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To cite this article: C J H Rikhof *et al* 2024 *J. Neural Eng.* **21** 021001

Journal of Neural Engineering

TOPICAL REVIEW

Robot-assisted support combined with electrical stimulation for the lower extremity in stroke patients: a systematic review

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Keywords: stroke, rehabilitation, electrical stimulation, robot

OPEN ACCESS

RECEIVED
25 July 2023

REVISED
22 January 2024

ACCEPTED FOR PUBLICATION
25 March 2024

PUBLISHED
3 April 2024

Abstract

Objective. The incidence of stroke rising, leading to an increased demand for rehabilitation services. Literature has consistently shown that early and intensive rehabilitation is beneficial for stroke patients. Robot-assisted devices have been extensively studied in this context, as they have the potential to increase the frequency of therapy sessions and thereby the intensity. Robot-assisted systems can be combined with electrical stimulation (ES) to further enhance muscle activation and patient compliance. The objective of this study was to review the effectiveness of ES combined with all types of robot-assisted technology for lower extremity rehabilitation in stroke patients. *Approach*. A thorough search of peer-reviewed articles was conducted. The quality of the included studies was assessed using a modified version of the Downs and Black checklist. Relevant information regarding the interventions, devices, study populations, and more was extracted from the selected articles. *Main results*. A total of 26 articles were included in the review, with 23 of them scoring at least fair on the methodological quality. The analyzed devices could be categorized into two main groups: cycling combined with ES and robots combined with ES. Overall, all the studies demonstrated improvements in body function and structure, as well as activity level, as per the International Classification of Functioning, Disability, and Health model. Half of the studies in this review showed superiority of training with the combination of robot and ES over robot training alone or over conventional treatment. *Significance*. The combination of robot-assisted technology with ES is gaining increasing interest in stroke rehabilitation. However, the studies identified in this review present challenges in terms of comparability due to variations in outcome measures and intervention protocols. Future research should focus on actively involving and engaging patients in executing movements and strive for standardization in outcome values and intervention protocols.

1. Introduction

Stroke is one of the leading causes of disability in adults. At the beginning of the 21st century, around 1.1 million people in the European Union (EU) suffered from a new stroke every year, and currently approximately 6 million people in the EU are stroke survivors. The incidence of stroke events is expected to increase to approximately 1.5 million in 2025, due to the aging population [1]. Therefore, the demand for rehabilitation will increase as well.

Most people survive the initial injury, but experience longer term residual problems, e.g. motor impairments and limitations in daily activities [2]. These daily life problems are frequently caused through hemiparesis of the arm and/or leg. Hemiparesis encompasses weakness, motor abnormalities, and spasticity of one of the limbs [3]. The motor impairment significantly influences the quality of life of a stroke patient. Therefore, stroke rehabilitation mainly focuses on restoring and maintaining function for use in daily activities. Previous research

indicates that early intensive and task-specific rehabilitation is beneficial for stroke patients [4, 5].

To provide high-intensity rehabilitation with decreasing availability of healthcare professionals, robot-assisted devices are researched extensively. Due to the rapid evolution of technology, robot-assisted systems are increasingly used in the rehabilitation of stroke patients [6]. The increase in popularity of robot-assisted neurorehabilitation is caused by easy deployment and high measurement reliability [3]. In stroke rehabilitation, robot-assisted devices are frequently used to execute specific motor coordination exercises, with a high frequency of repetitions or for a long duration. Particularly in addition to physical therapy, robot assistance can help increase the intensive nature of the therapy and the likelihood of achieving independent walking after stroke [6, 7].

The compliance of patients is limited in most robot-assisted devices [8]. Especially, active muscle activation in bedridden or non-ambulatory patients in gait robots can be challenging. To provide muscle activation, also in severely affected stroke patients, electrical stimulation (ES) of specific muscles can be used. Clinically, ES is frequently used to improve muscle strength, increase range of motion, and decrease atrophy and edema [9]. Several types of ES can be distinguished. Neuromuscular electrical stimulation (NMES) is used to produce muscle contraction. Transcutaneous electrical nerve stimulation (TENS) is frequently used for sensory stimulation, e.g. to override pain impulses. Furthermore, functional electrical stimulation (FES) is a frequently used term and usually refers to stimulation during or to create a functional movement [10]. Furthermore, it is reported that ES improves motor function, motor cortex excitability and functional cortical reorganization [8]. A recent umbrella review showed positive effect of FES on walking, both for orthotic and therapeutic effects. In addition, it was more effective than physical therapy alone [11].

The combination of robot-assisted therapy and ES is expected to provide intensive rehabilitation with active involvement of the stroke patients. A previous review by Anaya *et al* (2018) focused on these hybrid robot-assisted rehabilitation systems [8]. It studied the working mechanism of FES in combination with a rehabilitation robot, with a focus on mechanical design, actuation, and control strategies. They included studies discussing various robot-assisted gait training devices, both passive (energy dissipating) and active (torque generating) regardless whether it was tested on humans or not. In total twenty-eight hybrid systems were evaluated. However, only a few combinations of ES and robotic device were tested on stroke patients. All combinations were evaluated from a technical viewpoint. They recommend including principles like 'assist-as-needed' to improve functional outcomes [8].

Research into the combination of robot-assisted devices and ES has primarily been conducted for the upper extremity and/or only from a technical perspective [8, 12]. There is a need to gain more knowledge about robot-assisted devices combined with ES with a focus on lower extremity function. Therefore, in the current systematic review the combination of robot-assisted technology and ES for rehabilitation of the lower extremity in stroke patients is investigated from a clinical perspective. This review assessed the effect of any robot-assisted technology combined with ES to identify promising rehabilitation techniques and its potential to improve the lower extremity function post-stroke.

2. Method

2.1. Search strategy

A search was conducted in electronic databases until August 2022, without time constraints. The databases that were used are PubMed, Scopus, Web of Science, Cochrane Trial Register and Embase. The following search terms or equivalents were used *stroke, robot, ES, and lower extremity*. An overview of the search strategy used in PubMed can be found in appendix A. In addition, the reference list of the included articles were screened for suitable articles as well.

2.2. Study selection

The in- and exclusion criteria for the study selection can be found in table 1. We did not exclude based on study design. In case of a mix of participants in the study population, with at least one stroke patient, articles were included. If possible, only the effect on stroke patients was considered. In addition, if healthy volunteers were also included, they were also not taken into account. Technology was only considered to be a robot if it applied force or replaced human effort in assisting or executing a movement. In other words, only cycling was not considered robot technology if it was not producing power or replace human effort. Furthermore, articles needed to have at least one stroke-related outcome, in order to evaluate the effect of the device on stroke patients. Articles that only had a technical evaluation of the device were excluded. Two independent reviewers (CR and YF) selected the articles, by discarding the articles that did not meet the inclusion criteria. First based on title and abstract screening, followed by full-text screening. Findings were discussed and in case of discrepancies between the two reviewers, a third person was consulted (GP).

2.3. Methodology quality assessment

To determine the quality of the included studies, a modified version of the Downs & Black checklist was applied. The original checklist can be used for randomized and non-randomized trials and the

Table 1. Overview of in- and exclusion criteria for the study selection.

Criteria	Inclusion criteria	Exclusion criteria
1	Peer-reviewed (full) papers	Conference abstract, editor notes, and if only abstract was available
2	Stroke patients	All articles not including stroke patients (e.g. only spinal cord injury, cerebral palsy, or healthy volunteers)
3	Robot technology as part of intervention, such as: - Assistive cycling - Robotic gait - Assistive technology (Applying force/replacing human effort to assist or execute a movement)	No robot involved
4	Electrical stimulation: - FES - TENS - NMES	Brain or spinal cord stimulation (central stimulation), transcranial magnetic stimulation, or no stimulation
5	Lower extremity (leg and foot)	Only the upper extremity involved
6	Available in English or Dutch	Articles in other languages
7	Outcomes are related to stroke (e.g. gait analysis, clinical measurement, joint forces, kinematics, patient satisfaction etc.)	Only device-related outcomes on a technical level.

FES = Functional Electrical stimulation; TENS = Transcutaneous electrical nerve stimulation; NMES = Neuromuscular electrical stimulation.

feasibility is shown by Downs & Black [13]. The original checklist composed of 27 questions was shortened to 15 questions that were applicable to the present review (maximum quality score was 15 for randomized trials and 14 for non-randomized trials, see table 2). An explanation when a score of one was assigned to a question and justification for the excluded questions can be found in appendix B, in case of unable to determine (UTD) a score of zero was given. Considering that only randomized studies could obtain an excellent quality level in the scoring methodology of Downs & Black, the following quality levels were determined: excellent (score of 15), good (12–14), fair (9–11) and poor ($\leqslant$8).

Quality assessment was conducted by two independent reviewers (CR and YF). The agreement between the two independent reviewers was expressed in percentage. A consensus was achieved between the two reviewers if needed after consulting a third reviewer (GP). Based on the consensus scores, all articles of poor quality (score below 9) were excluded from the results.

2.4. Data extraction & analysis

The following data was extracted from each article:

- number of (stroke) patients
- subject characteristics (e.g. group averages of time since stroke, severity, age, etc.)
- device combination
- control method
- assistance parameters (stimulation intensity, robot force)
- study design
- intervention (sessions, time, frequency)
- outcome variables
- outcomes reported
- effect sizes for gait velocity, if possible.

Stroke severity was based on the baseline characteristics: gait velocity, functional ambulation categories (FAC) or Fugl–Meyer assessment (FMA) lower extremity. The severity was first based on gait velocity and the following distinction was made: $<$0.4 m s^{-1} household ambulatory; 0.4–0.8 m s^{-1} limited community walker and $>$0.8 m s^{-1} community walker [14]. If gait velocity was not measured, severity was based on FAC, with the following distinction: FAC 0 = non-ambulatory; FAC 2–3 = dependent walker and FAC 4–5 = independent walker. If both gait velocity and FAC were not known, the FMA was used to classify the severity. The following distinction was made: $<$21 low mobility function and $\geqslant$21 high mobility function [15].

A classification of the control method for the different devices was made separately for robot and ES (table 3) based on features of modalities of human-robot interaction (HRI), adapted from the definitions applied to HRI in Basteris *et al* (2014), to also include ES [16]. Using this classification, the type of support

Table 2. Methodology quality assessment checklist modified from Downs and Black (1998) [13]. With 15 different questions (item), the and the scoring options.

	Item	Scoring options
Q1	Is the hypothesis/aim/objective of the study clearly described?	0/1
Q2	Are the main outcomes to be measured clearly described in the introduction or method section?	0/1
Q3	Are the characteristics of the patients included in the study clearly described?	0/1
Q4	Is the intervention clearly described?	0/1
Q6	Are the main findings of the study clearly described?	0/1
Q7	Does the study provide estimates of the random variability in the data for the main outcomes?	0/1
Q8	Have all important adverse events that may be consequences of the intervention been reported?	0/1
Q9	Have the characteristics of the patients lost to follow-up/during intervention been described?	0/1
Q10	Have actual probability values been reported for the main outcomes (except where the probability value is less than 0.001)?	0/1
Q11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	0/1/UTD
Q16	If any of the results of the study were based on 'data dredging', was this made clear?	0/1/UTD
Q18	Were the statistical test used to assess the main outcome appropriate?	0/1/UTD
Q20	Were the main outcome measures used accurate (valid and reliable)?	0/1/UTD
Q23	Were study subjects randomized to intervention groups?	0/1/UTD
Q26	Were losses of patients to follow-up taken into account?	0/1/UTD

UTD = unable to determine.

that patients received via mechanical and ES assistance was defined separately at first (i.e. were patients active or passive during training, or were movements performed against resistance, etc.), after which the resulting type of assistance that patients received from the combined robot + ES system was defined.

Outcomes were divided into parameters that measure at body function and structure level (BFS) and activity level (ACT) of the International Classification of Function, Disability and Health (ICF) model [17]. In case the same device was studied in multiple articles, with the same patient(s), with different objectives and therefore different outcome variables and/or analysis both studies were considered as one study. This means that the patients were only counted once, and the different outcomes were related to the same device combination and intervention. In addition effect sizes were calculated for the outcome measures that was most frequently reported, gait velocity, for changes from pre- to post-intervention in the experimental group (time) and for differences pre-post changes between the experimental group, if possible.

To gain insight into potential patient or intervention characteristics that may influence research outcome study outcomes were compared across various parameters. Firstly, outcomes were compared in terms of subject characteristics (time post-stroke and functional ability). Secondly, outcomes were compared between more-intensive and less-intensive training, where high-intensive training was defined as containing more than 100 min of training per week. Additionally, outcomes were compared between different control methods that define the type of support the patients received via mechanical and/or ES assistance (as defined in table 3).

3. Results

In total 712 unique articles were identified through database searching, and all titles and abstracts were screened, resulting in 98 articles. After full-text screening 23 articles met the selection criteria. In five articles out of the 98 a third person (GP) was consulted. Three articles were retrieved from references from the included studies, which resulted in 26 included studies that were analyzed. An overview of the process can be found in figure 1.

3.1. Methodological assessment

The initial agreement on quality assessment scores (table 4) was 97% based on the individual questions, consensus was achieved without consulting the third reviewer. In total three articles scored below nine and were excluded due to poor methodological quality [18–20]. Therefore, 23 articles were included for data extraction, and discussed in the results below [21–42].

3.2. Study population

The included studies (table 5) described robot-assisted devices combined with ES which were tested in 442 stroke patients. Three articles were based on overlapping study populations with previous articles of the same authors, indicated with α, β and δ in table 4. The inclusion ranged between 1 (case study) to 68 stroke patients. The mean age of all stroke patients was 60.8 years (SD: 10.7 years) and the time since stroke was on average 13.9 months (SD: 28.1 months). Ten of the 24 articles had participants with severe limitations (household ambulatory walkers, non-ambulatory walkers or low mobility) [22–24, 31–33, 38, 40, 42], six with moderate limitations (limited community walkers) [21, 27, 29, 30, 36, 37] four

Table 3. Features of modalities of physical human system interaction adapted from [16]. CC BY 2.0, modified to include ES, to define control methods.

Feature	Specification robot	Specification ES
Passive	The device is programmed to follow a desired trajectory/force profile with a strong attractor.	Stimulation is applied following a pre-defined pattern, regardless of movement of the participant.
Moving attractor	The assistance is lower than in passive control, the robot is still attracted towards a minimum jerk or smooth trajectory but the amount of assistance can be modulated.	Stimulation is provided based on movement of the participant (e.g. gait phase or crank angle)
Triggered assistance	The subject initiates a movement without assistance. The robot observes the on-going performance if the task is not completed.	Stimulation is initiated by a movement/effort of the participant and only provided if the on-going performance is not completed. In addition, the amplitude or timing is adapted based on the participant's effort.
Assistive constant force	Force oriented towards the target or weight support when movement is against gravity.	Not applicable
EMG-proportional	The power of the EMG signal is used to control the actuators and/or stimulation amplitude	The timing and/or amplitude of the stimulation is based on the EMG signal of the participant.
Pushing force	A force aligned with the movement direction assist the subject only if there is a delay in comparison with a scheduled motion pattern.	Stimulation (pre-defined) was provided if there was deviation from the scheduled motion pattern.
Spring-damper guidance	Elastic or visco-elastic force fields aim at reducing the lateral displacement from desired trajectory	Not applicable
Tunnels	Haptic feedback is provided only if error overcomes a (large) threshold value. A tunnel can be seen like a lateral spring-damper system plus a dead band zone.	Not applicable
Spring against movement	The device opposes movements through an elastic force-field pulling back to the start position.	Not applicable
Damper against movement	The device generates a force opposing the movement based on current velocity. Although this increases the effort of the subject, it also stabilizes the movement by damping oscillations	Not applicable
Not clear	The information in the article was not sufficient to allow for classification.	The information in the article was not sufficient to allow for classification

EMG = electromyography and ES = electrical stimulation.

with mild limitations (high mobility) [25, 34, 39, 41]. One article had an experimental group that had high mobility and a control group with low mobility [35]. For three articles it was unable to determine the limitation of the included study population as they did not measure any of the three baseline characteristics (gait velocity, FAC or FMA) [26, 28, 43]. Of the 23 studies analyzed, twelve (52%) included patients in the (sub)acute phase (within 6 months of the stroke event), involving in total 314 patients (71%). Nine studies used ES-cycling as the intervention and three used RAGT + ES. The other studies (48%) included chronic stroke patients (>6 months after stroke), involving 128 patients (29%). Five of those studies used ES-cycling as intervention, six articles used RAGT + ES and one article used ankle platform combined with ES (ankle +ES).

3.3. Study design

Three of the articles employed a cross-sectional design, involving 26 participants. In contrast, 20 articles utilized a longitudinal design, with multiple measurements taken over time, involving 416 participants. The articles with a longitudinal design can be divided in controlled and uncontrolled interventions. Eight articles adopted an uncontrolled longitudinal design, involving 53 participants. Of these eight articles, two can be classified as case reports. The other twelve out of 20 articles were randomized controlled trials with multiple measurements over time, involving 362 participants. Furthermore, five studies included a follow-up, published in seven articles [22, 30, 31, 33, 36, 42].

3.4. Devices

The devices can be divided into two main categories, namely motorized cycling combined with ES (ES-Cycling) and robot-assisted gait training combined with ES (RAGT-ES). We identified fourteen articles (61%) that combined motorized cycling with ES (ES-cycling) as an intervention. Two had a cross-sectional design [25, 41] and twelve had a longitudinal design [21, 22, 24, 27, 33–37, 39, 42, 43], from these 12 articles eight conducted controlled trials. In total they comprised 312 patients (71%). The sample size ranged from 6 to 66 per article. The intervention dose

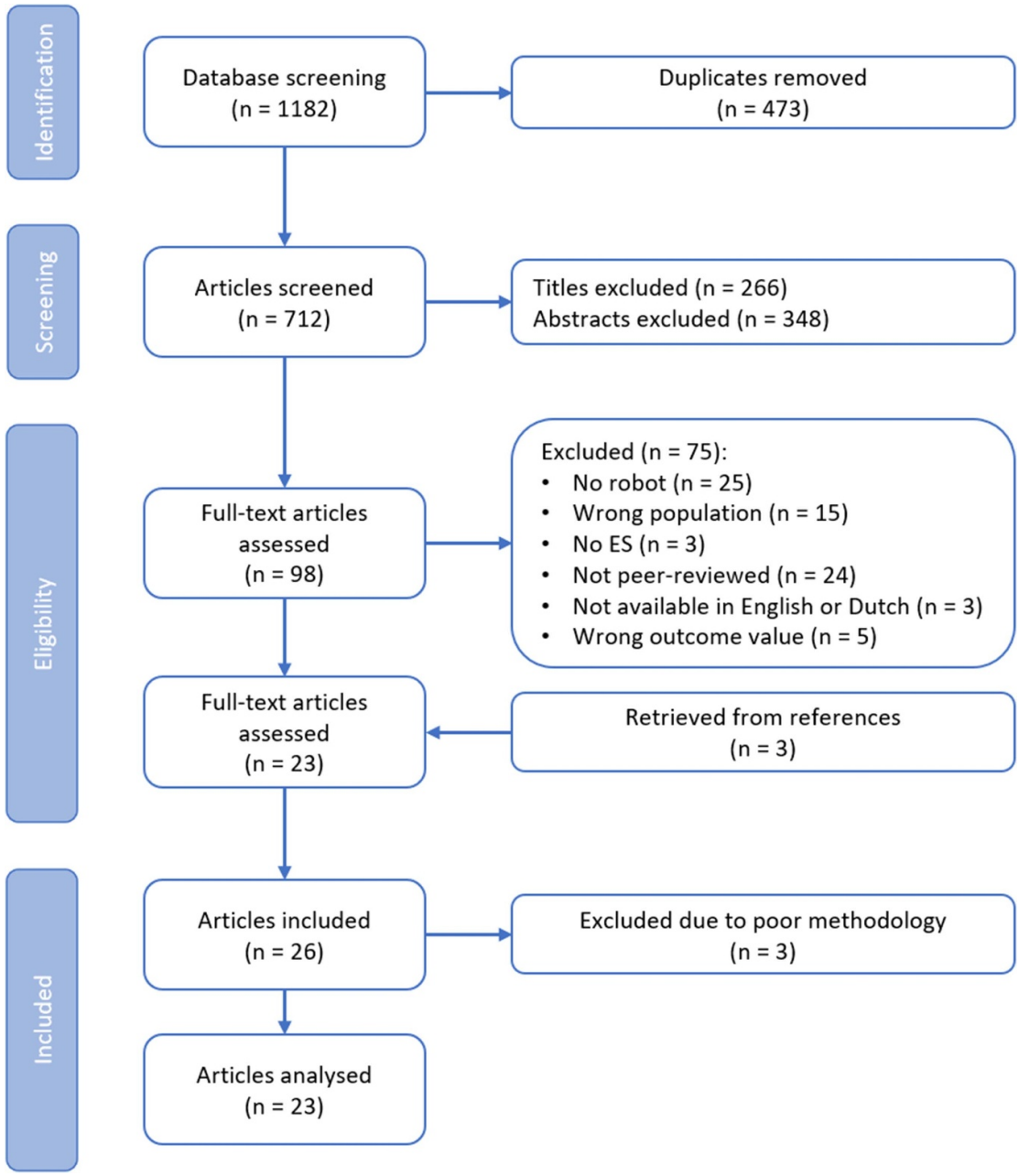


Figure 1. Overview of the article selection process, including the number of articles per step. ES = electrical stimulation.

ranged from 10 to 1440 min (24 h) for the entire intervention period. Three articles conducted a follow-up after an intervention of ES-cycling, they all had a randomized controlled trial design [22, 36, 42].

Eight articles (35%) evaluated RAGT combined with ES, including 95 stroke patients (23%). One article had a cross-sectional (case report) design [28], the remaining seven articles conducted a longitudinal study. Of these seven articles, three conducted a randomized controlled trial [30, 32, 40] and four an uncontrolled trial [28, 30, 31, 38]. Of the four uncontrolled trials, three were case reports. Five of these eight combined a harness with a motor driven orthosis during treadmill walking (RAGT-treadmill) [26, 28–30, 40] and two combined a harness with two footplates [31, 32]. The last of these eight articles used a platform that supported the pelvis during overground walking [38]. Overall, the sample size ranged from 1 to 50 stroke patients. The intervention dose ranged from 8 to 800 min (13.3 h) for the entire intervention period. Two articles conducted a follow-up measurement, all without a control group [29, 31].

The remaining article, including 35 patients in total, was classified as ankle + ES. They used platforms underneath the feet in sitting position to train ankle movements. This study executed a randomized controlled trial and the control group received ES only, without the assistance of a robot [23].

Table 4. Methodology assessment scores per article, per question, according to the modified checklist of Downs and black [13] Within the last column the meaning of the total score.

Author, year / Question	Q1. Aim	Q2. Main outcome	Q3. Population	Q4. Intervention	Q6. Main findings	Q7. Random variability	Q8. Adverse Events	Q9. Lost to follow-up	Q10. Actual probability values	Q11. Representative subjects	Q16. Data dredging	Q18.appropiate statistics	Q20. Accurate outcome	Q23. Randomized	Q26. Accounted for losses	Total score	Quality
Aquirre-Ollinger *et al* 2019 [18]	0	0	1	1	1	0	0	1	0	0	1	0	1	0	1	7	Poor[a]
Alon *et al* 2010 [21]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14	Good
Ambrosini *et al* 2011 [22]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	14	Good
Ambrosini *et al* 2012 [33]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	14	Good
Ambrosini *et al* 2020 [36]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	Excellent
Ambrosini *et al* 2020 [37]	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	13	Good
Anaya-Reyes *et al* 2020 [38]	1	1	1	1	1	0	0	1	0	0	1	0	1	0	1	10	Fair
Au *et al* 2019 [39]	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	11	Fair
Bae *et al* 2014 [40]	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	13	Good
Bao *et al* 2019 [41]	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	11	Fair
Bauer *et al* 2015 [42]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	Excellent
Cho *et al* 2022 [23]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	14	Good
Ferrante *et al* 2008 [24]	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	11	Fair
Iyanaga *et al* 2019 [20]	1	1	1	0	1	0	0	1	0	0	1	1	0	0	0	7	Poor[a]
Kobravi *et al* 2020 [19]	1	0	1	0	1	1	0	1	0	0	1	0	1	0	1	8	Poor[a]
Lee *et al* 2013 [43]	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	12	Good
Lo *et al* 2018 [25]	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	11	Fair
McCabe *et al* 2008 [26]	1	1	1	1	1	1	1	1	0	1	1	0	1	0	1	12	Good
Peri *et al* 2016 [27]	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	13	Good
Spaich *et al* 2014 [28]	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	12	Good
Srivastava *et al* 2015 [29]	1	1	1	1	1	0	0	0	1	0	1	1	1	0	0	9	Fair
Srivastava and Kao 2016 [30]	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	12	Good
Tong *et al* 2006 [31]	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	11	Fair
Tong *et al* 2006 [32]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	Excellent
Wang *et al* 2018 [34]	1	0	1	1	1	1	0	0	1	1	1	1	1	0	0	10	Fair
Zhang *et al* 2021 [35]	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	14	Good
Total	27	24	28	25	28	23	8	19	20	19	28	21	27	12	17		

[a] articles with poor quality were excluded from future analysis.

3.5. Outcome measures

Eighteen of the 23 articles measured outcome values in both BFS and ACT domain. Three only had outcome values in BFS domain and two only in ACT domain. Eighteen articles (78%) used gait velocity or the six-minute walking test (6MWT) as outcome value or to characterize the baseline of the included subjects. Furthermore, sixteen articles (70%) measured FMA or motricity index (MI) to quantify the lower extremity function. Balance was also frequently measured, using the Berg balance scale (BBS) or trunk control test (TCT), in eleven articles (48%).

3.6. Control method

Table 6 shows the classification of the devices and the control methods, based on the training modalities of the combined system and HRI features, for robot and ES separately, per article. In addition, an overview of the settings for robot and/or stimulation are shown if they are provided in the article. The robot force or revolution per minute (rpm) was most frequently noted for cycling + ES. The rpm ranged from 10–50 rpm. The stimulation intensity ranged from 10–100 mA, however 100 mA was reported as the maximum value, it was not mentioned if this was provided in the intervention. In figure 2(a) an overview of the number of devices that contain the specific training modalities and the number of devices per HRI feature (figure 2(b)). These results show that 13 out of 23 articles used passive or partly passive devices, which means no voluntary effort of the patient was needed or even required. There were 11 out of 23 articles that used active or partly active devices. However, only in 4 out of 11 it was a prerequisite for the training, in the remaining 7 it was encouraged or allowed to actively contribute to the training.

Table 5. Overview of the study characteristics of the included studies and corresponding outcomes (primary outcome measures in bold), including effect sizes of changes in gait velocity from pre to post robot + ES training and of differences between experimental and control groups, grouped per study design.

	Subject info				Intervention		Outcomes Pre- to post-intervention[f]		Outcomes experimental vs. control[f]		Effect size of changes in GV[e]
Article	Participants (drop out)	Age (in years)[a]	Time since stroke[a]	Functional ability	Type	Duration	Body function & structure	Activity	Body function & structure	Activity	
Cross-sectional study design											
Bao *et al* 2019 [41]	16	8.5 ± 10.3	5.5y ± 3.6y Chronic	High mobility function	ES-Cycling (passive, active and NMES)	Total: 10 min in 1 session: NMES during 10 min of 25RPM pedaling			• **EEG (partly)** + • **Muscle activity—EEG (ascending pathways)** +		
Lo *et al* 2018 [25]	9	62.9 ± 2.6	Mean 12.6 mth ± 5.6 mth Chronic	High mobility function	ES-cycling (Different amplitudes of ES tested within participants)	Total: 24 min in 1 session: 3 trials of 8 repetitions of 1 min			• **Cortical activation** + • **Inter-hemispheric correlation coefficient (only sensorimotor cortex)** +		
Spaich *et al* 2014 [28]	1	79	2 w (sub)acute	Unable to determine	RAGT + ES (RAGT with and without ES)	Total: 8 min in 1 session: 4 min RAGT only and 4 min RAGT + FES			• Swing angle ankle + • Peak PF/DF angle +		

(Continued.)

Table 5. (Continued.)

Longitudinal case study ($n \leqslant 2$)											
Anaya-Reyes *et al* 2020 [38]	1	57	19 mth Chronic	Household ambulatory	RAGT + ES	Total: 150 min in 5 sessions: 2-3x/w 30 min/ session	• Ankle angle	+	• Gait param	+	NA
Tong *et al* 2006 [31]	2	75 and 59	4 w (sub)acute	Household ambulatory	RAGT + ES	Total: 400 min in 20 sessions: 5x/w, 20 min/ session	• MI	+	• GV • FAC • 5 MWT • BI • BBS	+ + + + +	NA
Uncontrolled clinical trials											
Alon *et al* 2010 [21]	10	Mean 59 ± 13.2	7.7mth ±10.5 mth Chronic	Limited community walker	ES-cycling—no control group	Total: 720 min in 24 sessions: 3x/w, 30 min/ session	• Heart rate	=	• TUG • GV	+ +	Time: 0.29
Ambrosini *et al* 2020 [37]	9[c]	Mean 75 ± 4	Mean 14d ± 8d (sub)acute	Limited community walker	ES-cycling—no control group	Total: 375 min in 15 sessions: 5x/w, 25 min/ session	• MI • **EMG and Synergy**	+ =	• BBS • FIM • Gait param • Pedaling unbalance	+ + + +	

(Continued.)

Table 5. (Continued.)

Article	Subject info				Intervention		Outcomes Pre- to post-intervention[f]				Outcomes experimental vs. control[f]		Effect size of changes in GV[e]
	Participants (drop out)	Age (in years)[a]	Time since stroke[a]	Functional ability	Type	Duration	Body function & structure		Activity		Body function & structure	Activity	
Au *et al* 2019 [39]	10	Mean 58.4 ± 12.5	Mean: 6.9y ± 2.1y Chronic	High mobility function	ES-cycling—no control group	Total: 600 min in 20 sessions: 2-4x/w, 30 min/ session (3x10 min, of which 3x7min ES)	• FMA	+	• BBS • 6MWT	+ +			
McCabe *et al* 2008 [26]	6 (2)	Range 47–77	Range 6–18 mth Chronic	Unable to determine	RAGT + ES	Total: 1440 min in 48 sessions: 4x/w, 30 min/ session			• Subject satisfaction • 6MWT *No statistics*				
Srivastava *et al* 2015 [29]	9[d]	Median 67 (43–80)	Median 38 mth (3–149 mth) Chronic	Limited community walker	RAGT + ES (Assist-as-needed RAGT + ES and visual feedback)	Total: 600 min in 15 sessions: 5x/w, 40 min/ session of 8×5 min training bouts/ session	• FMA • Joint excursion hip, knee, and ankle	+ +	• GV • Dynamic Gait Index	+ +			NA

(Continued.)

Table 5. (Continued.)

Wang *et al* 2018 [34]	6	Median 59 (54–72)	5.75y (2–14y) Chronic	High mobility function	ES-Cycling	Total: 420 min in 20 sessions: 3x/w, 3 trials/ session, 7 min/trial	• FMA	=	• 6MWT • Force/ pedaling balance	+ +					
Randomized controlled clinical trials															
Ambrosini *et al* 2011 [22]	17[b] (2)	Exp: mean 59 ± 10	Exp: mean 48d ± 43d (sub)acute	Household ambulatory	ES-cycling	Total: 500 min in 20 sessions: 5x/w, 25 min/ session	• **MI** • UMCT • TCT	+ + +	• **GV**	+	• **MI** • UMCT • TCT	+ + +	• **GV**	=	Time: 1.01 Group: 0.37
	18[b] (3)	Con: mean 56 ± 14	Con: mean 48d ± 36d (sub)acute	Household ambulatory	Passive cycling with placebo FES										
Ambrosini *et al* 2012 [33]	17[b] (2)	Exp: 59 ± 10	Exp: 48d ± 3d (sub)acute	Household ambulatory	ES-cycling	Total: 500 min in 20 sessions: 5x/w, 25 min/ session	• MI • **EMG & strength**	+ +	• GV •**Pedaling unbalance**	+ +	• MI • **EMG & strength**	+ +	• GV •**Pedaling unbalance**	= +	NA
	18[b] (3)	Con: 56 ± 14	Con: 48d ± 36d (sub)acute	Household ambulatory	Passive cycling with placebo FES										

(Continued.)

Table 5. (Continued.)

Article	Subject info: Participants (drop out)	Subject info: Age (in years)[a]	Subject info: Time since stroke[a]	Subject info: Functional ability	Intervention: Type	Intervention: Duration	Outcomes Pre- to post-intervention[f]: Body function & structure		Outcomes Pre- to post-intervention[f]: Activity		Outcomes experimental vs. control[f]: Body function & structure		Outcomes experimental vs. control[f]: Activity		Effect size of changes in GV[e]
Ambrosini *et al* 2020a [36]	34[c] (4) 34[c] (7)	Exp: 73.7 ± 11.7 Con: 74.9 ± 12.8	Exp: 13.9d ±5.0d (sub)acute Con: 18.0d ± 14.3d (sub)acute	Limited community walker Limited community walker	ES-cycling Usual care	Total: 300 min in 15 sessions of FES (total 30 sessions): 5x/w, 20 min/ session	● MI ● TCT	+ +	● **GV** ● 6MWT ● FIM-MS ● BBS ● Fall Efficacy Scale	+ + + + +	● MI ● TCT	- =	● **GV** ● 6MWT ● FIM-MS ● BBS ● Fall Efficacy Scale	= = = = =	Time: 0.62 Group: 0.04
Bae *et al* 2014 [40]	10 10	Exp: 45.4 ± 19.7 Con: 52.0 ± 16.1	Exp: 9.8m ± 6.0 m chronic Con: 11.5 m ± 5.1 m Chronic	Household ambulatory Household ambulatory	RAGT + ES RAGT	Total: 450 min in 15 sessions: 3x/w, 30 min/ session	● MMAS + ● Kinematics	+ +	● Gait param ● TUG ● BBS	+ + +	● MMAS ● Kinematics (knee flexion)	= +	● Gait param ● TUG ● BBS	= = =	Time: 0.35 EXP-Con: 0.08
Bauer *et al* 2015 [42]	21 (2) 19 (1)	Exp: 59 ± 14 Con: 64 ± 11	Exp: 62d ± 43d (sub)acute Con: 42d ± 45d (sub)acute	Non-independent walker Non-independent walker	ES-Cycling Active cycling without ES	Total: 240 min in 12 sessions: 3x/w, 20 min/ session	● MI ● MAS	+ =	● **FAC** ● **POMA**	+ +	● MI ● MAS	= =	● **FAC** ● **POMA** ● 10MWT	+ + -	

(Continued.)

Table 5. (Continued.)

Cho *et al* 2022 [23]	18 17 (5)	Exp: 51.8 ± 12.0 Con: 55.0 ± 10.9	Exp: 11.6 m ± 4.1 m Chronic Con: 8.6 m ± 3.9 m Chronic	Household ambulatory Household ambulatory	Ankle + ES ES without robot	Total: 800 min in 20 sessions: 5x/w, 40 min/ session	• **Ankle proprioception** = • **pROM** + • **Strength** + • FMA +	• BBS + • GV + • Step length + • TUG + • FESc +	• **Ankle proprioception (only dorsiflexion)** = • **pROM** + • **Strength** + • FMA =	• BBS = • GV = • Step length = • TUG = • FESc =	Time: 0.31 Group: 0.11
Ferrante *et al* 2008 [24]	10 10	Exp: 51 ± 12 Con: 56 ± 9.2	Exp: 56.1d ± 22.8d (Sub)acute Con: 50.8d ± 24.5d (sub)acute	Household ambulatory Household ambulatory	ES-Cycling Usual care	Total: 980 min in 28 sessions: 7x/w, 35 min/ session	• MVC Quadriceps • MI • UMCT • TCT *No statistics reported*	• GV • Sit-to-stand ability *No statistics reported*	• MVC Quadriceps + • MI = • UMCT = • TCT =	• GV = • Sit-to-stand ability +	NA
Lee *et al* 2013 [43]	8 8	Exp: 63.25 ± 15 Con: 63.25 ± 14.12	Exp: 62.50d ± 52.23d (Sub)acute Con: 57.38d ± 34.63d (sub)acute	Unable to determine Unable to determine	ES-cycling Assistive cycling	Total: 600 min in 20 sessions: 5x/w, 30 min/ session	• VO2 peak + • Heart Rate + • Blood pressure +	• 6MWT + • BBS + • mBI +	• VO2 peak = • Heart Rate = • Blood pressure =	• 6MWT = • BBS = • mBI =	
Peri *et al* 2016 [27]	8 8	Exp: 71.8 ± 12.9 Con: 76.4 ± 8.7	Exp: 14.4d ± 2.7d (sub)acute Con: 16.0d ± 5.5d (sub)acute	Limited community walker Limited community walker	ES-cycling Usual care	Total: 375 min in 15 sessions: 5x/w, 25 min/ session	• **GV** + • 6MWT + • FIM + • Double support time +			• **GV** = • 6MWT = • FIM = • Double support time =	Time: 0.68 Group: 0.33

(Continued.)

Table 5. (Continued.)

Article	Subject info: Participants (drop out)	Age (in years)[a]	Time since stroke[a]	Functional ability	Intervention: Type	Duration	Outcomes Pre- to post-intervention[f]: Body function & structure		Activity		Outcomes experimental vs. control[f]: Body function & structure		Activity		Effect size of changes in GV[e]
Srivastava and Kao 2016 [30]	6[d]	Exp: 63.5 (43–80)	Exp: 36.5 m (3–149 m) Chronic	Limited community walker	RAGT + ES	Total: 600 min in 15 sessions: 5x/w, 40 min/ session of 8×5 min training bouts/ session	• FMA (*no statistics reported)*		• FGA • 6MWT • TUG • GV	+ = + +	• FMA • Kinematics • EMG	= = =	• FGA • 6MWT • TUG • GV	= = = =	Time: 0.40 Group: -0.22
	6	Con: 58.5 (48–75)	Con: 13 m (3–35) Chronic	Limited community walker	BWSTT with manual assistance		• Kinematics • EMG	+ +							
Tong *et al* 2006 [32]	15	RAGT-ES: 61.8 ± 10.8,	RAGT-ES: 2.3 w ± 1.0 w (sub)acute	Household ambulatory	RAGT + ES	Total: 400 min in 20 sessions: 5x/w, 20 min/ session	• MI	+	• GV+ • FAC + • 5MWT = • BI = • BBS + • FIM + • EMS +	+ + = = + + +	*Control group = RAGT/Usual* • MI	=/+	*Control group = RAGT/Usual* • GV • FAC •5MWT • BI • BBS • FIM • EMS	=/+ = /+ =/ = =/ = =/ = =/ = =/+	Time: 2.41 EXP-Con: 0.78 (vs RAGT) 1.65 (vs conv)
	15	RAGT: 66.1 ± 9.9,	RAGT: 2.7 w ± 1.3 w (sub)acute	Household ambulatory	RAGT										
	20 (4)	Conv: 71.4 ± 14.0,	Conv: 2.7 w ± 1.2 w (sub)acute	Household ambulatory	Conventional gait training (based on Bobath concept)										

(Continued.)

Table 5. (Continued.)

Zhang *et al* 2021 [35]	33	Exp: 55.76 ± 11.78	Exp: 43.45d ± 5.66 (sub)acute	High mobility function	ES-cycling	Total: 1440 min in 48 sessions: 6x/w, 30 min/ session	• FMA • **EMG**	+ +	• mBI	+	• FMA • **EMG**	+ +	• mBI +	+
	33	Con: 57.31 ± 10.53	Con: 42.45d ± 4.75 (sub)acute	Low mobility function	Cycling without ES									

[a] Age and time since stroke are presented with mean (standard deviation) or median (range).

[b] Same patients were used in both articles.

[c] The nine patients of the second study of the same author, is a subpart of the larger group of 68 patients.

[d] Six of the nine patients were also included in the second study with 12 patients, of which six were in the intervention group. All healthy volunteers are not considered into the included number of participants.

[e] Effect sizes of changes in gait velocity between pre- and post-assessment (time) are displayed for experimental groups (robot + ES) of longitudinal studies (time); for longitudinal studies including control group an additional effect size of difference in change of gait velocity (pre-post) between experimental and control group (group) is displayed.

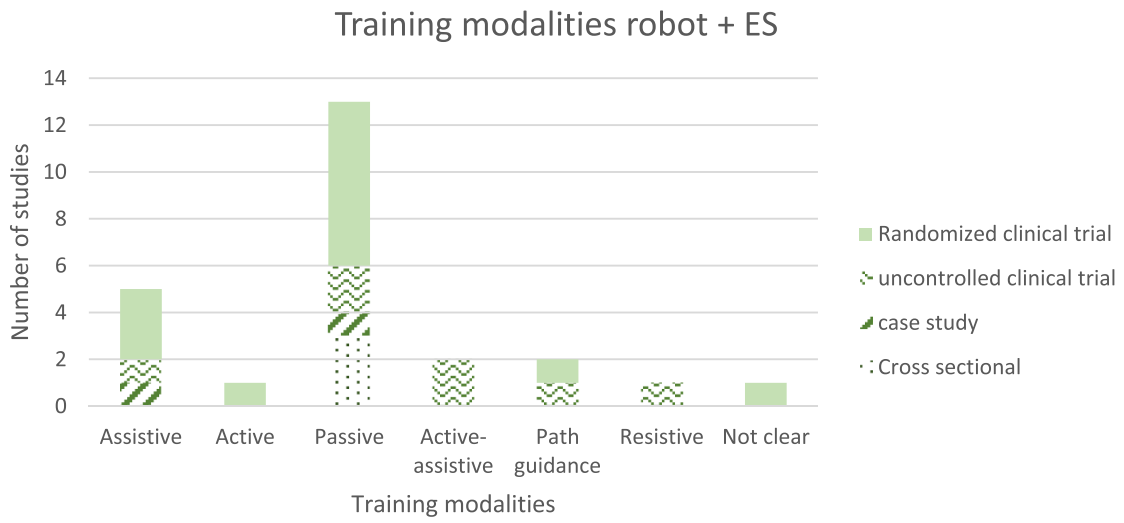
[f] For the outcome values, + means a significant improvement of the experimental group over time or compared against the control group,—significant deterioration and = means no significant difference.

Abbreviations: NA = Not applicable, values were not provided. GV = gait velocity, ES = electrical stimulation, RAGT = robot assisted gait training, Con = control group, int = intervention group, y = years, m = months, w = weeks, d = days, min = minutes, s = seconds, RCT = randomized controlled trial, FMA = Fugl–Meyer assessment lower extremity, MI = motricity index lower extremity, (m)BI = (modified) Barthel Index, BBS = Berg balance scale, 6MWT = 6-minute walking test, 5MWT/10MWT = 5 or 10 meter walking test, FAC = functional ambulation categories, FIM = functional independence measure, TUG = timed up and go, (p)ROM = (passive) range of motion, MAS = modified Ashworth scale, TCT = trunk control test, POMA = performance-oriented mobility assessment, MVC = maximal voluntary contraction, EMS = elderly mobility scale, FGA = functional Gait assessment, EMG = muscle activity, UMCT = upright motor control test, MMAS = modified motor assessment scale, param = parameters, FESc = Fall efficacy scale, DF = dorsiflexion and PF = plantarflexion.

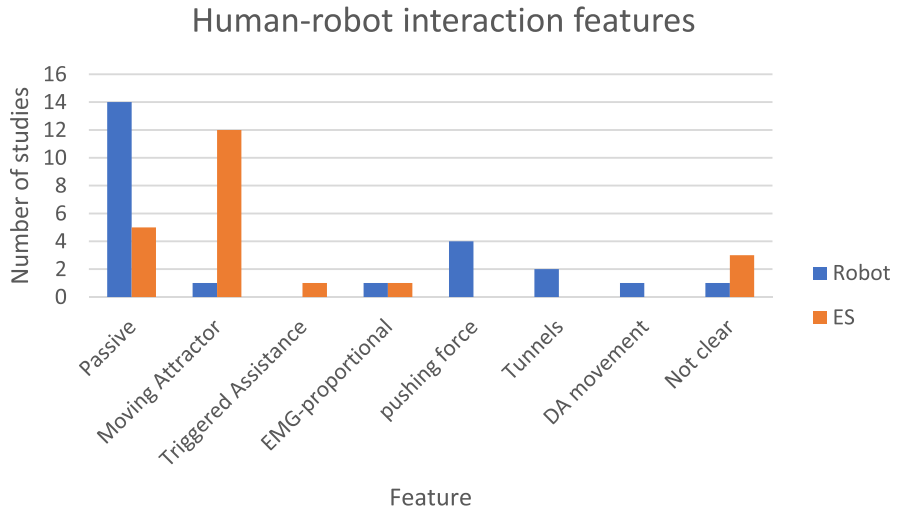
Table 6. Overview of the control method for robot and ES separately (HRI feature) and for the combined device (Training modality), including specification of the set-up of robot and ES.

Article	HRI feature robot	HRI feature ES	Cycling rate/robot force	Stimulation intensity	Combined training modality
			Cross-sectional study		
Bao *et al* 2019 [41]	Passive	Passive	25 rpm	20 mA	Passive
Lo *et al* 2018 [25]	Passive	Passive	50 rpm	10 mA (low intensity) 30 mA (high intensity)	Passive
Spaich *et al* 2014 [28]	Passive	Moving attractor	Guidance force 100%	23 mA	Passive
			Longitudinal case study ($n \leqslant 2$)		
Anaya-Reyes *et al* 2020 [38]	Pushing force	Triggered assistance	Adjusted for gait speed	32, 34, 38, 50 and 48 mA respectively for the 5 sessions	Assistive
Tong *et al* 2006 [31]	Passive	Moving attractor	Not provided	Individually set by therapist	Passive
			Uncontrolled clinical trials		
Alon *et al* 2010 [21]	Passive, damper against movement, pushing force	Passive	Min 45 rpm	7.0−10.32 Coulomb	Active-assistive or resistive
Ambrosini *et al* 2020 [37]	Pushing force	Moving attractor	Not provided	Individually set	Assistive
Au *et al* 2019 [39]	EMG—proportional	EMG—proportional	10–25 rpm	Based on EMG.	Active -assistive
McCabe *et al* 2008 [26]	Passive	Passive	Not provided	20 mA	Passive
Srivastava *et al* 2015 [29]	Tunnel	Not clear	Assist-As-Needed compliant	150 volt	Path guidance
Wang *et al* 2018 [34]	Passive	Moving attractor	25–25–20 rpm	Individually set between 0–100 mA	Passive
			Randomized controlled clinical trials		
Ambrosini *et al* 2011 [22]	Passive	Moving attractor	20 rpm	Individually set	Passive
Ambrosini *et al* 2012 [33]	Passive	Moving attractor	20 rpm	Individually set between 20–60 mA	Passive
Ambrosini *et al* 2020 [36]	Pushing force	Moving attractor	Minimum 20 rpm	Individually set	Assistive
Bae *et al* 2014 [40]	Moving attractor	Moving attractor	Guidance force was set between 0%–100%	Mean of 36 mA (range: 24–60 mA) for quadriceps and 35 mA (range: 18–60 mA) for hamstring	Assistive
Bauer *et al* 2015 [42]	Pushing force	Moving attractor	Min 20 rpm	Individually set	Assistive
Cho *et al* 2022 [23]	Passive	Passive	2.14 degree/seconds	Individually set	Passive
Ferrante *et al* 2008 [24]	Passive	Moving Attractor	40 rpm	Individually set	Passive
Lee *et al* 2013 [43]	Passive	Passive	30 rpm	Individually set, max 100 mA	Passive
Peri *et al* 2016 [27]	Passive	Not clear	Not provided	Individually set	Passive or Active
Srivastava and Kao 2016 [30]	Tunnel	Not clear	Assist-as-needed compliant guidance force	150 volt	Path guidance
Tong *et al* 2006 [32]	Passive	Moving attractor	Not provided	Individually set	Passive
Zhang *et al* 2021 [35]	Not clear	Not clear	Not provided	Individually set, between 4–20 mA	Not clear

GV = gait velocity, HRI = human-robot interaction, ES = electrical stimulation and rpm = revolution per minute.



(a) overview of the resulting training modality of robot+ES combined

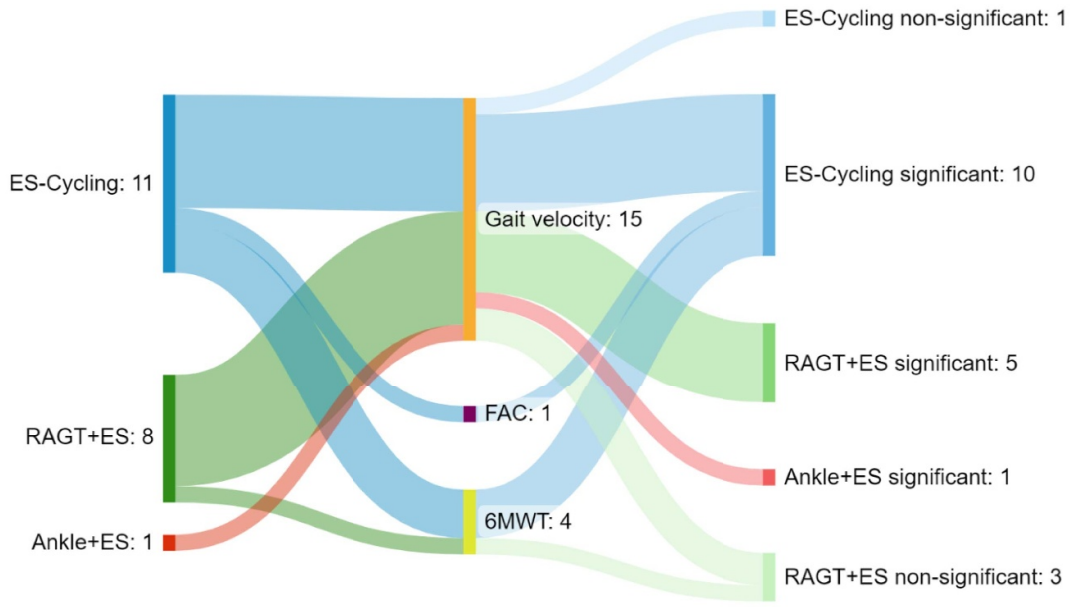


(b) Number of studies per human-robot interaction feature for robot (blue) and ES (orange) separately.

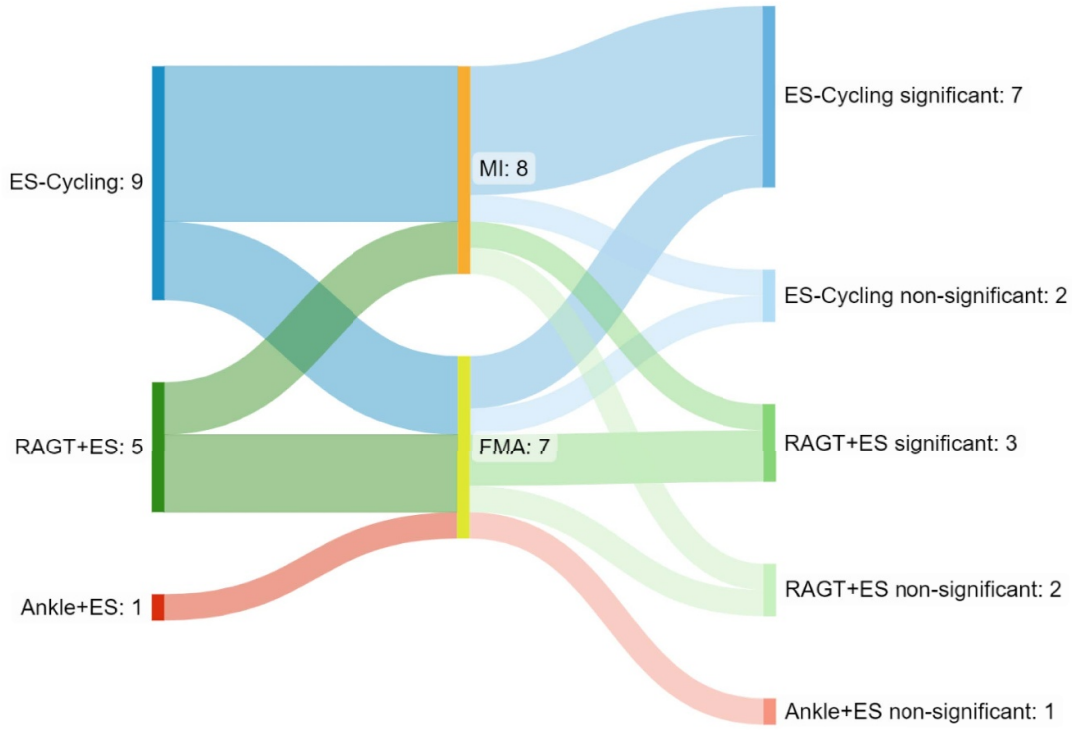
Figure 2. Number of studies across control methods, based on the classification of Basteris *et al* (2014), for robot and ES support separately (a) and the combination (robot + ES) (b). Please note that (b) is defined from the patients' perspective (e.g. passive means that the patient did not need to perform voluntary movements; the system provided energy). Abbreviations: DA movement = damper against movement, ES = electrical stimulation.

3.7. Effect of robot-assistance combined with ES

A graphical overview of the outcomes per device group is shown in figure 3. Of the seven articles measuring gait velocity after ES-cycling, six reported significant improvements [21, 22, 27, 33, 36, 37]. Effect sizes of changes in gait velocity after ES-cycling varied from 0.29 to 1.01 (table 5), meaning that all articles found at least medium effect sizes [44]. In the remaining article, the authors were unable to execute statistical test on the gait velocity because only 4 out of 20 patients were able to walk pre-intervention [24]. Post-intervention, 18 out of 20 were able to walk, also indicating improved gait. Furthermore, three articles (that did not measure gait velocity) found significant improvement on the 6MWT [34, 39, 43], showing improvement in walking endurance, and one article showed significant improvement on the FAC score [42]. All three parameters indicate improvement in activity level and components of gait after stroke (figure 3(a)). Seven out of the nine articles including at least one measure of motor function (FMA and/or MI) reported improvement after ES-cycling, one article found no significant improvement [34] and in the remaining article no statistical tests were conducted [24]. The results did show that all individual stroke patients improved or remained stable on the MI post-intervention compared to pre-intervention (figure 3(b)).



(a) Gait parameters activity level



(b) Measure of motor function body function and structure level

Figure 3. Overview of the significant and non-significant parameters over time per group for gait related outcome parameters (ACT level) in A and motor function related outcome parameters (BFS level) in B. ES = electrical stimulation, FAC = functional ambulation categories, 6MWT = 6-minute walk test, MI = motricity index, FMA = Fugl–Meyer assessment and RAGT = robot assisted gait training.

Of the six articles measuring gait velocity after RAGT + ES, four reported improvements [29, 30, 32, 40], with effect sizes for RAGT + ES ranging between 0.35 and 2.41 (table 5), meaning that all articles found at least medium effect sizes [44]. The other two articles did not perform statistical tests on gait velocity due to limited number of patients (one/two included patients) (figure 3(a)). Nevertheless, in these two articles stroke patients did improve gait velocity [31, 38]. One article measured the 6MWT without statistical testing, due to a limited number of stroke patients included. All stroke patients that finished the interventions showed improvement in the 6MWT [26]. One article out of four that included measures for

motor function found significant improvement after RAGT + ES [32]. From the remaining three articles one was a case report (two stroke patients) which showed individual improvement without statistical testing [31] and two found no significant effect of the FMA over time [29, 30] (figure 3(b)).

The article, classified as ankle + ES, measured gait velocity (ACT) and FMA-LE (BFS). Both had significant improvement over time, but no significant difference was observed between the experimental and control group.

Concerning the added value of ES combined with robotic support over other (control) interventions, twelve articles (45%) are relevant in which a controlled trial was performed with at least two groups, including a total of 378 stroke patients (84%). Of those, 179 patients were included in the experimental group and 199 in the control group. Eight articles compared ES combined with robot-supported movements, totaling 109 patients, against only robot in the control group involving 110 patients [22, 30, 32, 33, 35, 40, 42, 43]. One article used the same study population and will therefore be considered as one study [22, 33]. Two of the seven articles found significant improvement on both BFS and ACT level [22, 33, 35], one article on BFS level only [40] and one on ACT level only [42] for the robot + ES group compared to the control group (only robot) (figure 4). However, the remaining three articles did not find any significant differences between experimental group (robot + ES) and control group (robot) [30, 32, 43]. These articles had a variety of outcome parameters in both BFS and ACT domain. Of the four studies among those seven studies including GV as ACT outcome measure, effect sizes of differences in GV changes from pre to post intervention ranged from −0.22 to 0.78, meaning that the effect sizes ranged from small to large [44].

In one article, the control group received only ES (17 participants), compared to the intervention group that received robot + ES (18 participants). The experimental group showed more strength and passive range of motion (BFS level) compared to the control group receiving only ES. Both groups improved at ACT level to a similar extent [23] (figure 4). Effect size between groups in this study was 0.11, indicating a small effect size [44]. Furthermore, four studies provided the control group (72 patients) with usual care in comparison against robot + ES (67 patients) [24, 27, 32, 36]. Two of the four studies showed improvement in both BFS and ACT level in favor of the experimental group (figure 4). One of these two found improvement on muscle strength of the quadriceps and the sit-to-stand, but no significant difference was found for gait velocity and a measure for motor function (MI) [24]. The other two studies did not show significant improvement on either BFS or ACT level. Effect sizes between groups in this study ranged between 0.04 and 1.56, ranging from small to large effect sizes [44]. Three articles with a control group also employed a follow-up measurement [22, 36, 42]. They all conduced ES-cycling in the intervention period. Two of these articles found significant improvement in favor of the ES-cycling group post-intervention [22, 42]. These significant difference between groups were not maintained at follow-up. However, the gained improvements were maintained at follow-up for all three studies that included the follow-up.

To summarize, more than half of the articles (seven of eleven) found significant improvement in favor of the robot + ES group, when considering all outcomes on both BFS and ACT level. When looking specifically at effect sizes of gait velocity over time all articles had at least a medium effect size. The effect sizes of the difference in gait velocity change from pre- to post-intervention between the experimental and control group ranged from small to large. Half of the effect sizes (four of eight) were small and the other half was medium to large. To have a better understanding which intervention works for which patients, the next section elaborates on specific patient groups and/or characteristics of the intervention.

3.8. Influence of subject characteristics

Five of the seven articles that showed improvement on BFS and/or ACT included sub-acute stroke patients. This effect was seen most clearly in studies that included patients relatively shortly after stroke, mostly within 3 months [22, 24, 32, 33, 35, 36]. Although the (sub)acute stroke patients showed more improvement than the chronic stroke patients, most studies including chronic stroke survivors did show improvement on BFS and ACT level and only three of the randomized controlled trials included chronic stroke patients [23, 30, 40]. Two of these three studies showed superior improvement compared to the control group on BFS level and none of the four articles, with chronic stroke patients found improvement on ACT level.

Three out of five studies without significant improvement in favor of the robot + ES group included moderate affected stroke patients [27, 30, 36]. In one of the remaining two articles stroke severity was unknown [43] and the other included severe stroke patients [32]. Six of the seven articles that showed significant improvement on BFS and/or ACT level included severe stroke patients [22–24, 32, 33, 40, 42]. The remaining article had mild stroke patient in the intervention group and severe stroke patient in the control group [35].

3.9. Influence of training intensity

The intensity of the training, in terms of dosage, is provided in table 5. Of the 20 longitudinal studies, the average number of sessions per study was 18.2 (SD: 11.9) with an average duration of 26.2 min (SD:

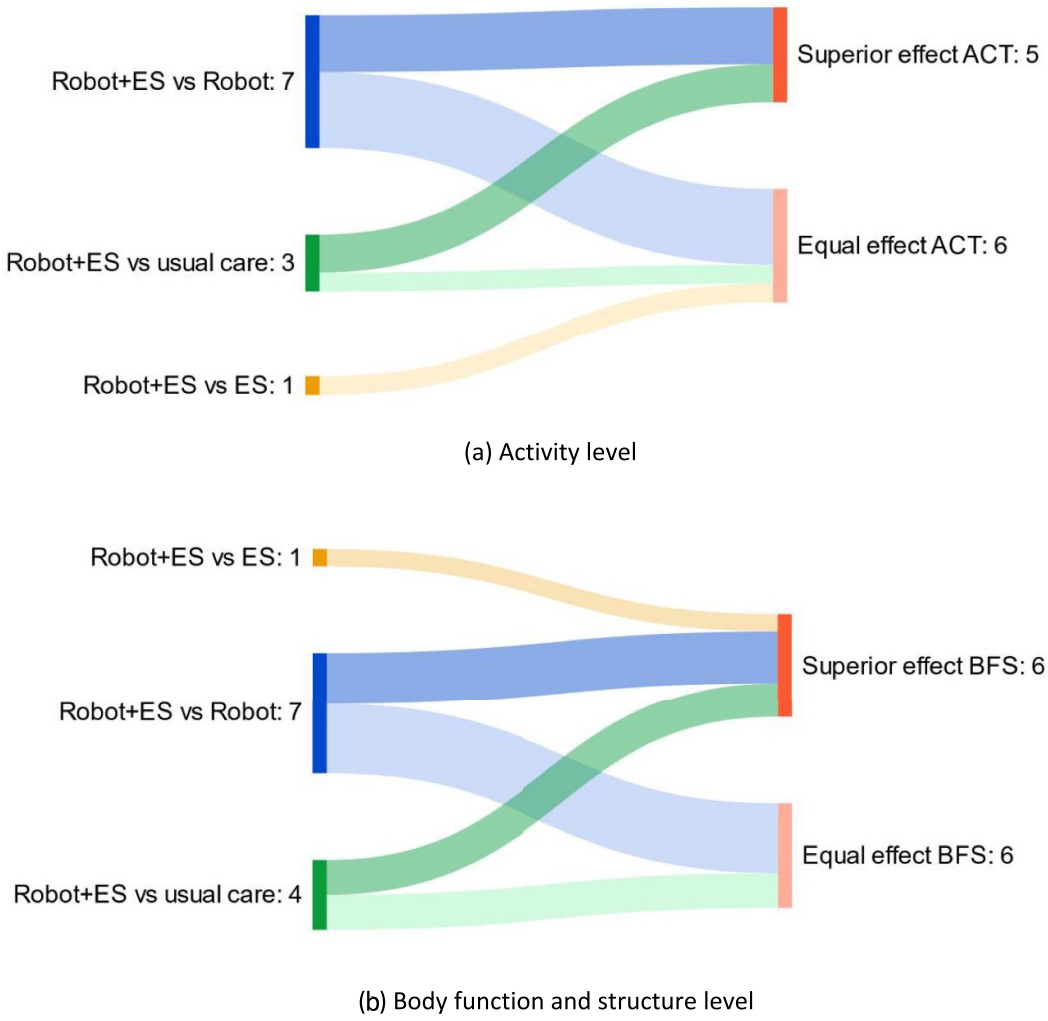


Figure 4. Graphical overview of the comparison of robot + ES with a control group, sub-divided in ICF level, significance, and control group, separately for the effect on ACT level (a) and BFS level (b). ES = electrical stimulation, ACT = activity level and BFS = body function and structure level.

8.5 min). On average the interventions took 4.8 weeks (SD: 2.3) with 4.6 sessions per week (SD: 1.1). All articles with a control group provided the control group with the same intensity of therapy as the experimental group. Ten articles were regarded as high-intensive intervention [22–24, 26, 27, 29, 30, 33, 35, 43] and ten were not [21, 31, 32, 34, 36–40, 42]. The intervention consisted of 120–245 min per week for the intensive group and 60–100 for the less-intensive group. Four of the six articles that found superior effect on BFS level provided an intensive intervention [23, 24, 35, 40]. In addition, all articles that found superior effect on ACT level had less-intensive intervention. Of the five articles that found no improvement in favor of the intervention group, three performed an intensive intervention [27, 30, 43].

3.10. Influence of control method

Thirteen out of the 23 articles performed an intervention with (partly) passive control method, which means the effort of the patient was not needed for triggering or continuation of the training. For control of robot support, 14 studies (8 RAGT + ES, 6 ES-cycling) used a passive control method, while ten used a method that required at least some active involvement (i.e. active, EMG-proportional, moving attractor, tunnel, pushing force and damper against movement). There are several ways to initiate ES during the intervention. In 14 of 23 studies (8 with ES-cycling and 5 with RAGT + ES), this initiation was based on movement phase (e.g. crank angle or specific gait cycle event), classified as moving attractor and triggered assistance (figure 2(b)) [22, 24, 25, 28, 31–34, 36–38, 40, 42, 43]. In four studies (two ES-cycling and two RAGT + ES), the timing of the stimulation was based on pre-determined patterns (e.g. models from healthy volunteers or an experienced cyclist) [21, 26, 30, 41]. In one article the stimulation was provided manually by the therapist (e.g. on visual judgment)[23]. The pre-determined patterns and manually applied ES were classified as passive. Furthermore, one article used an EMG triggered

method [24], where timing and the amplitude of ES were based on muscle activity (EMG-proportional). In the remaining three studies the control method for ES was not clear [27, 29, 35]. This means that in more than half of the studies (15/23, of which 13 longitudinal studies) the control method for ES could be based on active contribution to the movement.

When considering the 13 longitudinal studies, were the control method could be based on active contribution, no clear differences between control methods of ES were observed. 11 (of the 13) studies with active components of the control methods found significant improvements on ACT level and 10 also found significant improvement on BFS level [22, 24, 32–34, 36, 37, 39, 40, 42, 43] (one article found no significant improvement on BFS level [34]). From the two longitudinal studies that used a passive control method to initiate ES, both found significant improvements on ACT level [21, 30] and one also on BFS level [30].

Of the seven articles that found superior effect on BFS and/or ACT level, five had a control method for ES based on Moving attractor [22, 24, 32, 33, 40, 42], one article applied manual stimulation (passive) [23] and the remaining article had no clear description of the triggering method [35]. Furthermore, two out five articles that found equal effect of the intervention compared to control group, moving attractor as control method for ES [32, 36], one used a predetermined pattern (passive) [43] and the last two articles had no clear description of the triggering method [27].

To summarize, the majority of the articles that showed improvement in favor of robot + ES on both or either BFS or ACT level included (sub) acute stroke patient with pre-intervention severe limitations in the lower extremity. No clear difference between the group that showed superior effect on BFS and/or ACT level and the group with equal effect of both experimental and control group, where shown based on intensity and control method.

4. Discussion

This systematic literature review aimed to assess the potential effects of interventions involving robot assistance combined with ES on clinical and/or gait parameters in stroke patients. The identified devices can be broadly categorized into two main categories: motorized cycling +ES and RAGT +ES. Motorized cycling combined with ES was the most extensively researched device, with over half of the included studies investigating this combination. Furthermore, studies utilizing motorized cycling combined with ES included the largest population of stroke patients compared to other devices identified in this review. Overall, all included studies demonstrated improvements in body function and/or activity levels after an intervention for robot or cycling combined with ES, with effect sizes of changes in gait velocity between pre- and post-intervention ranging between 0.29 and 2.41. Meaning that the effect sizes over time ranged from medium to large. However, the wide range of parameters that was used to quantify the effects on stroke patients precluded the execution of a meta-analysis. The main findings of this review indicated that in 64% of the included articles the addition of ES to a robot or motorized cycling had a superior effect on lower limb recovery, whereas the other studies found no added benefit. The majority of the articles that showed superiority included severely affected stroke patients in contrast to the studies with equal effects including mostly moderately affected patients. The improvements in favor of robot + ES were not maintained at follow-up (2 weeks–6 months), suggesting that the addition of ES promotes a faster recovery, but the end point is equal for both robot + ES and the control groups. Interestingly, the one study comparing robot + ES with ES only showed significant improvement on BFS level in favor of robot + ES. This suggests that the combination of robot + ES could be associated with a favorable effect on impairment level over the addition of ES in itself.

To the best of our knowledge, no previous review has been conducted into the clinical effects of an intervention that combines robot and ES. Anaya *et al* (2017) reviewed hybrid FES-robotic gait rehabilitation technologies, with a focus on the technical side, such as actuation type and control strategies [8]. They identified 28 different hybrid systems, which could be divided into orthotic based and non-orthotic based systems. In contrast to the current review, they also included non-motorized spring-based systems. Furthermore, because the focus was on the technical viewpoint, they also included systems that were not tested. They found that most of the hybrid systems were evaluated on safety and energy performance, based on these results they concluded that the hybrid systems are proven to be functional. However, there was no evidence yet that the reviewed hybrid systems influence lower extremity function, which the present review has provided.

The effect of only one intervention, either robot-based therapy or ES has been investigated more extensively. Mehrholz *et al* (2020) reviewed the effect of electromechanical-assisted gait training in stroke patients [45], concluding that electromechanically assisted gait training in combination with normal physiotherapy is beneficial to improve walking ability. Furthermore, they found that more severely affected, dependent walkers, were more likely to restore walking ability with higher velocity then less affected stroke patients (ambulatory patients). This is in accordance with the finding of the current review that severely affected stroke patients seem to benefit more compared to moderately affected stroke patients. Multiple reviews assessed the effect of ES

compared to or in addition to other interventions [46–50], investigating distinct types of ES or the effect on different parameters, such as balance, mobility or gait speed. Nevertheless, they all found positive effects of ES on the investigated parameter in stroke patients. Shariat *et al* (2019) [49] found a positive effect of cycling on gait velocity, walking ability and balance. Adding FES had a beneficial effect on balance compared to cycling alone. These results are in line with the current review, cycling combined with ES had a positive effect on both ACT and/or BFS level.

Although the dosage of the intervention differed between the included articles, in all controlled trials the intervention group and control group received the same dosage of training, which is important for comparability. When the same intensity of training is applied to both the intervention and usual care or control group, previous research has shown that experimental interventions are not always superior to the control group [4, 43]. Robot assistance can therefore be a means towards achieving a high(er) intensity of training, without the involvement of (multiple) therapists [7]. This could contribute to achieving recommended high-intensity therapy times (i.e. a minimum of 45 min of every therapy that is required), which is thought to be important for optimal results in stroke rehabilitation [51]. The current review showed no differences in outcome with respect to intensity of the intervention. Improvements were found on both or either BFS or ACT level, regardless of the dosage of the intervention. This suggests that with at least 150 min of robot + ES training a positive effect on BFS and ACT level can be achieved, but not superior to a control group. Veerbeek *et al* (2014) suggested that an additional therapy of 17 h over 10 weeks is necessary to improve on different levels of the ICF model [4]. This corresponds with total of 1020 min intervention (in 10 weeks). In the present review, only two articles had a dosage above 1020 min in 8 and 12 weeks. Whether robot + ES training in higher intensities would result in more pronounced effects needs further research. Furthermore, due to the wide variety of stimulation intensity and force/rpm applied, it is impossible to relate the effect of different stimulation intensity or assistance of the robot to the effects of the interventions.

Previous research indicates that active involvement of the participant in the intervention is beneficial for the recovery [16, 52]. Most research regarding EMG-driven stimulation or intent based stimulation is conducted for the upper extremity [16, 53], showing that active-assistive training modalities facilitates better improvement in upper limb function than passive training. The current review showed that stimulation was mostly based on crank angle or gait phase, however this was sometimes combined with passive training due to the robot support applied, which resulted in passive movement training when applying the combination of robot and ES. The main results show that improvement was found on both or either ACT level or BFS level, regardless of the control method for the ES. In contrast to previous research [16, 53], no superiority was found in favor of interventions with active contribution, compared to only passive control methods. However, the active involvement of the participant in studies where the trigger was based on crank angle or gait phase (moving attractor) is difficult to determine, because the movement could be initiate by the robot/motor of the device, which was not clearly described in most articles. Remarkably, three studies (published in four articles) specifically instructed participants not to participate [22, 24, 25, 33]. In the articles that instructed the patient to participate actively during the intervention, the actual active involvement of the participants compared to the robot and/or stimulation was not evaluated. Active involvement would be ensured if the timing of the stimulation or robot support is dependent on active movement intent by the patient. One way to achieve actively triggered stimulation in more severely affected patients is using muscle activity, which was applied in only one article. In this study improvements on BFS and ACT level were found, but lack of a control group prevented comparison of its added value in the present review. Therefore, more research is needed to examine the influence of control methods and active contribution to robot and/or ES assisted training on lower limb function. Furthermore, research that emphasize the active involvement of the participants is needed, for example with assist-as-needed control methods. Similar as in upper extremity applications, it is important that the active involvement and/or the modality of HRI is described more clearly in future studies [16].

The current review provided an underestimation of the significant improvement because studies that were unable to perform statistical test were considered as non-significant. This does not mean there were no improvements seen in these studies. The overall quality of the studies in the current review was relatively good, ranging from fair to excellent after the exclusion of four articles that were of poor quality. Nevertheless, only half of the studies had a control group, limiting assessment of added value of robot + ES training against other interventions. Furthermore, methodological assessment revealed that only eight of the 26 included articles mentioned the occurrence of adverse events, which limited assessment of practical applicability in clinical practice. A previous review on adverse events in RAGT showed that not all studies mentioned whether adverse events occurred, and of those that do, 36% do not provide a complete description [54]. Thorough reporting of adverse events is important for adequate evaluation of clinical applicability of emerging technology-supported treatment options.

4.1. Future research

The articles included in this review exhibited significant heterogeneity across several aspects, such as outcome measures and intervention type. Ideally, each study should include at least one functional measure, one balance measure as well as gait velocity to assess the effect of an intervention on BFS and ACT level [55]. Future research should also aim for more standardized study designs, such as well-designed RCTs, to provide more robust evidence and enable more rigorous comparisons between different interventions in robot-assisted rehabilitation therapy. Furthermore, as mentioned above it is often not measured what the participants involvement is. In future research the amount of muscle activity or force produced by the participant can be used to determine if and to what extend a participant is actively involved in the intervention. Besides the clinical effectiveness also the implementation into a clinical setting of a hybrid robot and electrostimulation device should be topic of future research, because only 23 articles did measure patient and not every article tested their device in clinical environment. This can identify obstacles and/or needs from a clinical perspective.

5. Conclusion

This review assessed the effect of robot-assisted training combined with ES on lower extremity function after stroke among studies with overall good methodological quality (ranging between fair and excellent). Two main categories of devices were identified: motorized cycling combined with ES and RAGT combined with ES. Despite the heterogeneity of the studies, all types of devices demonstrated a positive effect on lower extremity function, as measured by parameters related to BFS and ACT level. Training in the early phase after stroke seems to offer greater benefits, at least in the short-term, although chronic stroke patients also improved lower extremity function. Robot + ES had greater benefits for stroke patients with severe limitation pre-intervention, compared to mild and/or moderate limitation pre-intervention. This review showed that in 64% of the included studies training with the combination of robot + ES was superior over robot training alone or over conventional treatment, whereas the other studies found no added benefit. No difference was observed between studies involving a potentially active control method of robot and/or ES support and those that did not, but this was hindered by a lack of information about actual active contribution of the patients. Although robot + ES seems promising as intervention for especially subacute stroke patients with severely-moderately affected lower extremity function, conclusive outcomes on superiority of robot + ES are impeded by heterogeneity of the studies, a limited number of controlled studies and unclear HRI modalities.

Data availability statement

No new data were created or analysed in this study.

Acknowledgments

The authors declare that they have no conflict of interest.

Appendix A

Search strategy

The search strategy used in PubMed specified per search term can be found below. The total search consisted of: #1 AND #2 AND #3 AND #4.

Stroke patients	(Stroke) OR (Hemip*) OR (CVA) OR ((Cerebral OR Cerebro*) AND (Accident OR Disease))	#1
Robotic therapy	(Robot*) OR (Robotics) OR (Cycling) OR (Assistive Technology)	#2
Electrostimulation	(Electrical Stimulation) OR (Electr* AND stimulation) OR (FES) OR (TENS) OR (NEMS)	#3
Lower extremity	(Lower extremity) OR (Gait) OR (Walking) OR (lower Limb)	#4

Appendix B

Methodology assessment: question interpretation, justification, and explanation

The methodology assessment in the current review is based on 15 questions of the 27 items of the Downs & Black checklist. Twelve questions were removed because they go into depth about the statistical analysis which is not applied in all types of study design and was not the aim of the current review. Below an explanation of the questions and scoring is provided of the included questions.

Q1: is the hypothesis/aim/objective of the study clearly described? This question was answered 'yes' if the aim of the study was described in the introduction section and when it was clear what goal the authors meant to achieve with the study.

Q2: are the main outcomes to be measured clearly described in the Introduction or Methods section? This question was answered 'no' if the main outcomes were first mentioned in the result section. If the main outcomes were mentioned in the introduction or method section, the question was answered 'yes'.

Q3: are the characteristics of the patients included in the study clearly described? For case studies and series, a case definition had to be given in order to

score 'yes' on this question. Information about age and time since stroke had to be involved in the definition. For cohort studies and randomized controlled trials, the question was answered 'yes' if in- and exclusion criteria were provided.

Q4: is the intervention clearly described? We scored this question 'yes' if the duration and frequency of training sessions were made clear and both the motorized and the ES intervention were clearly described in terms of product used, amplitude and frequency of stimulation, etc.

Q6: are the main findings of the study clearly described? The main outcome data had to be clearly reported for all major findings. The results were preferably presented in both tables or graphs and text. Tables and graphs had to be understood without reading the textual explanation.

Q7: does the study provide estimates of the random variability in the data for the main outcomes? The presentation of data distribution had to be clear. In non-normally distributed parameters, medians and range of results should be provided. In normally distributed variables, a mean and standard deviation (SD) should be given. We decided on a cut of value of 10 participants when evaluating whether a usually normally distributed variable should be considered normally distributed in the study. The question was answered 'no' if inappropriate items were presented (e.g. mean and SD in a case series with 6 patients).

Q8: have all important adverse events that may be a consequence of the intervention been reported? If adverse events were reported, a 'yes' was scored. When a study mentioned that no adverse events had taken place, this question was answered 'yes'. The question was answered 'no' if (possible) adverse events had not been reported.

Q9: have the characteristics of patients lost to follow-up been described? This question was answered 'yes' in all studies that showed the number of patients lost to follow-up in either tables/graphs or text, with or without reason for loss. The question was answered 'no' when a study did not report the number of patients lost to follow-up. If the question did not apply to the study since no patients were lost to follow-up, the question was answered 'yes'.

Q10: have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? We scored 'yes' when an actual p-value was given in either tables, text, or both.

Q11: were the subjects asked to participate in the study representative of the entire population from which they were recruited? This question was answered 'no' if a study included less than 10 stroke patients, since such a small population sample was not considered representative of the entire population. It was scored 'yes' when a relatively large group of patients was included, when the patient characteristics were representative for the entire stroke population (e.g. in terms of age, gender, etc.) and the method of patient selection was clearly described.

Q16: if any of the results of the study were based on 'data dredging', was this made clear? This question would have been answered 'no' if outcome measures that were not mentioned in the introduction or method section appeared in the result section. However, this was not the case in any of the studies.

Q18: were the statistical tests used to assess the main outcomes appropriate? The statistical tests that were used had to be described, preferably in the method section. The tests had to be appropriate for the variables. E.g. for small sample sizes, nonparametric methods had to be used. If no statistical analysis was performed or the tests were not clearly described, this question was answered 'no'.

Q20: were the main outcome measures used accurate (valid and reliable)? When the outcome measures were clearly described and logically chosen for the aim/purpose of the study, this question was answered 'yes'.

Q23: were study subjects randomized to intervention groups? Studies that randomized subjects in 2 or more groups scored 'yes' on this question. Case studies/series and observational studies that lacked randomization scored 'no' on this question.

Q26: were losses of patients to follow-up taken into account? If the number of patients lost to follow-up was reported and considered in the analyses, this question was answered 'yes'. In case the number of subjects lost to follow-up was not mentioned, the question was answered 'unable to determine', and therefore received 0 points.

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