoller O, Waser M, Stammler L, Schuster C. Evaluation of robot-assisted gait training using integrated biofeedback in neurologic disorders. *Gait Posture.* (2012) 35:595–600. doi: 10.1016/j.gaitpost.2011.11.031

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A systematic review on functional electrical stimulation based rehabilitation systems for upper limb post-stroke recovery

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Background: Stroke is one of the most common neurological conditions that often leads to upper limb motor impairments, significantly affecting individuals' quality of life. Rehabilitation strategies are crucial in facilitating post-stroke recovery and improving functional independence. Functional Electrical Stimulation (FES) systems have emerged as promising upper limb rehabilitation tools, offering innovative neuromuscular reeducation approaches.

Objective: The main objective of this paper is to provide a comprehensive systematic review of the start-of-the-art functional electrical stimulation (FES) systems for upper limb neurorehabilitation in post-stroke therapy. More specifically, this paper aims to review different types of FES systems, their feasibility testing, or randomized control trials (RCT) studies.

Methods: The FES systems classification is based on the involvement of patient feedback within the FES control, which mainly includes "Open-Loop FES Systems" (manually controlled) and "Closed-Loop FES Systems" (brain-computer interface-BCI and electromyography-EMG controlled). Thus, valuable insights are presented into the technological advantages and effectiveness of Manual FES, EEG-FES, and EMG-FES systems.

Results and discussion: The review analyzed 25 studies and found that the use of FES-based rehabilitation systems resulted in favorable outcomes for the stroke recovery of upper limb functional movements, as measured by the FMA (Fugl-Meyer Assessment) (Manually controlled FES: mean difference = 5.6, 95% CI (3.77, 7.5), $P < 0.001$; BCI-controlled FES: mean difference = 5.37, 95% CI (4.2, 6.6), $P < 0.001$; EMG-controlled FES: mean difference = 14.14, 95% CI (11.72, 16.6), $P < 0.001$) and ARAT (Action Research Arm Test) (EMG-controlled FES: mean difference = 11.9, 95% CI (8.8, 14.9), $P < 0.001$) scores. Furthermore, the shortcomings, clinical considerations, comparison to non-FES systems, design improvements, and possible future implications are also discussed for improving stroke rehabilitation systems and advancing post-stroke recovery. Thus, summarizing the existing literature, this review paper can help researchers identify areas for further investigation. This can lead to formulating research questions and developing new studies aimed at improving FES systems and their outcomes in upper limb rehabilitation.

KEYWORDS

stroke, rehabilitation, functional electrical stimulation (FES), upper limb neurorehabilitation, post-stroke therapy, stroke rehabilitation systems

1 Introduction

Stroke occurs when blood flow to the brain is acutely compromised, resulting in neural injuries and subsequently functional impairment and sometimes long-term disabilities (1, 2). This life-changing event can significantly impair cognitive, emotional, and physical functions. Studies show that individuals convalescing from a stroke frequently experience feelings of frustration, helplessness, and social isolation, which can lead to a higher risk of depression and a reduced capability to perform daily activities (3, 4). A study estimated that in 2016, stroke caused approximately 5.5 million deaths and 116.4 million DALYs (disability-adjusted life-years) worldwide (5). Among stroke survivors, upper limb hemiparesis, i.e., weakness or lack of ability to move the upper limb on one side of the body is a common condition (6). Further, ∼55–75% of stroke patients with a hemiplegic arm still have a defective function in arm movements after 3 to 6 months of rehabilitation (7).

Post-stroke care primarily aims to rehabilitate patients to effectively recover lost functions and help them in their daily activities. This allows them to have their independence and reintegrate into society. Among different rehabilitation methods, occupational and physical therapies are the most common stroke rehabilitation methods for restoring motor functions (8). These approaches use task-specific and repetitive training to induce motor recovery, leveraging innate motor learning and neuroplasticity mechanisms. However, functional recovery is not always satisfactory, as only 20% of patients are fully able to resume their social life after physical rehabilitation (9). This shows a significant gap in the overall effectiveness of the rehabilitation and recovery processes, thus indicating the need for new approaches to restore patients' functional mobility and ultimately improve their quality of life (10).

Advancements in science and technology have introduced different stroke rehabilitation methods, among which the functional electrical stimulation (FES) is commonly being used (11). FES is a rehabilitation tool for restoring the motor skills of stroke survivors by applying electrical impulses through the skin surface to stimulate targeted nerves, thus instigating movements in paretic muscles (12–14). Electrical stimulation applied to the muscle is controlled so that the movement produced will provide a useful function and not a random trajectory. Depending on their mode of operation, FES systems fall into 2 major types: Open-loop FES and Closed-loop FES systems (Figure 1). In open-loop systems, FES is mainly applied by a therapist using preprogrammed patterns that cannot be controlled by the patient feedback to initiate the muscle activation (Figure 1A). Open-loop FES was first introduced to hemiplegia patients by Moe and Post (15) and later improved by Kralj et al. to treat patients with neural disorders (16). Many studies have validated the efficacy of open-loop FES in upper limb stroke rehabilitation application (17–24).

Rehabilitation therapies aim to restore brain connections that subserve motor recovery and function. Along with the therapist's assistance, the patient's active participation via feedback loop can further improve recovery outcomes. In this regard, closed-loop FES systems play a substantial part, mainly including brain-computer interface (BCI) and electromyogram (EMG) controlled FES systems (Figures 1B, C, respectively). In BCI-FES (also called electroencephalogram (EEG)-FES), motor imagery (MI) paradigms facilitate an effective approach to neurorehabilitation (25–28). A BCI system provides a direct interaction channel between the brain and a peripheral device by translating the brain's electrical activities (as captured by EEG) into control/command signals. For rehabilitation application, the MI training consists of representing imaginary movements of limbs without physically performing them. During rehabilitation, the MI activates the neural circuits involved in actual movements and could induce functional redistribution of neuronal circuits through neural plasticity (29–31). An MI-BCI is a computer-based system that records the EEG signals and translates the user's intention to perform the specific task based on MI events. Thus, the EEG signal is used to generate a muscle electrical stimulation pattern that matches the intended movements of user (the user imagines and tries to perform that movement). Such MI-BCI methods with FES systems have widely been used in stroke rehabilitation for motor and functional recovery (32–45).

Besides EEG, EMG-controlled FES has been proven to be an efficient method for stroke rehabilitation. EMG signal measures the electrical currents generated in muscles during their contraction, representing neuromuscular activity (46). Using EMG as feedback in the EMG-FES device enables real-time analysis of muscle activity and adjusts the amount of FES stimulation based on the muscle's requirement (47–49). Thus, the resulting movement and intrinsic multisensory activation are paired with the subject's active attention and intention. Furthermore, the muscle contraction is modulated by the subjects themselves, hence, facilitating fast motor learning and recovery of lost function. Finally, EMG-controlled FES limits the chances of excess electrical stimulation of muscles, which otherwise can cause muscle cramps and fatigue (50). Different studies have been performed to develop and test EMG-controlled FES systems for stroke rehabilitation applications (51–58).

To date, different review papers have been published regarding stroke rehabilitation, which include FES in rehabilitation engineering (59), the usability of FES in upper limb stroke rehabilitation (60), the effectiveness of upper limb FES after stroke (12), devices used in muscular electrical stimulation for stroke rehabilitation (61), EMG-triggered/controlled electrical stimulation for motor recovery of the upper limb (48), BCI systems for post-stroke rehabilitation (11, 62, 63), flexible technology in stroke rehabilitation systems (64), home-based technologies for stroke rehabilitation (65), efficacy of robotic exoskeleton for gait rehabilitation (66), game-based virtual reality system for upper limb rehabilitation (67), and different techniques to stimulate upper extremity stroke recovery (68). However, no review article lists and discusses the different types of FES systems for upper limb stroke rehabilitation. Hence, in this systematic review, we assessed the RCT, and feasibility testing studies related to different FES-based rehabilitation systems to determine their impact on improving upper limb functional movements among stroke patients. By examining the effectiveness and implications of various FES approaches, this review also provides a comprehensive overview of the potential benefits and challenges associated with FES-based stroke rehabilitation, offering insights into the future direction of this promising therapeutic modality.

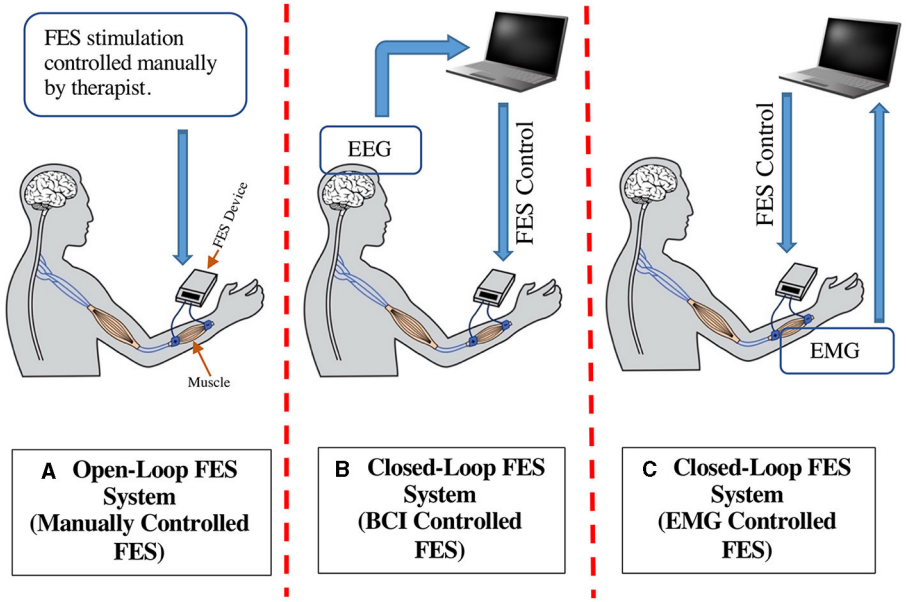

FIGURE 1
Types of FES based rehabilitation system for stroke recovery **(A)** Open-Loop FES System, **(B)** Closed-Loop FES System (BCI-FES), **(C)** Closed-Loop FES System (EMG-FES).

2 Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the systematic review. Three researchers independently performed the search strategy, eligibility criteria, and data extraction of included studies.

2.1 Search strategy

The review was conducted using four academic electronic databases including ScienceDirect, PubMed, Scopus, and IEEE databases using the keywords: stroke rehabilitation, functional electrical stimulation (FES), RCT, feasibility testing, upper limb functional movements, brain-computer interface (BCI), EMG-based rehabilitation, BCI-based rehabilitation, EEG-based rehabilitation, neurorehabilitation devices, upper limb rehabilitation, EMG-controlled FES, BCI-controlled FES, EEG-controlled FES. Figure 2 illustrates the PRISMA flow chart of study selection. Initially, 923 research articles were found from a keyword search in the different databases. Among them, 181 duplicates were removed. Then, the remaining 742 papers were evaluated, and based on their titles and abstract, 313 articles were excluded. Lastly, full-text screening was performed and only 25 manuscripts fulfilled the inclusion criteria and were included in this review paper. Of these, 8, 13, and 4 manuscripts involved open-loop FES, closed-loop BCI/EEG-FES, and closed-loop EMG-FES systems, respectively.

2.2 Eligibility criteria

A systematic search was performed based on predefined inclusion criteria (IC) and exclusion criteria (EC). In the final stage, only those research papers were selected that met all the conditions listed below:

IC1: Written in English.
IC2: Published on or after the year 2009.
IC3: Related to FES-based stroke rehabilitation in terms of "Manually operated" OR "BCI/EEG controlled" OR "EMG controlled".
IC4: Focus on upper limb stroke rehabilitation.
IC5: Have validated the system performance on stroke patients (feasibility study OR RCTs).
EC1: Application other than stroke.
EC2: For lower limb stroke rehabilitation.
EC3: Testing only on healthy individuals.

2.3 Data extraction

Three authors independently extracted the following information of each included study: type of used rehabilitation system, experimental and control groups, application as RCT/feasibility study, upper limb targeted areas, total number of therapy sessions, therapy session time and outcome measures/performance evaluation. Any disagreement during the process of data extraction were resolved through discussion among three authors.

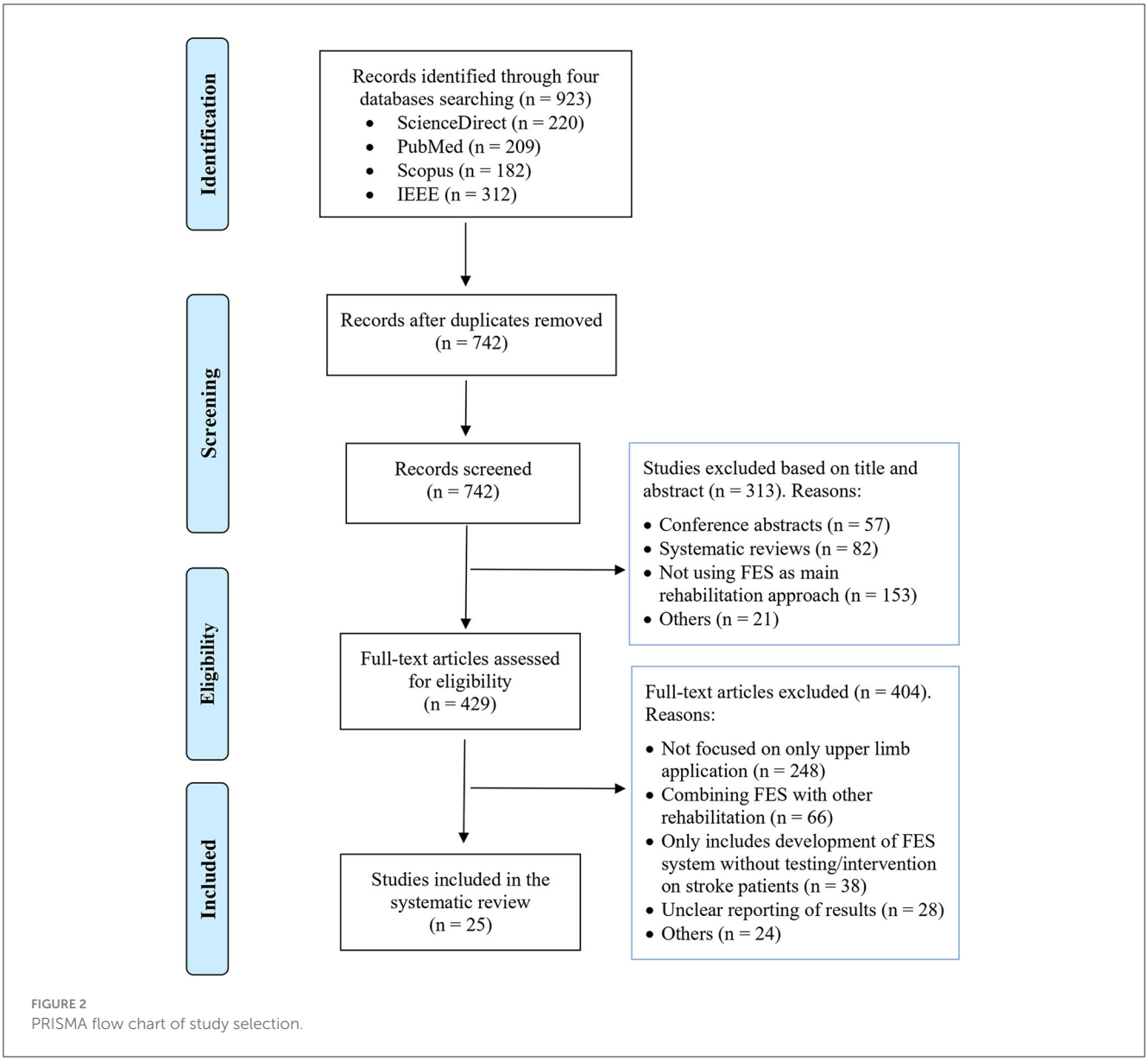

FIGURE 2
PRISMA flow chart of study selection.

2.4 Quality assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools. For randomized controlled trials, the Risk of Bias 2 (ROB2) tool was used to evaluate potential bias across five domains–randomization, deviations from intervention, missing outcome data, outcome measurement, and selection of reported results (69). The quality of observational case series studies was appraised using the NIH Quality Assessment tool, which contains 9 items assessing aspects like study objective, population description, intervention clarity, outcome validity, and follow-up (70). Finally, the included case reports were critically appraised using the Joanna Briggs Institute (JBI) checklist for case reports (71). This tool evaluates key domains such as patient demographics, clinical history, diagnosis assessment, intervention details, and outcome measures.

2.5 Statistical analysis

Continuous data was analyzed using OpenMetaAnalyst software. A fixed effect model calculated mean differences (MD) with 95% confidence intervals (CI) for continuous outcomes. Statistical homogeneity and heterogeneity were assessed using the I^2 statistic. An I^2 value >50% was considered indicative of substantial heterogeneity.

3 Results

3.1 Risk of bias in included studies

Among a total of 25 included studies, the quality of the 9 RCTs (17, 32–36, 51, 55, 56) was assessed using the "Risk of Bias 2 (ROB2)" tool (Supplementary Figures S1, S2). Overall, most

studies were rated as having a low risk of bias in terms of the randomization process, missing outcome data, and measurement of the outcome. However, in 4 studies (17, 32, 33, 35), some concerns were identified regarding deviations from intended interventions, resulting in a rating of "some concerns." The remaining five studies (34, 36, 51, 55, 56) were found to have an overall "low risk" of bias.

The quality of the 11 observational case series studies (18–22, 24, 41, 43–45, 58) was assessed using the "NIH Quality Assessment" tool. Based on the assessment, 7 studies were determined to be of "good quality", while 4 studies were evaluated as "fair quality" (Supplementary Table S1). In addition, five case reports (23, 37, 38, 40, 42) were included and appraised using the "Joanna Briggs Institute (JBI) Critical Appraisal" tool. The overall quality of each case report was "good" based on the JBI checklist (Supplementary Table S2).

3.2 Included studies regarding types of FES-based stroke rehabilitation systems

3.2.1 Open-loop FES system: pre-defined FES for stroke rehabilitation

An open-loop FES system comprises of a manually controlled device, which is operated by a therapist. During the therapy session, the therapist manually administers electrical stimulation to the specific muscles of the patient, using patient-specific predetermined stimulation parameters such as stimulation intensity, time duration, and ON/OFF cycle.

Numerous studies have been conducted utilizing open-loop FES systems for stroke rehabilitation to regain upper limb motor functions. Experimenting with the effectiveness of FES, Nakipoglu Yuzer et al. (17) applied FES (two channels and four surface electrodes) to the spastic muscles of 30 patients (an RCT), and the improvement of clinical scores indicates that FES effectively reduces wrist flexor spasticity. In (18), Makowski et al. showed that FES produces functional hand opening when the patient is relaxed, but it is overpowered by finger flexor coactivation when the patient voluntarily exerts effort to reach/open the hand. For that, their study proves that the amount of hand opening grows significantly (3.2–8.8 cm) when including FES for both reaching and hand opening muscles even in the presence of submaximal or zero effort. Moreover, Meadmore et al. (19) investigated FES of shoulder, elbow, and wrist muscles: five patients underwent 18 sessions and completed FMA (Fugl-Meyer Assessment) and ARAT (Action Research Arm Test) assessments. The study showed an improvement of 4.4, providing evidence that the integration of low-cost hardware with advanced FES controllers can reduce upper limb impairment. Sun et al. (20) reported the FES for upper limb functional activity practice, used by 9 therapists to set 8 sessions activities with 22 stroke patients. Among them, 17 patients showed a session completion rate >90%, demonstrating its capability of delivering high-intensity therapy compared to traditional face-to-face therapy. Also, Niu et al. (21) illustrated a technique for creating FES patterns based on muscle synergies of a normal subject (three patients–adjusted for each participant and task) using a programmable FES device. Followed by 5-day sessions of intervention using synergy-based FES delivery to another three patients. The outcome of the new technology was measured by improvement in FMA scores (28.6% ± 13.7%). In Chou et al. (22), made use of the latter in the design and test of an automated synergy-based FES system to match electrically induced movements to assist residual movements of patients. Results based on changes in FMA scores indicate that the synchronization produced more consistent compound movements with reduced RMS (root mean square) errors under different triggering conditions. Martín-Odriozola et al. (23) developed the Fesia Grasp device used for hand dexterity rehabilitation of a 69-yearold post-ischemic stroke woman. Following their first study (21), Niu et al. (24) conducted a TOT (Task-oriented training) protocol with repeated forward and lateral reaching movements assisted by synergy-based FES on 16 patients, divided into FES (EG) and Sham (CG) groups over 5-days. Findings of higher FMA than Sham indicate efficacy of open-loop FES system in post-stroke rehabilitation. A detailed overview of research studies regarding open-loop FES rehabilitation is provided in Table 1.

3.2.2 Closed-loop FES system: BCI controlled FES for stroke rehabilitation

According to Hebb's principle "cells that fire together wire together" (72, 73), suggesting that the coordination of cortical and physical activities during the rehabilitation therapies could lead to an effective improvement of the impaired motor function (74–77). Therefore, a more effective approach may be to interface the FES rehabilitation device with an external system that could enhance the simultaneous activation of the motor cortex during the rehabilitation sessions. In this regard, MI-based BCI systems are an optimum choice, which allows the rehabilitation system to perform the required task based on the patient's imagination of intended motion, allowing more active participation of brain throughout the stroke therapy (78).

A BCI-FES rehabilitation system mainly comprises of a BCI unit (containing EEG element), BCI-FES interface component, and FES module. Some BCI-FES systems also incorporate a virtual reality (VR) paradigm as a part of their setup (Figure 3). In such systems, firstly, the patient is provided the VR environment (on screen or the headset) that contains the pre-programmed therapy session of targeted motion e. g., hands extension/flexion (Figure 3A). The patient will be asked to imagine the task execution displayed in the virtual environment. Each task imagination generates a specific EEG signal, which will be acquired and processed by the BCI unit (Figure 3B). Depending on the imagination, the BCI-FES interface generates a trigger command to control the ON/OFF state of FES stimulation and will also control the stimulation parameters (Figure 3C). Lastly, the FES device provides electrical stimulation to the impaired muscles and hence, facilitate performing the required movements (Figure 3D). To make the strategy effective, the user typically undergoes training to establish a connection between their brain signals and specific motor tasks. This training involves practicing mental tasks or visualizing movements to generate distinct brain patterns that the BCI can recognize and translate into commands for the FES device.

BCI-FES systems are widely used for stroke rehabilitation and several randomized controlled trial (RCT) studies have been

TABLE 1 Research studies and their outcomes for open-loop FES neurorehabilitation systems.

Open-loop FES systems for upper limb stroke rehabilitation				
Study	Commercial/ customized open-loop FES rehabilitation system	Experimental group (EG) and control group (CG)	i. Upper limb targeted areas ii. Total sessions iii. Therapy time/session	Outcome measures/ performance evaluation/other comments
Nakipoglu Yuzer et al. (17)	Customized	RCT EG and CG: 30 post-stroke hemiplegic patients were randomly divided into EG and CG. FES was only applied to EG.	i. Wrist and finger extensors for wrist flexor spasticity ii. 20 iii. 30 min	ΔBI (EG) = 6.34 ± 1.06 ΔBI (CG) = 3 ± 1.02 ΔRMA (EG) = 0.66 ± 0.2 ΔRMA (CG) = 0.34 ± 0.31 ΔUEFT (EG) = 0.4 ± 0.28 ΔUEFT (CG) = 0.2 ± 0.08 ΔAROM (EG) = 6.73 ± 0.56 ΔAROM (CG) = 2.47 ± 0.62 ΔMAS3 (EG) = 80%-46.7% = 33.3% ΔMAS3 (CG) = 46.7%-40% = 6.7% A significant difference was found in favor of EG
Makowski et al. (18)	Customized	Feasibility study EG: 5 at least 6-months post-stroke patients.	i. Reaching and hand opening muscles ii. At least 3 sessions per patient iii. N/A	Hand opening average of participants increased significantly when including FES for reaching and hand opening in the presence of partial or zero reaching effort: ("+" sign shows the combination of two states) HE + RE = 3 cm (no stimulation) HE + RES = 3.2 cm RES + HES = 6.5 cm RES + HS = 8 cm RS + HS (0 effort - relaxed) = 8.8 cm
Meadmore et al. (19)	Customized (feasibility study)	Feasibility study EG: 5 stroke patients with hemiplegia CG: the same 5 patients completed 5 un-assisted tasks.	i. Shoulder, elbow and wrist muscle groups. ii. 18 sessions iii. 1 h	The FMA and ARAT were completed 1-6 days pre and post-intervention. Improvement was significant for both tests (Mean Results): ΔFMA (EG) = 23.2-18.8 = 4.4 ΔARAT (EG) = 7-2.6 = 4.4
Sun et al. (20)	Commercial FES-UPP flexible system (5 channels—FSM controller—feedback software)	Feasibility study EG: 22 patients with impaired upper limbs	i. Upper limb muscles ii. 8 tailored sessions per participant iii. N/A	Mean efficiency and mean number of successful repetitions of activities (NSR) in: Session 1: 12% Efficiency and 13 NSR Session 7: 34% Efficiency and 45 NSR 17 of 22 participants had a therapy completion rate >90%
Niu et al. (21)	Customized (Synergy based FES Device)	Feasibility study EG: 6 (3 pattern adjustment and 3 synergy-based FES testing)	i. Upper limb muscles ii. 5 iii. 1 h	Mean value of the change in FMA scores pre and post treatment indicate the improvement in functional movement. ΔFMA = 5.7 ± 2.5 (28.6% ± 13.7% change)
Chou et al. (22)	Customized (Automated FES System based on synergy FES)	Feasibility study EG: 5 patients (4 ischemic and 1 hemorrhagic all >MAS2) to test the system and 4 healthy patients to adjust the patterns	i. Upper limb muscles ii. 5 iii. 1 h	The lowest RMS errors of subjects (S0) under different trigger levels (TL) in each task (Forward or Lateral Reaching): S02 (TL 0.3) FR: 0.796 ± 0.290 S03 (TL 0.5) FR: 0.511 ± 0.190 S04 (TL 0.2) FR: 0.499 ± 0.227 S05 (TL 0.2) LR: 0.810 ± 0.372 S06 (TL 0.5) LR: 0.732 ± 0.213
Martín-Odriozola et al. (23)	Commercial (multi-field fesia grasp system FES)	Feasibility study EG: 69-year-old post ischemic stroke woman	i. Left hand dexterity. ii. 12 iii. 1 hour	ΔAROM (thumb) = +27° ΔAROM (index) = +8° ΔAROM (wrist) = +24° ΔGS = 2.9 kg
Niu et al. (24)	Customized	Feasibility study 16 patients with post-stroke hemiparesis EG: 9 FES CG: 7 Sham	i. 7 upper extremity muscles of elbow and shoulder ii. 5 iii. 1 h	FMA-UE scores of patients receiving FES increased by 6.67 ± 5.20 (28.13 ± 21.41%) FMA-UE scores of patients receiving Sham changed by 2.00 ± 2.38 (7.32 ± 16.11%)

HE, Max Hand Opening Effort; RE, Max Reaching Effort; RS, Reaching Stimulation; HS, Hand Opening Stimulation; RES, Partial Reaching Effort and Stimulation; HES, Partial Hand Opening Effort and Stimulation; FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; BI, Barthel Index; RMA, Rivermead Motor Assessment; UEFT, Upper Extremity Functional Index; AROM, Active Range of Motion; MAS, Motor Assessment Scale; NSR, Number of Successful Repetitions of Activities; RMS, Root Mean Square; FR, Forward Reaching; LR, Lateral Reaching; UE, Upper Extremity; GS, Grip Strength.

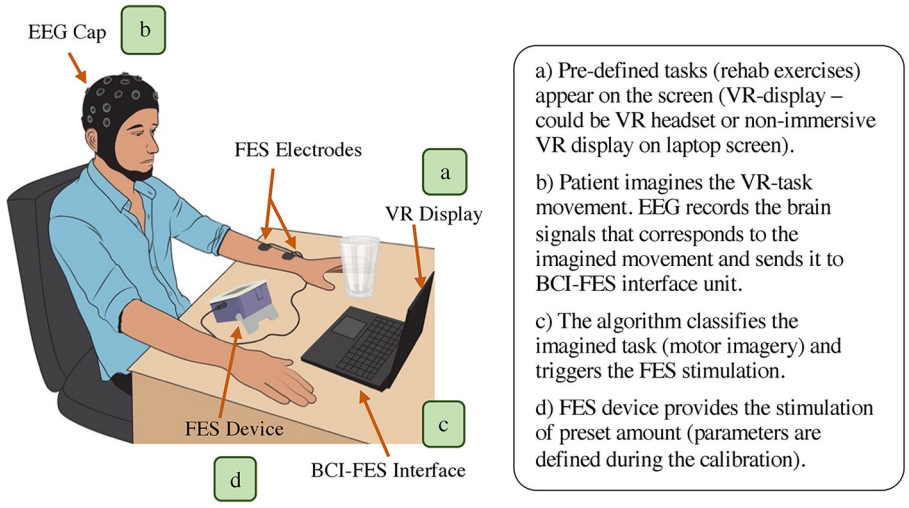

FIGURE 3
Overall representation of BCI-FES neurorehabilitation system (main components: EEG unit for BCI, BCI-FES interface, and FES module. Optional component: VR display/headset).

performed to investigate the efficiency of BCI-FES systems (32–36). In (32), Cincotti et al. performed an (RCT) to restore hand grasping movements. To assess post-stroke motor recovery, the FMA, MRC (Medical Research Council), and ESS (European Stroke Scale) scores were used. The results showed that the group with BCI-FES therapy achieved better motor recovery than the conventional FES group. Likewise, Li et al. (33) targeted stroke survivors with severe upper extremity paralysis. The study compared the efficiency of the BCI-FES system in comparison to the conventional FES system. The result showed a motor imagery task classification accuracy of 77%, along with a substantial improvement in the rehabilitation outcome scores within the BCI-FES group. In (34), Kim et al. accomplished an RCT to investigate the positive influence of the BCI-FES system on the motor recovery of upper extremities in stroke survivors. The measured outcomes validated the enhanced recovery via a BCI-based system compared to physical training. Additionally, in Miao et al. and Chen et al. (35, 36), the clinical application of the BCI-FES stroke rehabilitation system has been proposed to promote and improve upper extremity movements, along with motor activity restoration.

In addition to RCT, different feasibility studies for exploring the applicability of BCI-FES systems have also been carried out (37–45). In Daly et al. (37), Daly et al. performed a pilot study in which they tested a customized BCI-FES system on a stroke survivor having a joint extension problem in the index finger. During the first rehabilitation session, results showed a higher classification accuracy of 97% and 83% for "attempted movement" and "imagined movements" respectively. With every session, the muscle movement was gradually improving and by the end of nine sessions, the finger extension motion was completely recovered. Additionally, Mukaino et al. (38) developed a BCI-controlled neuromuscular electrical stimulator and conducted a case study on a stroke survivor (finger movement) to examine the effectiveness of BCI in stroke therapy. The results indicated that rehabilitation training with a BCI-controlled FES induces cortical plasticity and promotes functional recovery. Apart from customized BCI-FES stroke rehabilitation systems, "RecoveriX from g.tec" is commercially available stroke rehab systems (39). The RecoveriX system classifies the right and left wrist motion intention and is only meant for the wrist dorsiflexion rehabilitation paradigm. Hence, to validate the efficacy of RecoveriX system, Sabathiel et al. (40), Irimia et al. (41), Cho et al. (42), Qiu et al. (43), and Sebastián-Romagosa et al. (44) have conducted experiments on a set of stroke survivors for arm function restoration. Their results showed that the system depicts a classification accuracy of up to 95%. Furthermore, significant improvements of upper limb motor function scores suggest the post-stroke motor recovery. A detailed overview of research studies regarding BCI-FES rehabilitation is provided in Table 2.

3.2.3 Closed-loop FES system: EMG controlled FES for stroke rehabilitation

EMG provides information on the neural activity of muscles and can detect physical movement intentions. A method has been previously studied to engage a user during FES therapy by triggering the stimulation when a specific level of muscle activity is detected (79–83). In the "EMG triggered FES system", the EMG signal acts as a switch to trigger the delivery of FES stimulation at a predetermined level when the EMG magnitude reaches a certain threshold. However, this approach only uses the user's muscle activity to trigger FES and has not been conclusively proven advantageous over the open-loop FES method (79–83). Thus, another system, an "EMG controlled FES system" has been adopted that among with an FES trigger, also modulates the FES intensity in proportion to the real-time EMG signal (84).

EMG-controlled FES system mainly comprises of an EMG sensing unit, EMG-FES interface component, and FES module

TABLE 2 Research studies and their outcomes for BCI-FES neurorehabilitation systems.

BCI controlled FES systems for upper limb stroke rehabilitation (closed-loop system)						
Study	Commercial/ customized BCI-FES rehabilitation system	EEG device channels configuration	Experimental group (EG) and control Group (CG)	Therapy per participant (i. Total sessions, ii. Runs/session, iii. Trials/run or Trials/session)	i. Upper limb targeted areas ii. Therapy time/ session	Outcome measures/ performance evaluation/ other comments
Cincotti et al. (32)	Customized	32 channels	RCT: EG: 08 stroke patients CG (with conventional FES therapy): 08 stroke patients	i. 12 ii. 4 iii. 20 (per run)	i. Hand grasping movement (FES to paralyzed hand) ii. N/A	FMA, MRC and ESS score show a good recovery of hand function with BCI system as compared to the control group. Exact values of these scores have not been reported
Li et al. (33)	Customized	16 channels (G.tec Guger Technologies, Graz, Austria)	RCT: EG: 08 stroke patients CG (with conventional FES therapy): 07 stroke patients (Stroke Severity: subacute of severe level)	i. 24 ii. N/A iii. 20 (per session)	i. Upper extremity movements (FES stimulated the affected hand) ii. 1–1.5 h	FMA and ARAT score shows significant motor improvement. ΔFMA (EG) = 12.7, ΔFMA (CG) = 6.7, ΔARAT (EG) = 18.0; ΔARAT (CG) = 7.6
Kim et al. (34)	Customized	16 channels (PolyG-I by Laxtha Inc., Daejeon, Korea)	RCT: EG: 15 stroke patients CG (with conventional physical therapy): 15 stroke patients (Stroke Severity: Chronic of moderate level)	i. 20 ii. N/A iii. N/A	i. Shoulder and wrist movement (FES stimulated the affected hand) ii. 30 minutes	Improvement in FMA, MAL, MBI, and ROM was found. ΔFMA (EG) = 7.9, ΔFMA (CG) = 2.9
Miao et al. (35)	Commercial RecoveriX (g.tec GmbH, Austria)	16 channels (g.tec GmbH, Austria)	RCT: EG: 8 stroke patients CG (with conventional physical therapy): 8 stroke patients (Stroke Severity: Chronic of different levels)	i. 3 ii. 2 iii. 60 (per run)	i. Left or right wrist dorsiflexion (FES applied to both hands) ii. N/A	Average imagined task classification accuracy of 72.9%. Improvement in FMA score was found. ΔFMA (EG) = 3.5; ΔFMA (CG) = 0.9
Chen et al. (36)	Customized	32 channels (Neuroscan, USA)	RCT: EG: 16 stroke patients CG (with neuromuscular stimulation): 16 stroke patients (Stroke Severity: Chronic phase)	i. 11 ii. As much as possible (depending on each patient) iii. 10 (per run)	i. Left or right wrist extension ii. 40 minutes	FMA and Kendall MMT scores of the BCI-FES group was significantly higher than that in the control group.
Daly et al. (37)	Customized	58 channels (SynAmps, Compumedics, El Paso, TX)	Feasibility study EG: 01 stroke patient CG: N/A (Stroke Severity: 10 months post-stroke: Chronic of moderate to severe level)	i. 9 ii. N/A iii. 150 (per session)	i. Index finger joint extension (FES provided to isolated index finger extension) ii. 1.6 h	High accuracy in imagined movements (83%) and attempted movements (97%). Participants were able to execute 26 degrees of isolated index finger metacarpophalangeal joint extension
Mukaino et al. (38)	Customized	N/A	Feasibility study EG: 01 stroke patient CG (with conventional FES therapy): Same patient (Stroke Severity: Chronic of severe level)	(Total there are 4 phases) i. 10 (for each phase) ii. N/A iii. 600 (for each phase) (per session)	i. Finger movement (FES applied to the paralyzed finger) ii. 1 h	BCI-FES system efficacy reported via FMA and MAS score. ΔFMA (EG) = 3.5; ΔFMA (CG) = 0.5

(Continued)

TABLE 2 (Continued)

BCI controlled FES systems for upper limb stroke rehabilitation (closed-loop system)						
Study	Commercial/ customized BCI-FES rehabilitation system	EEG device channels configuration	Experimental group (EG) and control Group (CG)	Therapy per participant (i. Total Sessions, ii. Runs/Session, iii. Trials/Run or Trials/Session)	i. Upper limb targeted areas ii. Therapy time/ session	Outcome measures/ performance evaluation/ other comments
Sabathiel et al. (40)	Commercial RecoveriX (g.tec GmbH, Austria) (39)	24 channels (g.Hiamp device by g.tec GmbH, Austria)	Feasibility study EG: 02 stroke patients CG: N/A (Stroke Severity: Chronic of severe level)	i. 24 (patient 1) and 10 (patient 2) ii. N/A iii. N/A	i. Wrist dorsiflexion (FES applied to both affected and unaffected hands) ii. N/A	Higher classification accuracy obtained. Moreover, Nine-Hole Peg Test (9-HPT) is performed only of patient 1 and result shows steady improvement over about three months
Irimia et al. (41)	Commercial RecoveriX (g.tec GmbH, Austria)	45 channels (g.tec GmbH, Austria)	Feasibility study EG: 03 stroke patients CG: N/A (Stroke Severity: Chronic of severe level)	i. 24 ii. 6 iii. 40 (per run)	i. 120 left and 120 right hand movements (FES applied to both affected and unaffected hands) ii. N/A	High accuracy in task execution achieved (95% in at least one session) and Nine-Hole Peg Test (9-HPT) shows improved motor function.
Cho et al. (42)	Commercial RecoveriX (g.tec GmbH, Austria)	16 channels (g.LADYbird by g.tec GmbH, Austria)	Feasibility study EG: 02 stroke patients CG: N/A (Stroke Severity: Chronic of severe level)	i. 25 ii. 4 iii. N/A	i. Left or right wrist dorsiflexion (FES applied to both hands) ii. 25 60-min	Improved performance observed via FMA score (pre and post BCI) Patient 1: ΔFMA = 21.0 Patient 2: ΔFMA = 11.0
Qiu et al. (43)	Commercial RecoveriX (g.tec GmbH, Austria)	16 channels (g.tec GmbH, Austria)	Feasibility study EG: 10 stroke patients CG: N/A (Stroke Severity: Chronic of different levels)	i. 12 ii. 2 iii. 30 (per run)	i. Left or right wrist dorsiflexion (FES applied to both hands) ii. N/A	System accuracy of more than 95%. FMA score shows enhanced motor function recovery among 5 patients (pre and post BCI)
Sebastián-Romagosa et al. (44)	Commercial RecoveriX (g.tec GmbH, Austria)	16 channels (g.tec GmbH, Austria)	Feasibility study EG: 51 stroke patients CG: N/A (Stroke Severity: 45 Chronic and 6 subacute phase)	i. 25 ii. 3 iii. 80 (per run)	i. Left or right wrist dorsiflexion (FES applied to both hands) ii. 1 h	Significant increase in the motor function of affected upper limb (ΔFMA = 4.68) Reduction of the spasticity in the wrist and fingers (ΔMAS-wrist = −0.72 ΔMAS-fingers = −0.63)
Choi et al. (45)	Customized	32 channels (G.tec Guger Technologies, Graz, Austria)	Feasibility study EG: 08 stroke patients CG: N/A (Stroke Severity: Chronic phase)	i. 5 ii. N/A iii. 24 (per session)	i. Different tasks from right/left hand (FES applied to the affected hand) ii. 1 h	Average imagined task classification accuracy of 71.25%.

FMA, Fugl-Meyer Assessment; MRC, Medical Research Council; ESS, European Stroke Scale; ARAT, Action Research Arm Test; MAS, Modified Ashworth Scale; MAL, Motor Activity Log; MBI, Modified Barthel Index; ROM, Range of Motion; MMT, Manual Muscle Testing.

(Figure 4). Certain EMG-FES systems also integrate a virtual reality (VR) component into their configuration. In these systems, the initial phase entails immersing the patient in a VR environment, which can be presented on a screen or through a headset (Figure 4A). This VR environment includes a pre-programmed therapy session focused on specific movements, such as hand extension or flexion. Before the start of a therapy session, the system is calibrated for setting the EMG threshold level and required maximum FES stimulation (varies across subjects). The subject tries to perform the required task (for instance, wrist extension) and the intended motion is physically detected by the EMG sensing unit via analyzing the muscle activity (Figure 4B). The acquired EMG signal is processed by the EMG-FES interface and once the myoelectric activity reaches the pre-defined threshold level, the interface unit sends the trigger command to start the FES (Figure 4C). The applied stimulation activates the targeted muscle (or group of muscles) and helps the subject to achieve the desired motion (Figure 4D). In EMG-FES controlled system, the amount of stimulation does not stay constant and automatically adjusts throughout the therapy sessions proportional to real-time muscle activity.

Shindo et al. (51) performed an RCT to test the efficacy of the myoelectrical controlled electrical stimulator developed by Muraoka (52). The therapy sessions were performed for finger

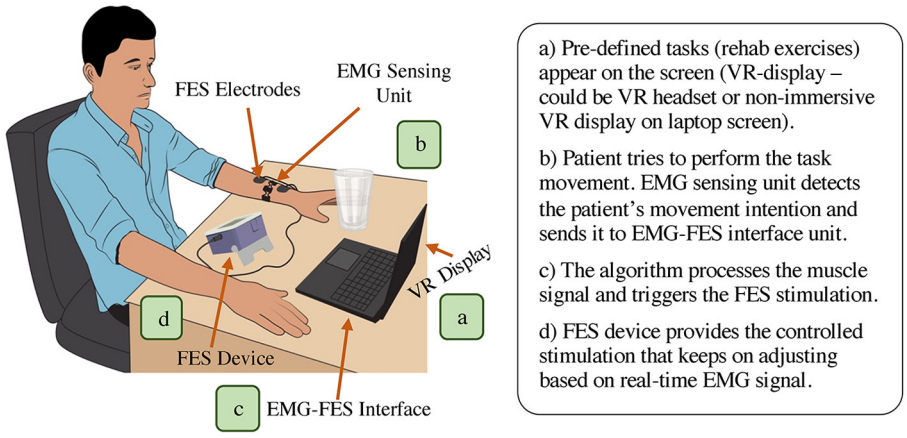

FIGURE 4
Overall representation of EMG-FES neurorehabilitation system (main components: EMG sensing unit, EMG-FES interface, and FES module. Optional component: VR display/headset).

extension rehabilitation (i.e., a functional opening of the hand) which lasted for 3 weeks (5 days/week). The EMG electrodes were placed on the paretic extensor digitorum communis muscles and based on the muscle activities the amount of applied stimulation was controlled. After completion of rehabilitation sessions, pre, and post-performance was evaluated via different clinical score metrics (FMA and ARAT). They found that the EMG-controlled FES was able to induce a greater level of improvement as compared to the control group. In (53, 54), an EMG-controlled FES system, "MeCFES" has been developed by Thorsen's group for upper limb stroke rehabilitation, which was tested via RCT on 11 stroke survivors (55). In the experimental group, the EMG electrodes were placed on wrist and finger extensors and their recorded muscle activity was used to control the applied electrical stimulation for wrist and finger extension. The clinical evaluation was performed through the ARAT, and results showed that the participants treated with MeCFES had a significant improvement in upper limb motor function. In (56), Thorsen's group conducted another RCT in which they tested the MeCFES for task-oriented therapy (TOT). This was the first large RCT (68 stroke survivors) in which multiple rehabilitation centers validated the performance of MeCFES-assisted TOT against standard TOT. In the end, promising results were obtained in terms of MeCFES functioning, and no adverse events were reported in any of the centers. They concluded that MeCFES is a safe and efficient myo-controlled FES system for the motor recovery of upper extremities among stroke survivors. Recently (57), they developed an updated version of MecFES, named "FITFES", which is wearable and portable in an ambulatory setting and best suitable for TOT applications. Thus far, only a working prototype has been tested on a single subject and no clinical evaluation has been performed. Moreover, Hara et al. (58) investigated the relationship between brain cortical perfusion (BCP) changes in the sensory-motor cortex (SMC) area and arm function improvement. A near-infrared spectroscopy (NIRS) approach was adopted to analyze BCP changes. It was found that EMG-FES rehabilitation improved FMA and GS (grip strength) scores. Also, NIRS showed increased SMC activation during therapy, confirming the functional improvement due to the EMG-FES system. A detailed overview of research studies using EMG-FES rehabilitation is provided in Table 3.

3.3 Meta-analysis interpretation

3.3.1 Change in fugl-meyer assessment (FMA) score

Among open-loop FES systems, the pooled analysis of 3 studies (19, 21, 24) including 17 stroke patients showed a significant increase in FMA score [MD = 5.6, 95% CI (3.77, 7.5), $P < 0.001$], and the data were found to be homogenous ($I^2 = 0$, $P = 0.657$) (Supplementary Figure S3).

For BCI-controlled FES, the meta-analysis of 6 studies (33–36, 38, 44) with a total of 99 patients exhibited an improvement in FMA score [MD = 5.37, 95% CI (4.2, 6.6), $P < 0.001$], along with the homogeneity in data ($I^2 = 0$, $P = 0.198$) (Supplementary Figure S3).

Finally, after analyzing the data from 3 EMG-controlled FES studies (51, 56, 58) involving 60 patients, it was found that EMG-FES rehabilitation led to a significant increase in FMA score [MD = 14.14, 95% CI (11.72, 16.6), $P < 0.001$], and the data were homogenous ($I^2 = 0$, $P = 0.006$) (Supplementary Figure S3).

3.3.2 Change in action research arm test (ARAT) score

The meta-analysis of 3 EMG-based FES studies (51, 55, 56) including 49 patients indicated a statistically significant increase in the ARAT score [MD = 11.9, 95% CI (8.8, 14.9), $P < 0.001$], and the data demonstrated homogeneity ($I^2 = 0$, $P = 0.534$) (Supplementary Figure S4).

TABLE 3 Research studies and their outcomes for open-loop FES neurorehabilitation systems.

EMG Controlled FES systems for upper limb stroke rehabilitation (closed-loop system)				
Study	Commercial/ customized EMG-FES rehabilitation system	Experimental group (EG) and control group (CG)	i. Upper limb targeted areas ii. Total sessions iii. Therapy time/session	Outcome measures/ performance evaluation/other comments
Shindo et al. (51)	Customized (two channels EMG) (52)	RCT: EG: 12 stroke patients CG (physical and occupational therapy without FES): 12 stroke patients (Stroke Severity: stroke within 60 days of onset: Subacute level)	i. Fingers extension ii. 15 iii. N/A	Different clincal scores show significant motor improvement. ΔFMA (EG) = 12.2 $\pm$ 5.3; ΔFMA (CG) = 5.5 $\pm$ 6.0 ΔARAT (EG) = 13.2 $\pm$ 7.6; ΔARAT (CG) = 8.3 $\pm$ 8.1
Thorsen et al. (55)	Customized MeCFES (53, 54) (multi-channel EMG)	RCT: EG: 5 stroke patients CG (conventional FES without EMG): 6 stroke patients	i. Wrist and finger extension ii. 25 iii. 45 min	Improvement in ARAT score ΔARAT (EG) = 9.0; ΔARAT (CG) = 2.0
Jonsdottir et al. (56)	Customized MeCFES (53, 54) (multi-channel EMG)	RCT: EG: 32 stroke patients CG (task oriented standard therapy without FES): 36 stroke patients (Stroke Severity: Chronic and subacute level)	i. Task-oriented arm rehabilitation ii. 25 iii. 45 min	Improvement in clinical scores ΔFMA (EG) = 4.5; ΔFMA (CG) = 3.5 ΔARAT (EG) = 3.0; ΔARAT (CG) = 2.0
Hara et al. (58)	Commercial PAS System GD601 (t–wo channels EMG) (OG GIKEN Company, Okayama, Japan)	Feasibility study EG: 16 stroke patients CG: N/A (Stroke Severity: Chronic with moderate residual hemiparesis)	i. Supination and pronation, flexion and extension of individual fingers. Flexion and extension of the wrist. Flexion and extension of the elbow. Adduction and abduction of the shoulder. ii. 20-40 sessions iii. 40 min	Difference in pre and post rehabilitation scores show a good recovery of physical functions. ΔFMA = 20.0; ΔGS = 5.5 $\pm$ 11.0

FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; GS, Grip Strength.

4 Discussion

FES-based stroke rehabilitation systems have been increasingly used as a therapeutic tool to restore physical movements with post-stroke motor impairment. The rehabilitation outcomes may vary depending on the type of FES administered (open-loop or closed-loop). In either case (open-loop/closed-loop), the patient is instructed to actively attempt the required task, hence ensuring the cortical involvement during the training that plays a vital role in motor recovery. This review paper provides an in-depth literature review of open-loop and closed-loop FES systems for upper limb rehabilitation in terms of their design, advantages, and clinical stroke application (including RCTs and feasibility studies). We conducted a meta-analysis of the included studies to assess the effectiveness of different FES-based upper limb rehabilitation systems (Pre-defined FES, BCI-FES, and EMG-FES). Firstly, we performed the quality assessment of the included articles to ensure the high quality of the provided information. As a result, it was found that most of the articles come under the "Good" quality category. Additionally, all the studies in our analysis exhibited homogeneous data. Data homogeneity in meta-analysis suggests that the findings from individual studies are consistent with each other, thereby enhancing the reliability of drawing conclusions from the aggregated data. Moreover, the statistical analysis was performed individually on each study within sub-groups of "Pre-defined FES, BCI-controlled FES, and EMG-controlled FES". The meta-analysis results showed that each FES-based rehabilitation system significantly improved upper limb motor function in stroke patients, as measured by FMA and ARAT scores (Supplementary Figures S3, S4). Despite comprehensive search strategies, there is a possibility of having the following limitations in our review process:

- **Incomplete Retrieval of Studies**: It is possible to miss relevant studies, especially if they are published in non-indexed journals, not available in electronic databases, or written in languages not included in the search criteria.
- **Reporting Bias**: In some cases, relevant data is incomplete or unavailable. For instance, some studies have not reported the outcome measures that are used to assess the effectiveness of interventions and track the progress of individuals recovering from a stroke. Hence, incomplete reporting of outcomes can lead to reporting bias, affecting the completeness and accuracy of the data available for analysis.

To conclude the discussion on FES-based upper limb stroke rehabilitation systems, it is important to address some key questions related to the current level of implementation, design feasibility, practical credibility, clinical considerations, and future interpretation. These questions will help clarify the current state of these systems and inform their future development.

4.1 Are FES based therapies more effective than non-FES conventional therapies for stroke rehabilitation?

Several studies have compared FES and non-FES upper limb stroke rehabilitation (17, 34, 35, 51, 56). In (17), a study of 30 stroke survivors (experimental FES and non-FES control group) demonstrated improvement in clinical scores, suggesting that FES reduces wrist flexor spasticity as compared to non-FES. Kim et al. (34) and Miao et al. (35) in an RCT investigated the influence of the BCI-FES system on the motor recovery of upper extremities in stroke survivors. The measured outcomes validated enhanced recovery via BCI-based system as compared to physical training. Similarly, Shindo et al. (51) and Jonsdottir et al. (56) in an RCT tested the performance of a EMG-controlled FES against non-FES conventional therapies. Following the completion of the rehabilitation sessions, the pre- and post-performance of participants were evaluated using various clinical scores such as FMA and ARAT. EMG-FES induced a greater level of improvement in comparison to the non-FES control group. In addition to EMG-controlled FES, EMG-triggered FES also shows promising results when compared with non-FES rehabilitation therapies (85–88).

4.2 What are the main clinical considerations for the use of electrical stimulation?

To ensure the safe use of FES in clinical applications, it is important to consider some key precautions and factors that may affect its delivery beyond the targeted muscle, leading to unexpected consequences. In (89), Marquez-Chin et al. give a complete list of clinical considerations that include:

- **Pregnancy:** The effect of FES on pregnancy or the fetus is not known and therefore, should be avoided to use (90).
- **Lesions:** The application of FES should be avoided on open skin lesions, as it can increase irritation and further damage the existing lesion (90).
- **Cardiac pacemakers:** Electrical stimulation may interfere with the electrical signals from pacemakers, potentially affecting their functioning (91).
- **Congestive heart failure conditions:** The cardiovascular demand resulting from the muscle contractions produced by the FES may require special attention before and during the delivery of stimulation (92, 93).

4.3 Based on the reported studies, which FES neurorehabilitation system can be considered the best among all?

There is no so-called "BEST" system, as every FES system has pros and cons, and its selection depends on the required stroke application. For instance, open-loop FES and BCI-FES can be used by stroke survivors with no muscle activity, whereas EMG-FES can only be used by the ones having residual muscle activity. However, regardless of their encouraging results, the reported FES-based rehabilitation studies contain certain limitations and shortcomings.

4.3.1 No RCT is conducted

Numerous studies did not conduct randomized controlled trials; instead, they just conducted feasibility studies within the stroke population (18–24, 37–45, 58). Such studies included no control group and only performed the rehabilitation protocols on the experimental group. A control group provides a baseline against which the treatment group can be compared. Without a control group, assessing whether any observed changes are greater or different from what would naturally occur without the intervention is challenging. Also, it may be challenging to generalize the study's findings to a broader population or to other settings because there is no comparison to determine whether the effects are consistent across different contexts.

4.3.2 Small sample size

Reported RCTs (17, 32–36, 51, 55, 56) and feasibility studies (19, 21, 23, 24, 38, 42, 44, 58) claimed statistical significance results; however, their sample size is not large enough (lies between 1 and 51 stroke patients in one group). According to Kaptein (94), a conventional RCT requires a group size of at least 64 individuals in each group to obtain statistically significant results. Hence, a small sample size questions the credibility and reliability of studies. It indicates that further investigation or a larger sample size may be needed to establish a more definitive relationship.

4.3.3 Lack of follow-up data

Also, there was no mention of the follow-up data to determine whether the improvement was retained or not (17–24, 32–45, 58). The absence of follow-up data in rehabilitation can impede the assessment of long-term outcomes, the identification of relapses, and the ability to make informed decisions about treatment effectiveness and planning. It is crucial for both clinical practice and research to include follow-up assessments to ensure that the benefits of rehabilitation are sustained and optimized over time.

4.3.4 Lack of neuroplasticity validation

When an individual experiences functional improvement, such as regaining motor skills after a stroke rehabilitation, the brain can reorganize its neural circuits and establish new connections or strengthen existing ones to support improved function (95, 96). These neuronal changes can be determined by different techniques, which mainly include electroencephalography (EEG)/evoked

potentials (ERPs), structural and functional magnetic resonance imaging (MRI), and transcranial magnetic stimulation (TMS) (97). Studies (17, 19, 21, 23, 24, 32–36, 38, 42, 44, 51, 55, 56) have shown that the different FES-based rehabilitation causes functional improvement among stroke patients, but none of them has validated their findings by presenting the neuroplasticity outcomes. Thus, it remains uncertain to what extent neuroplasticity has occurred due to open/closed-loop FES rehabilitation.

Hence, it is hard to conclude which specific FES system is best. However, many research studies showed that closed-loop FES is more effective than open-loop FES for motor recovery (32–35, 38, 55). Among closed-loop FES, which system is more efficient (either BCI-FES or EMG-FES) remains unknown, as currently, no RCT has been conducted to directly compare their efficacy in neurorehabilitation. Furthermore, from the clinical implementation point of view, an open-loop FES has been widely used clinically for many years (for stroke rehabilitation), whereas closed-loop FES is mainly applied in the laboratory as a research protocol (especially BCI-FES). As per our knowledge, "RecoveriX from g.tec" (39) is the only commercially available BCI-FES system for stroke rehabilitation, which is also in its initial phases to be adopted by clinicians/therapists.

4.4 Can the effectiveness of FES systems be further enhanced by combining them with other systems/paradigm?

To enhance the performance of FES rehabilitation, it can either be combined with other rehabilitation systems (like robotic systems and exoskeletons) or any additional paradigm (like virtual reality), hence, developing a "Hybrid FES Rehabilitation System".

4.4.1 Hybrid with other rehabilitation systems (robotics system and exoskeleton)

In (98), the integration of electrical stimulation with robotic arm training resulted in significant improvements in the range of motion for shoulder and elbow movements in subacute stroke survivors, compared to conventional robotic training. Meadmore et al. (99) developed a new rehabilitative system, featuring FES, robotic support, and voluntary effort. The results demonstrated improvements in arm impairment among five stroke survivors. Another study (100) tested an EMG-driven FES-robotic system on 11 chronic stroke survivors to rehabilitate finger, wrist, and elbow movement. Significant improvement in physical functions and arm impairment has been obtained. Qian et al. (101) used the same FES-robotic system on 24 sub-acute stroke survivors, which showed higher motor outcomes at the distal joints than the control group (conventional therapy). Although there are potential advantages in using hybrid FES robotic systems for upper limb rehabilitation, a review study has revealed that only a limited number of hybrid systems have undergone testing with stroke survivors (102). This could be due to challenges associated with integrating both rehabilitation technologies or the absence of integrated platforms that could be user-friendly and easy to set up.

Ambrosini et al. (103) developed a novel hybrid neurorehabilitation system that integrated a passive exoskeleton (named RETRAINER) with an EMG-triggered FES unit. In (103), they tested the feasibility and functionality of the hybrid system in a clinical environment. Later, they performed a pilot study (104) and RCT (105) to test the performance of the developed system for upper limb recovery. The pilot study was implemented on seven post-acute stroke survivors. Preliminary results confirmed that the hybrid FES exoskeleton system can be used for stroke rehabilitation, positively impacting arm functional recovery (104). In (105), an RCT involving 72 stroke survivors validated the performance of a hybrid system compared to advanced conventional therapy (ACT) for task-oriented arm training. The findings showed that the hybrid FES exoskeleton system achieved a significantly better improvement in upper limb functionality.

4.4.2 Hybrid with additional paradigm (virtual reality)

During the FES-based rehabilitation therapy, the participants started losing interest, and it became difficult for them to maintain the training motivation. This decline in the level of engagement could be attributed to the extended duration of the sessions, the repetitive exercises involved, and the clinical environment in which the rehabilitation took place (106). Therefore, physical therapists increasingly turn to virtual reality (VR) paradigms and incorporate VR into their neurorehabilitation protocols (107). By providing a virtual environment with thrilling, stimulating, and entertaining tasks, VR can keep participants more focused and motivated during rehab exercises, potentially engaging additional neural circuits to restore motor functions more effectively. Hence, the RecoveriX system combines VR with FES and commercially introduced hybrid VR-based BCI-FES stroke rehabilitation systems (39). Different studies (40–44) suggested that the RecoveriX system caused the improvement in upper extremity movements via stroke rehabilitation.

However, as VR is a newly adopted method in neurorehabilitation, initial testing has mostly been performed on small populations. Furthermore, low-quality VR may cause simulator sickness in stroke survivors, thus necessitating high-quality VR that replicates actual environments as realistically as possible. Thus, more research is needed to investigate the practical implementation and feasibility of hybrid VR-based FES systems for neurorehabilitation.

4.5 As flexible electronics (FE) is nowadays being integrated within the healthcare system, what is the emerging potential of FE combined with FES and other technologies for stroke rehabilitation?

Regarding the future of FES-based neurorehabilitation systems, it is highly likely that "Flexible Electronics" (FE) will be integrated into this field. FE is an innovative technology that offers a flexible hardware platform to perform signal amplification, precise sensing, and delivery of FES (64). Modern FES devices typically employ a pair of large gel electrodes, which generate multiple current paths, hence stimulating various muscles. This results in an inability to

activate specific muscles selectively and can lead to muscle fatigue (108). To address this issue and enable selective stimulation, a flexible multiple-electrode array has been created, which can be conveniently applied to curved surfaces and cover several targeted areas at a single location (109–113). This array allows for individual electrode activation, providing selective stimulation to targeted muscles. Moreover, research has demonstrated that distributing the stimulation spatially across multiple electrodes can also delay the occurrence of muscle fatigue (114–116).

De Marchis et al. (109) used an FE array comprising 27 electrodes to administer FES. Eight healthy participants were tested using the system to execute various wrist and finger movements of the left arm. The findings indicate that the electrode array can deliver precise stimulation to specific muscles, making it a viable option for stroke rehabilitation. In (110), a flexible 24-electrode array named "e-sleeve" was built for an FES rehabilitation device. The performance of the e-sleeve was evaluated on eight stroke patients with upper limb disability for executing "hand opening and pointing" actions. Similarly, Yang et al. (111) and Loitz et al. (112) developed screen-printed fabric electrode arrays (FEAs) for a wearable FES device. The findings indicate that the FEAs can successfully facilitate desired movements, such as "open hand," "pinch," and "pointing" gestures. Another flexible FES electrode array was designed by Maleševic et al. (113), called "Intelligent FES (INTFES)". It was tested on three stroke survivors to produce grasping movements. The outcomes demonstrated that INTFES activates the appropriate electrode configuration (thus, muscles) and successfully achieves grasping movements while maintaining wrist stabilization.

EEG and EMG acquisition systems are also a key part of FES rehabilitation systems, underscoring the need for flexible EEG/EMG electrodes to support advanced solutions for acquiring brain and muscle signals. FE electrodes are recommended over conventional electrodes because they can be placed on curved body surfaces and also incorporated into wearable devices of various shapes. FE electrodes enable the design of portable systems and optimize the overall compactness (117). This makes them feasible for everyday use and enables patients to carry out long-lasting rehabilitation therapies with greater ease and comfort (118). Several studies have developed and tested flexible EEG (119, 120) and EMG (121–123) electrodes for signal acquisition. Moreover, in 2019, research was published in "Nature Machine Intelligence," in which Mahmood et al. designed a fully portable, flexible, and wireless BCI system for EEG data acquisition (124).

Thus, it is clear that FE technology is rapidly growing in healthcare; however, its neurorehabilitation application is still in its infancy as very little testing is performed on stroke survivors (mainly done on healthy subjects). In the future, there is a high chance that flexible technology will become mature enough to be largely used for designing flexible and portable stroke rehabilitation systems.

5 Conclusion

This systematic review provides a comprehensive overview of three types of FES systems used for post-stroke upper limb rehabilitation: Manual FES, BCI-FES, and EMG-FES. A meta-analysis has been performed that validated the effectiveness of FES-based systems for upper limb stroke rehabilitation. Among the feasibility tests and RCTs for stroke application, it provides a comprehensive understanding of the design, effectiveness, and limitations. The article also discusses some of the hybrid approaches, including robotics systems and virtual reality, which can contribute to enhancing the efficacy of FES-based rehabilitation systems. Thus, this review article will help researchers to: (1) identify the new research gaps in stroke rehabilitation; (2) assess the possibility of integrating flexible electronics and hybrid approaches while developing new FES systems in the future; (3) consider the shortcomings of previous clinical studies while designing the new rehabilitation protocols; (4) determine the usefulness of different types of FES rehabilitation approaches and perform different RCTs to compare their performance.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MK: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing, Visualization. HF: Writing – original draft. HG: Writing – original draft. IB: Writing – review & editing. SP: Supervision, Writing – review & editing. BR: Supervision, Writing – review & editing. ML: Supervision, Writing – review & editing. AP: Supervision, Writing – review & editing. KM: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1272992/full#supplementary-material

References

1. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurological Res Pract*. 2:1. doi: 10.1186/s42466-020-00060-6

2. Cramer SC, Wolf SL, Adams HP, Chen D, Dromerick AW, Dunning K, et al. Stroke recovery and rehabilitation research: issues, opportunities, and the NIH StrokeNet. *Stroke*. (2017) 48:813–9. doi: 10.1161/STROKEAHA.116.015501

3. Robinson RG, Jorge RE. Post-stroke depression: a review. *Am J Psychiatry*. (2016) 173:221–31. doi: 10.1176/appi.ajp.2015.15030363

4. Khedr EM, Abdelrahman AA, Desoky T, Zaki, Gamea AF. Post-stroke depression: frequency, risk factors, and impact on quality of life among 103 stroke patients—hospital-based study. *Egypt J Neurol Psychiat Neurosurg*. (2020) 56:1. doi: 10.1186/s41983-020-00199-8

5. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. (2019) 18:439–58. doi: 10.1016/S1474-4422(19)30034-1

6. Page SJ, Levine P, Sisto S, Johnston MV. A randomized efficacy and feasibility study of imagery in acute stroke. *Clin Rehabil*. (2001) 15:233–40. doi: 10.1191/026921501672063235

7. Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. *Arch Phys Med Rehabil*. (2002) 83:1629–37. doi: 10.1053/apmr.2002.35473

8. Claflin ES, Krishnan C, Khot SP. Emerging treatments for motor rehabilitation after stroke. *Neurohospitalist*. (2014) 5:77–88. doi: 10.1177/1941874414561023

9. Di Carlo A. Human and economic burden of stroke. *Age Ageing*. (2009) 38:4–5. doi: 10.1093/ageing/afn282

10. Caramenti M, Bartenbach V, Gasperotti L, Oliveira da. Fonseca L, Berger TW, Pons JL. Challenges in nerurorehabilitation and neural engineering In: Pons JL, Raya R, González J, editors. *Emerging Therapies in Neurorehabilitation II Switzerland*. Cham: Springer International Publishing. (2016).

11. Khan MA, Das R, Iversen HK, Puthusserypady S. Review on motor imagery based BCI systems for upper limb post-stroke neurorehabilitation: from designing to application. *Comp Biol Med*. (2020) 123:103843. doi: 10.1016/j.compbiomed.2020.103843

12. Eraifej J, Clark W, France B, Desando S, Moore D. Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis. *Systematic Rev*. (2017) 6:1. doi: 10.1186/s13643-017-0435-5

13. Jaqueline da Cunha M, Rech KD, Salazar AP, Pagnussat AS. Functional electrical stimulation of the peroneal nerve improves post-stroke gait speed when combined with physiotherapy. A systematic review and meta-analysis. *Ann Phys Rehabilitat Med*. (2020) 64:1. doi: 10.1016/j.rehab.2020.03.012

14. Khan A, Abdullah M, Serpelloni S, Sardini E. Design of FES based muscle stimulator device using EMG and insole force resistive sensors for foot drop patients. *Adv Mater Lett*. (2018) 9:776–80. doi: 10.5185/amlett.2018.2170

15. Moe JH, Post HW. Functional electrical stimulation for ambulation in hemiplegia. *J Lancet*. (1962) 82:285–8.

16. Kralj A, Bajd T, Turk R. Enhancement of Gait Restoration in Spinal Injured Patients by Functional Electrical Stimulation. *Clini Orthop Related Res*. (1988) 233:34–43. doi: 10.1097/00003086-198808000-00006

17. Nakipoglu Yuzer GF, Köse Dönmez B, Özgirgin N. A randomized controlled study: effectiveness of functional electrical stimulation on wrist and finger flexor spasticity in hemiplegia. *J Stroke Cerebrovas Dis*. (2017) 26:1467–71. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.011

18. Makowski NS, Knutson JS, Chae J, Crago PE. Functional electrical stimulation to augment poststroke reach and hand opening in the presence of voluntary effort. *Neurorehabil Neural Repair*. (2013) 28:241–9. doi: 10.1177/1545968313505913

19. Meadmore KL, Exell TA, Hallewell E, Hughes A-M, Freeman CT, Kutlu M, et al. The application of precisely controlled functional electrical stimulation to the shoulder, elbow and wrist for upper limb stroke rehabilitation: a feasibility study. J NeuroEng Rehabilitat. (2014) 11:105. doi: 10.1186/1743-0003-11-105

20. Sun M, Smith C, Howard D, Kenney L, Luckie H, Waring K, et al. *FES-UPP: A Flexible Functional Electrical Stimulation System to Support Upper Limb Functional Activity Practice*. (2018). p. 12.

21. Niu CM, Bao Y, Zhuang C, Li S, Wang T, Cui L, et al. Synergy-based FES for post-stroke rehabilitation of upper-limb motor functions. *IEEE Trans Neural Syst Rehabilitat Eng*. (2019) 27:256–64. doi: 10.1109/TNSRE.2019.2891004

22. Chou CH, Wang T, Sun X, Niu CM, Hao M, Xie Q, et al. Automated functional electrical stimulation training system for upper-limb function recovery in poststroke patients. *Med Eng Phys*. (2020) 84:174–83. doi: 10.1016/j.medengphy.2020.09.001

23. Martín-Odriozola A, -de-Pablo R, Zabaleta-Rekondo H. Hand dexterity rehabilitation using selective functional electrical stimulation in a person with stroke. *BMJ Case Rep*. (2021) 14:8. doi: 10.1136/bcr-2021-242807

24. Niu CM, Chou CH, Bao Y, Wang T, Gu L, Zhang X, et al. A pilot study of synergy-based FES for upper-extremity poststroke rehabilitation. *Neurosci Lett*. (2022) 780:136621. doi: 10.1016/j.neulet.2022.136621

25. Machado TC, Carregosa AA, Santos MS, Ribeiro NM, Melo A. Efficacy of motor imagery additional to motor-based therapy in the recovery of motor function of the upper limb in post-stroke individuals: a systematic review. Top Stroke Rehabilitat. (2019) 16:1–6. doi: 10.1080/10749357.2019.1627716

26. Johnson SH, Sprehn G, Saykin AJ. Intact motor imagery in chronic upper limb hemiplegics: evidence for activity-independent action representations. *J Cogn Neurosci*. (2002) 14:841–52. doi: 10.1162/089892902760191072

27. Sharma N, Pomeroy VM, Baron J-C. Motor imagery. *Stroke*. (2006) 37:1941–52. doi: 10.1161/01.STR.0000226902.43357.fc

28. Das R, Lopez PS, Khan MA, Iversen S, Puthusserypady HK. *FBCSP and Adaptive Boosting for Multiclass Motor Imagery BCI Data Classification: A Machine Learning Approach*.

29. Braun S, Kleynen M, van Heel T, Kruithof N, Wade, Beurskens DA. The effects of mental practice in neurological rehabilitation; a systematic review and meta-analysis. *Front Human Neurosci*. (2013) 7:390. doi: 10.3389/fnhum.2013.00390

30. Uyanik C, Khan MA, Brunner IC, Hansen JP, Puthusserypady S. Machine Learning for Motor Imagery Wrist Dorsiflexion Prediction in Brain-Computer Interface Assisted Stroke Rehabilitation. In: *44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. Glasgow, UK: IEEE. (2022). p. 11–15.

31. Voinas AE, Das R, Khan MA, Brunner I, Puthusserypady S. Motor imagery EEG signal classification for stroke survivors rehabilitation. In: *10th International Winter Conference on Brain-Computer Interface (BCI)*. Gangwon-do, Korea: IEEE. (2022). p. 21–23. doi: 10.1109/BCI53720.2022.9734837

32. Cincotti F, Pichiorri F, Arico P, Aloise F, Leotta F, de Vico Fallani F, et al. EEG-based Brain-Computer Interface to support post-stroke motor rehabilitation of the upper limb. In: *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. San Diego, USA: IEEE. (2012).

33. Li M, Liu Y, Wu Y, Liu S, Jia J, Zhang L. Neurophysiological substrates of stroke patients with motor imagery-based brain-computer interface training. *Int J Neurosci*. (2014) 124:403–15. doi: 10.3109/00207454.2013.850082

34. Kim T, Kim S, Lee B. Effects of action observational training plus brain-computer interface-based functional electrical stimulation on paretic arm motor recovery in patient with stroke: a randomized controlled trial. *Occup Ther Int*. (2016) 23:39–47. doi: 10.1002/oti.1403

35. Miao Y, Chen S, Zhang X, Jin J, Xu R, Daly I, et al. BCI-based rehabilitation on the stroke in sequela stage. *Neural Plast*. (2020). doi: 10.1155/2020/8882764

36. Chen L, Gu B, Wang Z, Zhang L, Xu M, Liu S, et al. EEG-controlled functional electrical stimulation rehabilitation for chronic stroke: system design and clinical application. *Front Med*. (2021) 15:740–9. doi: 10.1007/s11684-020-0794-5

37. Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K, Dohring M. Feasibility of a new application of noninvasive brain computer interface (BCI): a case study of training for recovery of volitional motor control after stroke. *J Neurol Phys Ther*. (2009) 33:203–11. doi: 10.1097/NPT.0b013e3181c1fc0b

38. Mukaino M, Ono T, Shindo K, Fujiwara T, Ota T, Kimura A, et al. Efficacy of brain-computer interface-driven neuromuscular electrical stimulation for chronic paresis after stroke. *J Rehabilitat Med.* (2014) 46:378–82. doi: 10.2340/16501977-1785

39. Irimia D, Sabathiel N, Ortner R, Poboroniuc M, Coon W, Allison C, Guger BZ. recoveriX: a new BCI-based technology for persons with stroke. In: *38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. Orlando, USA: IEEE. (2016).

40. Sabathiel N, Irimia DC, Allison BZ, Guger C, Edlinger G. (2016). *Paired Associative Stimulation with Brain-Computer Interfaces: A New Paradigm for Stroke Rehabilitation*. p. 261–272.

41. Irimia DC, Poboroniuc M, Ortner R, Allison C, Guger BZ. Preliminary results of testing a BCI-controlled FES system for post-stroke rehabilitation. In: *7th Graz Brain-Computer Interface Conference*. (2017) p. 18–22.

42. Cho W, Heilinger A, Xu R, Zehetner M, Schobesberger S, Murovec N, et al. Hemiparetic stroke rehabilitation using avatar and electrical stimulation based on non-invasive brain computer interface. *Int J Phys Med Rehabilitat*. (2017) 05:04. doi: 10.4172/2329-9096.1000411

43. Qiu Z, Chen S, Daly I, Jia J, Wang J, Jin X. BCI-based strategies on stroke rehabilitation with avatar and FES feedback. *ArXiv*. (2018). doi: 10.48550/arXiv.1805.04986

44. Sebastián-Romagosa M, Cho W, Ortner R, Murovec N, Von Oertzen T, Kamada K, et al. Brain computer interface treatment for motor rehabilitation of upper extremity of stroke patients—a feasibility study. *Front Neurosci.* (2020) 14. doi: 10.3389/fnins.2020.591435

45. Choi I, Kwon GH, Lee CS, Nam S. Functional electrical stimulation controlled by motor imagery brain-computer interface for rehabilitation. *Brain Sci*. (2020) 10:512. doi: 10.3390/brainsci10080512

46. Abdullah S, Khan AM, Serpelloni E, Sardini M. Hybrid EEG-EMG based brain computer interface (BCI) system for real-time robotic arm control. *Adv Mat Lett*. (2018) 10:35–40. doi: 10.5185/amlett.2019.2171

47. Piyus CK, Cherian S, Nageswaran VA. EMG based FES for post-stroke rehabilitation. In: *IOP Conference Series: Materials Science and Engineering*. (2017). p. 263.

48. Monte-Silva K, Piscitelli D, Norouzi-Gheidari N, Batalla MAP, Archambault P, Levin MF. Electromyogram-related neuromuscular electrical stimulation for restoring wrist and hand movement in poststroke hemiplegia: a systematic review and meta-analysis. *Neurorehabil Neural Repair*. (2019) 33:96–111. doi: 10.1177/1545968319826053

49. Hara Y. Rehabilitation with functional electrical stimulation in stroke patients. *Int J Phys Med Rehabilitat*. (2013) 01:06. doi: 10.4172/2329-9096.1000147

50. Karu ZZ, Durfee WK, Barzilai AM. Reducing muscle fatigue in FES applications by stimulating with N-let pulse trains. *IEEE Trans Biomed Eng.* (1995) 42:809–17. doi: 10.1109/10.398642

51. Shindo K, Fujiwara T, Hara J, Oba H, Hotta F, Tsuji T, et al. Effectiveness of hybrid assistive neuromuscular dynamic stimulation therapy in patients with subacute stroke. *Neurorehabil Neural Repair*. (2011) 25:830–7. doi: 10.1177/1545968311408917

52. Muraoka Y. Development of an EMG recording device from stimulation electrodes for functional electrical stimulation. *Front Med Biol Eng.* (2001) 11:323–33. doi: 10.1163/156855701321138969

53. Thorsen R. An artefact suppressing fast-recovery myoelectric amplifier. *IEEE Trans Biomed Eng.* (1999) 46:764–6. doi: 10.1109/10.764955

54. Thorsen R, Ferrarin M. Battery powered neuromuscular stimulator circuit for use during simultaneous recording of myoelectric signals. *Med Eng Phys.* (2009) 31:1032–7. doi: 10.1016/j.medengphy.2009.06.006

55. Thorsen R, Cortesi M, Jonsdottir J, Carpinella I, Morelli D, Casiraghi A, et al. Myoelectrically driven functional electrical stimulation may increase motor recovery of upper limb in poststroke subjects: a randomized controlled pilot study. *J Rehabil Res Dev*. (2013) 50:785–94. doi: 10.1682/JRRD.2012.07.0123

56. Jonsdottir J, Thorsen R, Aprile I, Galeri S, Spannocchi G, Beghi E, et al. Arm rehabilitation in post stroke subjects: A randomized controlled trial on the efficacy of myoelectrically driven FES applied in a task-oriented approach. *PLoS ONE*. (2017) 12:e0188642. doi: 10.1371/journal.pone.0188642

57. Crepaldi M, Thorsen R, Jonsdottir J, Scarpetta S, De Michieli L, Salvo MD, et al. FITFES: A wearable myoelectrically controlled functional electrical stimulator designed using a user-centered approach. *IEEE Trans Neural Syst Rehabilitat Eng.* (2021) 29:2142–52. doi: 10.1109/TNSRE.2021.3120293

58. Hara Y, Obayashi S, Tsujiuchi K, Muraoka Y. The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. *Clini Neurophysiol.* (2013) 124:2008–15. doi: 10.1016/j.clinph.2013.03.030

59. Zhang D, Guan TT, Widjaja F, Ang WT. Functional electrical stimulation in rehabilitation engineering: A survey. In: *1st International Convention on Rehabilitation Engineering and Assistive Technology: in Conjunction with 1st Tan Tock Seng Hospital Neurorehabilitation Meeting*. (2007).

60. Sousa AS, Moreira J, Silva C, Mesquita I, Macedo R, Silva A, Santos R. Usability of functional electrical stimulation in upper limb rehabilitation in post-stroke patients: a narrative review. *Sensors*. (2022) 22:4. doi: 10.3390/s22041409

61. Takeda K, Tanino G, Miyasaka H. Review of devices used in neuromuscular electrical stimulation for stroke rehabilitation. *Med Dev (Auckland, NZ).* (2017) 10:207–13. doi: 10.2147/MDER.S123464

62. Angerhöfer C, Colucci A, Vermehren M, Hömberg SR, Soekadar V. Post-stroke Rehabilitation of Severe Upper Limb Paresis in Germany – Toward Long-Term Treatment With Brain-Computer Interfaces. *Front Neurol*. (2021) 12:772199. doi: 10.3389/fneur.2021.772199

63. Cervera MA, Soekadar SR, Ushiba J, Millán J, del R, Liu M, et al. Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis. *Ann Clini Translat Neurol*. (2018) 5:651–63. doi: 10.1002/acn3.544

64. Khan MA, Saibene M, Das R, Brunner S, Puthusserypady I. Emergence of flexible technology in developing advanced systems for post-stroke rehabilitation: a comprehensive review. *J Neural Eng*. (2021) 18:6. doi: 10.1088/1741-2552/ac36aa

65. Chen Y, Abel KT, Janecek JT, Chen Y, Zheng K, Cramer SC. Home-based technologies for stroke rehabilitation: a systematic review. *Int J Med Inform*. (2019) 123:11–22. doi: 10.1016/j.ijmedinf.2018.12.001

66. Calafiore D, Negrini F, Tottoli N, Ferraro F, Ozyemisci-Taskiran O. Efficacy of robotic exoskeleton for gait rehabilitation in patients with subacute stroke: a systematic review. *Eur J Phys Rehabil Med.* (2022) 58:1. doi: 10.23736/S1973-9087.21.06846-5

67. Wang L, Chen JL, Wong AM, Liang KC, Tseng KC. Game-based virtual reality system for upper limb rehabilitation after stroke in a clinical environment: systematic review and meta-analysis. *Games Health J.* (2022) 11:277–97. doi: 10.1089/g4h.2022.0086

68. Hatem SM, Saussez G, Della Faille M, Prist V, Zhang X, Dispa D, et al. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Front Hum Neurosci.* (2016) 10:442. doi: 10.3389/fnhum.2016.00442

69. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Military Med Res*. (2020) 7:1–11. doi: 10.1186/s40779-020-00238-8

70. National heart lung and blood institute. *Quality Assessment Tool for Case Series Studies*. Available online at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed November 8, 2023).

71. Joanna Briggs Institute (JBI). *Joanna Briggs Institute (JBI) Checklist for Case Reports*. Available online at: https://jbi.global/critical-appraisal-tools (accessed November 8, 2023).

72. Morris RGM, Hebb DO. The organization of behavior, Wiley: New York; 1949. *Brain Res Bullet.* (1999) 50:437. doi: 10.1016/S0361-9230(99)00182-3

73. Shatz CJ. The developing brain. *Sci Am.* (1992) 267:60–7. doi: 10.1038/scientificamerican0992-60

74. Stefan K. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain.* (2000) 123:572–84. doi: 10.1093/brain/123.3.572

75. Taylor JL, Martin PG. Voluntary motor output is altered by spike-timing-dependent changes in the human corticospinal pathway. *J Neurosci.* (2009) 29:11708–16. doi: 10.1523/JNEUROSCI.2217-09.2009

76. McPherson JG, Miller RR, Perlmutter SI. Targeted, activity-dependent spinal stimulation produces long-lasting motor recovery in chronic cervical spinal cord injury. *Proc Nat Acad Sci.* (2015) 112:12193–8. doi: 10.1073/pnas.1505383112

77. Bunday, Karen L. and Perez, Monica A. Motor recovery after spinal cord injury enhanced by strengthening corticospinal synaptic transmission. *Curr Biol*. (2012) 22:2355–61. doi: 10.1016/j.cub.2012.10.046

78. Mrachacz-Kersting N, Kristensen SR, Jamil D, Farina M. Precise temporal association between cortical potentials evoked by motor imagination and afference induces cortical plasticity. *J Physiol*. (2012) 590:1669–82. doi: 10.1113/jphysiol.2011.222851

79. Bolton DAE, Cauraugh JH, Hausenblas HA. Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis. *J Neurol Sci.* (2004) 223:121–7. doi: 10.1016/j.jns.2004.05.005

80. De Kroon J, IJzerman M, Chae J, Lankhorst G, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *J Rehabilitat Med*. (2005) 37:65–74. doi: 10.1080/16501970410024190

81. De Kroon JR, IJzerman MJ. Electrical stimulation of the upper extremity in stroke: cyclic versus EMG-triggered stimulation. *Clin Rehabil.* (2008) 22:690–7. doi: 10.1177/0269215508088984

82. Meilink A, Hemmen B, Seelen H, Kwakkel G. Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. *Clin Rehabil.* (2008) 22:291–305. doi: 10.1177/0269215507083368

83. Wilson RD, Page SJ, Delahanty M, Knutson JS, Gunzler DD, Sheffler LR, et al. Upper-limb recovery after stroke. *Neurorehabil Neural Repair*. (2016) 30:978–87. doi: 10.1177/1545968316650278

84. Osuagwu BAC, Whicher R, Shirley E. Active proportional electromyogram controlled functional electrical stimulation system. *Scient Rep*. (2020) 10:1. doi: 10.1038/s41598-020-77664-0

85. Cauraugh J, Light K, Kim S, Thigpen M, Behrman A. Chronic motor dysfunction after stroke: recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. *Stroke*. (2000) 31:1360–4. doi: 10.1161/01.STR.31.6.1360

86. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. *Stroke*. (2002) 33:1589–94. doi: 10.1161/01.STR.0000016926.77114.A6

87. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G, et al. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. *Arch Phys Med Rehabil*. (1998) 79:570–5. doi: 10.1016/S0003-9993(98)90074-0

88. Hara Y, Ogawa S, Tsujiuchi K, Muraoka Y. A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. *Disabil Rehabil*. (2008) 30:296–304. doi: 10.1080/09638280701265539

89. Marquez-Chin MR, Popovic C. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. *BioMedical Eng OnLine*. (2020) 19:1. doi: 10.1186/s12938-020-00773-4

90. Alon G. Functional electrical stimulation (FES): transforming clinical trials to neuro-rehabilitation clinical practice-a forward perspective. *J Nov Physiother*. (2013) 3:2. doi: 10.4172/2165-7025.1000176

91. Crevenna R, Mayr W, Keilani M, Pleiner J, Nuhr M, Quittan M, et al. Safety of a combined strength and endurance training using neuromuscular electrical stimulation of thighs muscles in patients with heart failure and bipolar sensing cardiac pacemakers. *Wiener Klinische Wochenschrift*. (2003) 115:710–4. doi: 10.1007/BF03040887

92. Nuhr MJ, Pette D, Berger R, Quittan M, Crevenna R, Huelsman M, et al. Beneficial effects of chronic low-frequency stimulation of thigh muscles in patients with advanced chronic heart failure. *Eur Heart J*. (2004) 25:136–43. doi: 10.1016/j.ehj.2003.09.027

93. Deley G, Kervio G, Verges B, Hannequin A, Petitdant MF, Grassi B, et al. Neuromuscular adaptations to low-frequency stimulation training in a patient with chronic heart failure. *Am J Phys Med Rehabilitat*. (2008) 87:502–9. doi: 10.1097/PHM.0b013e318174e29c

94. Kaptein M. A practical approach to sample size calculation for fixed populations. *Contemp Clini Trials Commun*. (2019) 14: 100339. doi: 10.1016/j.conctc.2019.100339

95. Birbaumer N, Ruiz S, Sitaram R. Learned regulation of brain metabolism. *Trends Cogn Sci*. (2013) 17:295–302. doi: 10.1016/j.tics.2013.04.009

96. Ruiz Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, Sitaram R. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. *Biol Psychol*. (2014) 95:4–20. doi: 10.1016/j.biopsycho.2013.04.010

97. Van Ombergen A, Laureys S, Sunaert S, Tomilovskaya E, Parizel PM, Wuyts FL. Spaceflight-induced neuroplasticity in humans as measured by MRI: what do we know so far? *Npj Microgravity*. (2017) 3:2. doi: 10.1038/s41526-016-0010-8

98. Miyasaka H, Orand A, Ohnishi H, Tanino G, Takeda S, Sonoda K. Ability of electrical stimulation therapy to improve the effectiveness of robotic training for paretic upper limbs in patients with stroke. *Stroke*. (2016) 38:1172–5. doi: 10.1016/j.medengphy.2016.07.010

99. Meadmore KL, Hughes A-M, Freeman CT, Cai Z, Tong D, Burridge E, Rogers JH. Functional electrical stimulation mediated by iterative learning control and 3D robotics reduces motor impairment in chronic stroke. *J NeuroEng Rehabilitat*. (2012) 9:32. doi: 10.1186/1743-0003-9-32

100. Rong W, Li W, Pang M, Hu J, Wei X, Yang B, et al. A Neuromuscular Electrical Stimulation (NMES) and robot hybrid system for multi-joint coordinated upper limb rehabilitation after stroke. *J NeuroEng Rehabilitat*. (2017) 14:1. doi: 10.1186/s12984-017-0245-y

101. Qian Q, Hu X, Lai Q, Ng SC, Zheng W, Poon Y. Early stroke rehabilitation of the upper limb assisted with an electromyography-driven neuromuscular electrical stimulation-robotic arm. *Front Neurol*. (2017) 8:447. doi: 10.3389/fneur.2017.00447

102. Resquín F, Cuesta Gómez A, Gonzalez-Vargas J, Brunetti F, Torricelli D, Molina Rueda F, et al. Hybrid robotic systems for upper limb rehabilitation after stroke: a review. *Med Eng Phys*. (2016) 38:1279–88. doi: 10.1016/j.medengphy.2016.09.001

103. Ambrosini E, Ferrante S, Zajc J, Bulgheroni M, Baccinelli W, d'Amico E, et al. The combined action of a passive exoskeleton and an EMG-controlled neuroprosthesis for upper limb stroke rehabilitation: First results of the RETRAINER project. In: *IEEE International Conference on Rehabilitation Robotics (ICORR)* London, UK: IEEE, 56–61. (2017).

104. Ambrosini E, Russold M, Gfoehler M, Puchinger M, Weber M, Becker S, et al. A hybrid robotic system for arm training of stroke survivors: concept and first evaluation. *IEEE Trans Biomed Eng*. (2019) 66:3290–300. doi: 10.1109/TBME.2019.2900525

105. Ambrosini E, Gasperini G, Johannes Zajc, Immick N, Augsten A, Rossini M, et al. A Robotic System with EMG-Triggered Functional Eletrical Stimulation for Restoring Arm Functions in Stroke Survivors. *Neurorehabilitat Neural Repair*. 35:334–45. doi: 10.1177/1545968321997769

106. Kenah K, Bernhardt J, Cumming T, Spratt N, Luker J, Janssen H. Boredom in patients with acquired brain injuries during inpatient rehabilitation: a scoping review. *Disabil Rehabil*. (2017) 40:2713–22. doi: 10.1080/09638288.2017.1354232

107. Laver K, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation: an abridged version of a Cochrane review. *Eur J Phys Rehabil Med*. (2015) 51:497–506. doi: 10.1002/14651858.CD008349.pub3

108. Ferrante S, Schauer T, Ferrigno G, Raisch J, Molteni F. The effect of using variable frequency trains during functional electrical stimulation cycling. *Neuromodulation*. (2008) 11:216–26. doi: 10.1111/j.1525-1403.2008.00169.x

109. De Marchis C, Santos Monteiro T, Simon-Martinez C, Conforto A, Gharabaghi S. (2016). Multi-contact functional electrical stimulation for hand opening: electrophysiologically driven identification of the optimal stimulation site. *J NeuroEng Rehabilitat*. 13:1. doi: 10.1186/s12984-016-0129-6

110. Yang K, Meadmore K, Freeman C, Grabham N, Hughes A-M., Wei Y, et al. Development of user-friendly wearable electronic textiles for healthcare applications. *Sensors*. (2018) 18:8. doi: 10.3390/s18082410

111. Yang K, Freeman C, Torah R, Beeby S, Tudor J. Screen printed fabric electrode array for wearable functional electrical stimulation. *Sensors Actuators A: Phys*. (2014) 213:108–15. doi: 10.1016/j.sna.2014.03.025

112. Loitz JC, Reinert A, Neumann A-K, Quandt F, Schroeder D, Krautschneider WH. A flexible standalone system with integrated sensor feedback for multi-pad electrode FES of the hand. *Curr Direct Biomed Eng*. (2016) 2:391–4. doi: 10.1515/cdbme-2016-0087

113. Malešević NM, Maneski LZP, Ilić V, Jorgovanović N, Bijelić G, Keller DB, Popović T. A multi-pad electrode based functional electrical stimulation system for restoration of grasp. *J NeuroEng Rehabilitat*. (2012) 9:66. doi: 10.1186/1743-0003-9-66

114. Malešević NM, Popović LZ, Schwirtlich L, Popović DB. Distributed low-frequency functional electrical stimulation delays muscle fatigue compared to conventional stimulation. *Muscle and Nerve*. (2010) 42:556–62. doi: 10.1002/mus.21736

115. Sayenko DG, Nguyen R, Popovic MR, Masani K. Reducing muscle fatigue during transcutaneous neuromuscular electrical stimulation by spatially and sequentially distributing electrical stimulation sources. *Eur J Appl Physiol*. (2014) 114:793–804. doi: 10.1007/s00421-013-2807-4

116. Nguyen R, Masani K, Micera S, Morari M, Popovic MR. Spatially distributed sequential stimulation reduces fatigue in paralyzed triceps surae muscles: a case study. *Artif Organs*. (2011) 35:1174–80. doi: 10.1111/j.1525-1594.2010.01195.x

117. Lee JW, Golgouneh L, Dunne A. Comparative assessment of wearable surface EMG electrode configurations for biomechanical applications. In: *49th International Conference on Environmental Systems*. Boston, USA: IEEE. (2019).

118. Salvo P, Raedt R, Carrette E, Schaubroeck D, Vanfleteren J, Cardon L. A 3D printed dry electrode for ECG/EEG recording. *Sens Actuators A: Physical*. (2012) 174:96–102. doi: 10.1016/j.sna.2011.12.017

119. Ren L, Xu S, Gao J, Lin Z, Chen Z, Liu B, Liang L, Jiang L. Fabrication of flexible microneedle array electrodes for wearable bio-signal recording. *Sensors*. (2018) 18:1191. doi: 10.3390/s18041191

120. Grozea C, Voinescu S, Fazli CD. Bristle-sensors—low-cost flexible passive dry EEG electrodes for neurofeedback and BCI applications. *J Neural Eng*. (2011) 8:025008. doi: 10.1088/1741-2560/8/2/025008

121. Duente T, Pfeiffer M, Rohs M. On-skin technologies for muscle sensing and actuation. In: *ACM Int. Joint Conf. on Pervasive and Ubiquitous Computing: Adjunct*. New York, USA: IEEE. (2016)

122. Xu B, Akhtar A, Liu Y, Chen H, Yeo W-H, Park SS, et al. An epidermal stimulation and sensing platform for sensorimotor prosthetic control, management of lower back exertion, and electrical muscle activation. *Adv Mater*. (2016) 28:4462–71. doi: 10.1002/adma.201504155

123. Fall C, Roudjane M, Ghafouri S, Mascret Q, Bielmann M, Tam S, et al. Non-Invasive and Flexible Electrodes Based on Multimaterial Fiber for sEMG Signal Detection. In: *IEEE Life Sciences Conf. (LSC)*. Montreal, Canada: IEEE. (2018).

124. Musa Mahmood M, Mzurikwao D, Kim Y-S, Lee Y-K, Mishra S, Herbert RD, et al. Fully portable and wireless universal brain–machine interfaces enabled by flexible scalp electronics and deep learning algorithm. *Nat Mach Intell*. (2019) 1:412–22. doi: 10.1038/s42256-019-0091-7

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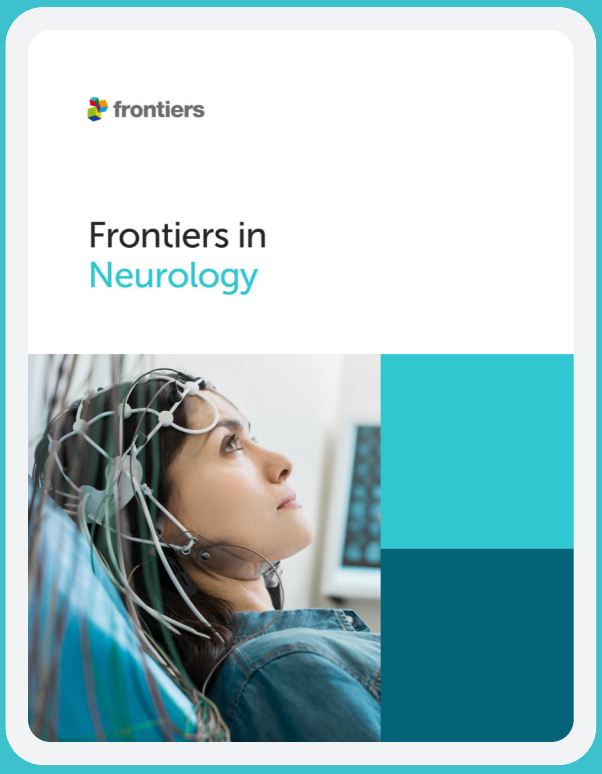

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