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Review Article

Neuromuscular Electrical Stimulation Improves Activities of Daily Living Post Stroke: A Systematic Review and Meta-analysis

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KEYWORDS
Cerebrovascular disorders;
Electric stimulation therapy;
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Abstract *Objectives:* (1) To elucidate the effectiveness of neuromuscular electrical stimulation (NMES) toward improving activities of daily living (ADL) and functional motor ability post stroke and (2) to investigate the influence of paresis severity and the timing of treatment initiation for the effectiveness of NMES.
Data Sources: PubMed, MEDLINE, Embase, Physiotherapy Evidence Database (PEDro) and Cochrane Library searched for relevant articles from database inception to May 2020.
Study Selection: The inclusion criteria were randomized controlled trials exploring the effect of NMES toward improving ADL or functional motor ability in survivors of stroke. The search identified 6064 potential articles with 20 being included.
Data Extraction: Two independent reviewers conducted the data extraction. Methodological quality was assessed using the PEDro scale and the Cochrane Risk of Bias Tool.
Data Synthesis: Data from 428 and 659 participants (mean age, 62.4 years; 54% male) for outcomes of ADL and functional motor ability, respectively, were pooled in a random-effect meta-analysis. The analysis revealed a significant positive effect of NMES toward ADL (standardized mean difference [SMD], 0.41; 95% CI, 0.14-0.67; *P*=.003), whereas no effect on functional motor ability was evident. Subgroup analyses showed that application of NMES in the subacute stage (SMD, 0.44; 95% CI, 0.09-0.78; *P*=.01) and in the upper extremity (SMD, 0.34; 95% CI, 0.04-0.64; *P*=.02) improved ADL, whereas a beneficial effect was observed for functional motor abilities in patients with severe paresis (SMD, 0.41; 95% CI, 0.12-0.70; *P*=.005).
Conclusions: The results of the present meta-analysis are indicative of potential beneficial effects of NMES toward improving ADL post stroke, whereas the potential for improving

List of abbreviations: ADL, activities of daily living; BRS, Brunnstrom recovery stages; CROB, Cochrane risk of bias; EMG, electromyogram; ES, electrical stimulation; FES, functional electrical stimulation; MMT, manual muscle test; NIHSS, National Institutes of Health Stroke Scale; NMES, neuromuscular electrical stimulation; PEDro, Physiotherapy Evidence Database; SMD, standardized mean difference; TES, therapeutic electrical stimulation.

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functional motor ability appears less clear. Furthermore, subgroup analyses indicated that NMES application in the subacute stage and targeted at the upper extremity is efficacious for ADL rehabilitation and that functional motor abilities can be positively affected in patients with severe paresis.

The global incidence of stroke is in the order of 13.7 million annually[1] and is a clinical condition typically associated with limb paresis[2] secondary to compromised function of upper motor neurons and associated neural pathways, with loss of locomotor function and the ability to perform activities of daily living (ADL) being functional manifestations hereof.[3-5] Although recent medico-scientific advances within the fields of thrombolysis[6,7] and thrombectomy[8] have spurred major changes to the treatment of acute ischemic stroke, stroke remains a leading cause of disability,[1] and effective rehabilitation modalities are thus of utmost importance.

In the newest Clinical Guidelines for Stroke Management[9] and Guidelines for Adult Stroke Rehabilitation and Recovery,[10] the rehabilitation modality of electrical stimulation (ES) is recommended as a supplementary therapy alongside the standard care modalities. ES can be broadly categorized into functional electrical stimulation (FES) and therapeutic electrical stimulation (TES). The primary difference between these 2 ES modalities is the degree of patient involvement; TES is administered with the patient completely passive or performing isolated muscle contractions, whereas FES is superimposed onto voluntary contractions while the patient is performing functional tasks such as walking, rising from a chair, or stair climbing.[11,12] As alluded by Kroon et al,[13] TES can be further subcategorized into neuromuscular electrical stimulation (NMES), electromyogram (EMG)-triggered ES, positional feedback stimulation training, and transcutaneous electrical nerve stimulation. In EMG-triggered and positional feedback stimulation, the electrical current is administered in response to the patient performing a minor contraction or movement, respectively, whereas NMES is administered according to a preprogrammed scheme and hence is received passively.[11,14,15] Evidence suggests that NMES has the ability to strengthen muscles,[16,17] reduce spasticity,[10] increase excitability of corticospinal neural pathways,[18] and augment neuroplasticity.[19,20] Furthermore, when ES is administered prior to or after voluntary contractions (eg, NMES) in persons without stroke, it has been demonstrated to be more effective in developing functional motor abilities than both voluntary contractions performed simultaneously with stimulation and voluntary contractions performed in isolation.[20,21] The apparent superiority could be governed by a cumulative effect of the 2 types of contractions and/or because of the unique motor drives associated with each type of contraction.[21,22]

According to the International Classification of Functioning, Disability, and Health, poststroke rehabilitation is a complex process that can be viewed in the context of function, activity, and participation domains.[23] The activity domain encompasses the full range of life areas from a performance and capacity point of view, the performance level describes an individual's abilities in the actual context in which they live (ADL), and the capacity level entails the ability to execute a specific task or action in a standard environment (functional motor ability).[23] ADL reflect the level of disability in daily life and are therefore thought of as the most clinically relevant outcomes in assessing poststroke recovery,[24] whereas functional motor abilities are viewed as good surrogate outcomes.

A number of systematic reviews concerning the effectiveness of ES toward regaining overall activity performance post stroke have been published, including 3 Cochrane reviews.[17,25,26] However, the majority of said reviews have pooled studies with a variety of ES methods[16,25,27-31] or investigated other specific aspects of ES, typically FES.[24,32-34] In contrast to previous systematic reviews, the aim of the present systematic review and meta-analysis was to elucidate the effectiveness of NMES in improving ADL and functional motor ability post stroke and additionally analyze data according to onset of NMES administration post stroke and paresis severity, which in our opinion are important additions to the stroke rehabilitation literature.

Methods

Literature search and study identification

Although the protocol was not preregistered, it was a priori specified and consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.[35] A systematic search of the literature was conducted in the scientific databases PubMed, MEDLINE, Embase, Physiotherapy Evidence Database (PEDro), and Cochrane Library for relevant English articles published between database inception and May 2020. The search was carried out using keywords related to stroke, rehabilitation, and ES (appendix 1). Reference lists of relevant articles were screened to identify additional articles of relevance. The screening process, carried out by 2 reviewers (M.G.H.K., H.B.) independently, was conducted through reading of titles and abstracts. Full-text versions of potentially relevant articles were obtained and selected according to the criteria listed below. Any disagreements were resolved through comprehensive discussion, and if an agreement could not be attained, a third reviewer (T.W.) was consulted. Data of included trials were extracted independently by each reviewer and recorded in predesigned data forms to ensure a systematic data collection process. If outcome data were not available or unclear, data were extracted from previous Cochrane reviews or authors were contacted. If data could not be obtained, the study was excluded from the meta-analysis.

Study selection

Participants

Trials included adults (18 years or older) with clinically diagnosed stroke.[1] No specific criteria were set regarding the participants' level of disability or the timing of intervention initiation in relation to the stroke.

Interventions

Trials were randomized controlled trials investigating the effect of NMES. As previously alluded to by Pomeroy et al,[25] the terminology used within the field of ES is quite inconsistent; we therefore included or excluded studies according to our interpretation of whether the intervention was consistent with NMES and not the terminology adopted by the respective authors. Only studies administering NMES to either the upper or lower extremity through surface electrodes were considered. No criteria were set regarding stimulation characteristics (pulse duration, frequency etc); however, the documentation of a visible muscle contractions was required. The only difference between the control and intervention groups was the administration of ES. Theses or articles published only as abstracts were not included.

Outcomes

Endpoint measurements explored activity outcomes defined by the International Classification of Functioning, Disability, and Health as the category Activity.[23] Primary outcomes were measures of ADL; secondary outcomes were measures of functional motor ability. Where multiple measures were available in 1 study at either the motor or ADL level, the measure with the highest prevalence in the present pool of studies was selected to minimize heterogeneity. Only outcome measures at the end of the treatment were identified.

Assessment of risk of bias

Study methodological quality was quantified by the PEDro scale[36] and the Cochrane risk of bias (CROB) tool.[37] The PEDro scale is widely used in the field of physical therapy and consists of 11 items, criteria 1 concerning external validity, criteria 2-9 encompassing various aspects of internal validity, and criteria 10-11 being associated with the degree of statistical availability. Each item is rated as "yes" or "no," and the final PEDro score is the number of items being satisfactorily fulfilled (excluding criteria 1 regarding external validity). Studies were scored according to the following system; excellent: 9-10 points, good: 6-8 points, fair: 4-5 points, and poor: $\leq$3 points. The CROB tool evaluates potential bias for 7 items across 6 domains: selection, performance, detection, attrition, and reporting bias and other sources of bias. Each of the 7 items is rated as "high," "unclear," or "low" risk of bias and are reported separately. Quality assessment was carried out independently by 2 reviewers (M.G.H.K., H.B.), with any disagreement resolved through discussion or consensus with a third reviewer (T.W.).

Data analysis

The extracted continuous outcomes (postintervention mean and SD) were subjected to a random-effect model calculating standardized mean difference (SMD) because of the different outcome measures.[38] If >2 intervention or control groups in a given trial were relevant to the present review, these were merged according to the recommendations of the Cochrane handbooks formulae[39] using the following equations:

$$Sample\ size_{pooled} N_1 + N_2$$

$$Mean_{pooled} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD_{pooled} = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

where N is the group sample size, M is the postintervention mean, SD the associated SD, and 1 and 2 the group designations.

Subgroup analyses were conducted to elucidate the importance of (1) location of stimulation (upper vs lower limb); (2) time since stroke (acute <7 days, subacute 7 days to 6 months, chronic >6 months)[40]; and (3) severity of paresis as assessed either by a global severity score (eg, National Institutes of Health Stroke Scale[41] [NIHSS], Brunnstrom recovery stages[42] [BRS]) or the level of muscle strength (eg, manual muscle test[43] [MMT]). Studies were grouped according to the severity of preintervention paresis; mild (NIHSS 1 [motor function arm/leg], BRS 5, MMT 3–4), moderate (NIHSS 2 [motor function arm/leg], BRS 3-4, MMT 2), or severe paresis (NIHSS 3-4 [motor function arm/leg], BRS 1-2, MMT 0-1). Interstudy heterogeneity was evaluated through I^2 statistic, with substantial heterogeneity defined as >50%.[38] To identify possible sources of heterogeneity, a leave-1-out sensitivity analysis was conducted to quantify the effect of individual trials on the merged results. All statistical analyses were carried out using Review Manager 5.3.[a]

Results

Search results

The literature search identified 6064 articles of potential relevance (fig 1), with title and abstract screening eliminating 5951, thus leaving 113 trials. No additional articles of relevance were identified through reference lists screenings. A total of 93 studies were excluded during the full-text review process, thus leaving 20 for final inclusion. Of these, 12 trials were included in the ADL analyses, 16 were included in the analyses pertaining to functional motor ability, and 8 trials were featured in both.

Participant characteristics

End of treatment results were collected from 956 patients with stroke (demographic data on 972 participants) with study sample sizes ranging from 14-163 participants. Eighty-nine dropouts were registered, with early discharge, death, or additional illness (eg, an additional stroke) being the

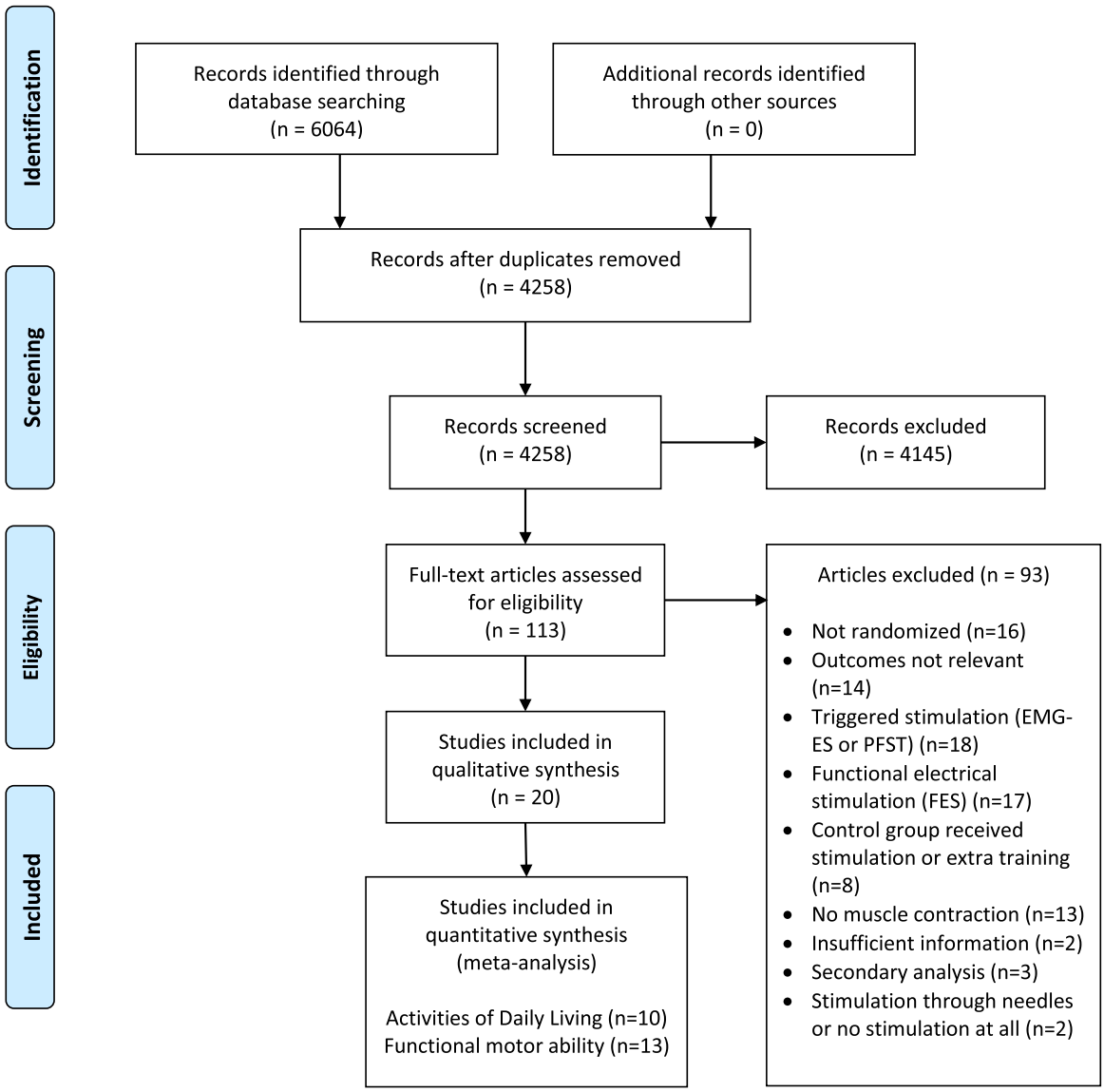

Fig 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for study identification. Abbreviation: PFST, positional feedback stimulation training.

most frequent causes. No adverse effects of stimulation were reported in any of the trials. Demographics and characteristics of included studies are presented in table 1. The participants were predominantly male (54%), with a mean age of 62.4 years (range, 51-75 years; 2 studies reported median age of 72.5 years [range, 64-81 years][44] and 71.5 years [range, 59-84 years][45]). Sixteen trials provided specific paresis information (57% left-sided) and type of stroke (79% infarcts). Thirteen trials investigated patients in the subacute stage, ranging from 9 days to 4 months post stroke, whereas 3 and 4 trials featured patients in the acute[44,45,50] and chronic[48,54,55,57] stages, respectively. Severity of paresis was most frequently reported as a measure of global severity, with 7 trials reporting BRS[47,54,57-59,61,63] and 3 NIHSS.[44-46] Five trials reported MMT,[49,50,52,60,62] whereas Rosewilliam et al[53] provided a direct measure of strength. Kim[48] and Sonde[55] and colleagues provided Fugl-Meyer Assessment scores (global impairment),[64] and McDonnell[51] and Zhou[56] and colleagues measured active range of motion. Five and 6 studies encompassed patients with moderate and severe paresis, respectively, with no studies including patients with mild paresis. Five studies failed to specify mean or median values and had wide ranging inclusion criteria such as mild to severe paresis (MMT≤3-4),[49,52] mild to moderate paresis (MMT 2-3),[60] and moderate to severe paresis (MMT≤2).[50,62]

Stimulation protocols

Thirteen trials administered stimulation to the upper extremity (5 with outcomes addressing functional motor ability,[44,47,48,50,51] 4 addressing ADL,[49,54-56] and 4 addressing both types of outcomes[45,46,52,53]), primarily to the shoulder abductors and wrist extensors in isolation or in conjunction with additional muscle groups such as

Table 1 Demographics and characteristics of included studies

Upper Limb Study	Participants	Intervention	Stimulation	Outcome
Church et al[44]	N=163 (89 exp/84 con) Age (y): 72.5 (range, 64-81) Time since stroke: 3-7 d Paresis: moderate (NIHSS mean 2 motor arm)	Exp: dual channel, 60 min Con: sham, 60 min 3/d × 7 d/wk × 4 wk	Muscles: shoulder abd. Frequency: 30 Hz Pulse width: NA Program: cyclic, 15 s on/off, 3 s up/down	Motor: ARAT ADL: only at follow-up
Fletcher-Smith et al[45]	N=35 (18 exp/17 con) Age (y): 71.5 (range, 59-84) Time since stroke: <72 h Paresis: severe (NIHSS median, 3-4 motor arm)	Exp: dual channel, 30 min Con: nothing 2/d × 5 d/wk × 3 mo	Muscles: wrist ext.+flex. Frequency: 40-60 Hz Pulse width: 450 μs Program: cyclic, constant current flex-hold-extend-hold pattern	Motor: ARAT ADL: BI
Hochsprung et al[46]	N=14 (7 exp/7 con) Age (y), mean ± SD: 62±9.6 Time since stroke: <6 mo Paresis: severe (NIHSS=4 motor arm)	Exp: dual channel, 30 min Con: nothing 1/d × 7 d/wk × 4 wk	Muscles: shoulder flex.+ext. Frequency: 30-50 Hz Pulse width: 250 μs Program: cyclic, 5 s on/7 s off, 0.6s ramp up	Motor: ARAT ADL: BI
Hsu et al[47]	N=66 (44 exp/22 con) Age (y): 63±11 Time since stroke: 21±17 d Paresis: severe (BRS mean, 2)	Exp: dual channel, 30 or 60 min Con: nothing 1/d × 5 d/wk × 4 wk	Muscles: finger ext.+flex./ finger ext./shoulder abd. Frequency: NA Pulse width: NA Program: NA	Motor: ARAT ADL: not measured
Kim et al[48]	N=30 (15 exp/15 con) Age (y): 62±9 Time since stroke: 13±10 mo Paresis: NA	Exp: dual channel, 30 min Con: sham, 30 min 1/d × 5 d/wk × 4 wk	Muscles: elbow+wrist ext. Frequency: 100 Hz Pulse width: 200 μs Program: NA	Motor: BBT ADL: not measured
Lin et al[49]	N=37 (19 exp/18 con) Age (y): 64±9 Time since stroke: 42±26 d Paresis: Mild to severe (MMT shoulder flexor ≤3)	Exp: dual channel, 30 min Con: nothing 1/d × 5 d/wk × 3 wk	Muscles: shoulder abd. +wrist ext. Frequency: 30 Hz Pulse width: 300 μs Program: cyclic, 5 s on/off, 1 s up/down	Motor: not measured ADL: MBI
Linn et al[50]	N=40 (20 exp/20 con) Age (y): 72 Time since stroke: 1-2 d Paresis: Moderate to severe (MMT upper limb ≤2)	Exp: dual channel 30 min → 60 min Con: nothing 4/d × 7 d/wk × 4 wk	Muscles: shoulder abd. Frequency: 30 Hz Pulse width: 300 μs Program: cyclic, 15 s on/off, 3 s up/down	Motor: MAS, upper arm section ADL: not measured
McDonnell et al[51]	N=20 (10 exp/10 con) Age (y): 66±12 Time since stroke: 4±2 mo Paresis: NA	Exp: dual channel, 60 min Con: sham, 60 min 1/d × 3 d/wk × 3 wk	Muscles: finger abd. Frequency: NA Pulse width: 100 μs Program: constant-current	Motor: ARAT ADL: not measured
Powell et al[52]	N=55 (27 exp/28 con) Age (y): 68±12 Time since stroke: 23±7 d Paresis: Mild to severe (MMT wrist extension ≤4)	Exp: dual channel, 30 min Con: nothing 3/d × 7 d/wk × 8 wk	Muscles: wrist+finger ext. Frequency: 20 Hz Pulse width: 300 μs Program: cyclic, 5 s on/20 s off → 5 s on/off, 1 s up/1,5 s down	Motor: ARAT ADL: BI
Rosewilliam et al[53]	N=80 (39 exp/41 con) Age (y): 75±11 Time since stroke: ≤6 wk Paresis: Severe (wrist ext. 0.1±0.4N)	Exp: single channel, 30 min Con: nothing 2-3/d × 5 d/wk × 6 wk	Muscles: wrist+finger ext. Frequency: 40 Hz Pulse width: 300 μs Program: cyclic, 15 s on/off, 6 s up/down	Motor: ARAT ADL: BI
Sahin et al[54]	N=42 (21 exp/21 con) Age (y): 60±8 Time since stroke: 30±20 mo Paresis: moderate (BRS median, 3)	Exp: single channel, 15 min Con: nothing 1/d × 5 d/wk × 4 wk	Muscles: wrist ext. Frequency: 100 Hz Pulse width: 100 μs Program: cyclic, 3 ms, 9 s off, interval 0.9 ms	Motor: not measured ADL: FIM
Sonde et al[55]	n = 44 (26 exp/18 con) Age (y): 72±5	Exp: dual channel, 60 min Con: nothing	Muscles: wrist ext± elbow ext./shoulder abd.	Motor: not measured ADL: BI

(*continued*)

Table 1 (*Continued*)

Upper Limb Study	Participants	Intervention	Stimulation	Outcome
	Time since stroke: 9±2 mo Paresis: NA	1/d × 5 d/wk × 3 mo	Frequency: 1.7 Hz Pulse width: NA Program: 8 trains, 14-ms interval	
Zhou et al[56]	N=49 (31 exp/18 con) Age (y): 62±11 Time since stroke: 90±98 d Paresis: NA	Exp: dual channel, 60 min Con: nothing 1/d × 5 d/wk × 4 wk	Muscles: shoulder abd. Frequency: 15 Hz Pulse width: 200 μs Program: 10 s on/off, 5 s up/down	Motor: not measured ADL: BI
Gürcan et al[57]	N=32 (19 exp/13 con) Age (y): 58±12.5 Time since stroke: 14±19 mo Paresis: moderate (BRS mean, 3)	Exp: dual channel, 20 min Con: nothing 1/d × 5 d/wk × 3 wk	Muscles: ankle ext. Frequency: 20 Hz Pulse width: 300 μs Program: NA	Motor: FAS ADL: FIM
Tan et al[58]	N=45 (30 exp/15 con) Age (y): 65±9 Time since stroke: 41±24 d Paresis: moderate (BRS mean, 3)	Exp: 4 or dual channel, 30 min Con: nothing 1/d × 5 d/wk × 3 wk	Muscles: hip, knee, and ankle flex. + ext. / ankle flex. Frequency: 30 Hz Pulse width: 200 μs Program: cyclic, to mimic gait	Motor: BBS ADL: MBI
Wang et al[59]	N=53 (36 exp/17 con) Age (y): 51±10 Time since stroke: 29±9 d Paresis: moderate (BRS mean, 4)	Exp: dual channel, 30 min Con: nothing 2/d × 5 d/wk × 4 wk	Muscles: ankle flex., toe ext. Frequency: 20 Hz Pulse width: 200 μs Program: cyclic, 5 s on/off, intensity according to group	Motor: TUG ADL: not measured
Yan et al[60]	N=26 (13 exp/13 con) Age (y): 69±8 Time since stroke: 9±5 d Paresis: Mild to moderate (MMT hip flexion 2-3)	Exp: 2 dual channel, 30 min Con: nothing 1/d × 5 d/wk × 3 wk	Muscles: hip, knee, and ankle flex.+ext. Frequency: 30 Hz Pulse width: 300 μs Program: cyclic, to mimic gait	Motor: TUG ADL: not measured
Yavuzer et al[61]	N=25 (12 exp/13 con) Age (y): 55±8 Time since stroke: 2±2 mo Paresis: moderate (BRS mean, 3)	Exp: single channel, 10 min Con: nothing 1/d × 5 d/wk × 4 wk	Muscles: ankle flex. Frequency: 80 Hz Pulse width: 100 μs Program: cyclic, 10 s on/50 s off, 2 s up/1 s down.	Motor: walking velocity ADL: not measured
You et al[62]	N=37 (19 exp/18 con) Age (y): 62±10 Time since stroke: 24±19 d Paresis: moderate to severe (MMT ankle dorsal flexion <3)	Exp: dual channel, 30 min Con: nothing 1/d × 5 d/wk × 3 wk	Muscles: ankle flex.+eversion Frequency: 30 Hz Pulse width: 200 μs Program: NA	Motor: BBS ADL: MBI
Zheng et al[63]	N=48 (33 exp/15 con) Age (y): 59±10 Time since stroke: 20±12 d Paresis: severe (BRS mean, 2)	Exp: 4 or dual channel, 30 min Con: sham, 30 min NA/d × NA d/wk × 3 wk	Muscles: hip, knee, ankle flex. + ext./ankle flex.+eversion Frequency: 30 Hz Pulse width: 200 μs Program: cyclic, to mimic gait	Motor: BBS ADL: MBI

Abbreviations: abd., abduction; ARAT, Action Research Arm Test; BBS, Berg Balance Scale; BBT, Box and Block Test; BI, Barthel Index; con, control; exp, experimental; ext., extension; FAS, Functional Ambulation Scale; flex., flexion; MAS, Motor Assessment Scale; MBI, Modified Barthel Index; NA, not available; TUG, timed Up and Go.

the wrist flexors, elbow extensors, and/or finger extensors and/or flexors. Seven trials used lower extremity stimulation (3 with outcomes addressing functional motor ability[59-61] and 4 addressing both ADL and functional motor ability outcomes[52,57,58,63]), most frequently targeting the ankle dorsal flexors exclusively or in conjunction with hip and knee flexors and extensors, toe extensors, and ankle evertors. The characteristics of the stimulation protocols are available in table 1. The intervention duration ranged from 3 weeks to 3 months, with most trials spanning 3-4 weeks with individual sessions of 10-60 minutes, 1-4 times daily, and 3-7 weekly sessions. The typical NMES protocol consisted of cyclic stimulation with a frequency of 30 Hz (range, 1.7-100Hz) at a fixed pulse width of 200-300 μs (range, 100-450μs). The amplitude was most frequently reported as being individually adjusted to achieve a visible muscle contraction or joint movement.

Risk of bias

The mean PEDro score was 5.8 (range, 4-8), and the majority of studies (n=13) were rated as "good." A detailed overview of the PEDro scoring is provided in table 2. The low scores were primarily because of lack of blinding because none of the included studies featured blinded therapists and only 2 studies encompassed participant blinding. According to the CROB tool assessment there were concerns regarding the description of the random sequence generation because the vast majority of the trials only described the process as being randomized without further elaboration. Six studies showed selective reporting, and 3 studies had high risk of "other bias," typically because of the sample size being smaller than needed according to a priori power analysis. The individual results are displayed and summarized in fig 2 and fig 3, respectively. None of the included studies exhibited significant asymmetry (ADL: 1.47; 95% CI, −2.94 to 5.87; *P*=.53. Functional motor ability: −0.005; 95% CI, −2.92 to 2.91; *P*>.99). according to Egger's test as calculated with RStudio.[b]

NMES and ADL

The effect of NMES toward ADL function was examined through a random-effect model by pooling postintervention data from 10 trials of 428 participants. A moderate effect of NMES toward ADL was observed compared with control (SMD, 0.41; 95% CI, 0.14-0.67; I^2=42%; *P*=.003) (fig 4). Powell[52] and Fletcher-Smith[45] and colleagues were not included in this part of the meta-analysis because of incomplete reporting of data. Subgroup analysis showed a significant positive effect in the upper extremity (SMD, 0.34; 95% CI, 0.04-0.64; I^2=29%; *P*=.02), whereas only a tendency was observed in the lower extremity (SMD, 0.49; 95% CI, −0.04 to 1.03; I^2=61%; *P*=.07) (fig 4). A significant positive effect was identified in the subacute stage (SMD, 0.44; 95% CI, 0.09-0.78; I^2=50%; *P*=.01), which was not the case in the chronic stage (SMD, 0.35; 95% CI, −0.14 to 0.84; I^2=42%; *P*=.16) (fig 5). No trials included participants with a stroke in the acute stage. No effect of paresis severity was observed, with both moderate (SMD, 0.21; 95% CI, −0.16 to 0.58; I^2=0%; *P*=.26; n=3) and severe (SMD, 0.36; 95% CI, −0.55 to 1.26; I^2=81%; *P*=.44; n=3) subgroups demonstrating positive but insignificant effects (fig 6).

NMES and functional motor ability

The effect of NMES toward functional motor ability was examined through a random-effect model by pooling data from 13 trials (659 participants), with 3 studies[45,51,52] not included because of incomplete reporting of data. No significant effect of NMES was detected (SMD, 0.15; 95% CI, −0.13 to 0.43; I^2=64%; *P*=.30) (fig 7), which was also the case when the upper (SMD, 0.18, 95% CI, −0.05 to 0.40; I^2=13%; *P*=.12) and lower limbs (SMD, 0.00; 95% CI, −0.56 to 0.56; I^2=78%; *P*=.99) (fig 7) were analyzed separately. The stage of stroke did not appear to affect the results because the acute (SMD, −0.03; 95% CI, −0.31 to 0.24; I^2=0%; *P*=.89), subacute (SMD, 0.22; 95% CI, −0.15 to 0.58; I^2=65%; *P*=.25), and chronic stages (SMD, 0.03; 95% CI, −1.40 to 1.46; I^2=87%; *P*=.97) (fig 8) did not demonstrate a positive effect. Subgroup analyses indicated a positive effect in patients with severe paresis (SMD, 0.41; 95% CI, 0.12-0.70; I^2=1%; *P*=.005; n=4), which was not the case in patients with moderate paresis (SMD, −0.24; 95% CI, −0.77 to 0.30; I^2=76%; *P*=.39; n=5), with no studies encompassing patients with mild paresis (fig 9).

Sensitivity analysis

The meta-analysis regarding functional motor ability was associated with substantial heterogeneity, and a leave-1-out sensitivity analysis was thus performed to assess the influence of the individual studies. This analysis revealed that the exclusion of Yavuzer et al[61] reduced the heterogeneity from I^2=64% to I^2=45% and furthermore resulted in a significant (*P*=.04) positive effect of NMES. This is further supported by the forest plot for functional motor ability (see fig 7) illustrating Yavuzer as a potential outlier. In the subgroup analyses, the heterogeneity was attenuated from I^2=78% to I^2=64% for the lower extremity and from I^2=65% to I^2=1% in the subacute stage, with the results becoming significant in the latter (*P*=.0009).

Discussion

The objectives of the present systematic review and meta-analysis were to explore the effect of NMES toward improving ADL and functional motor ability post stroke. In summary, NMES improved ADL, whereas no effect on functional motor ability was evident. Subgroup analyses showed that application of NMES in the subacute stage and applied to the upper extremity resulted in a significant improvement in ADL, with no apparent effect of treatment in the chronic stage and lower extremity application. Furthermore, NMES had a significant effect for improving functional motor abilities in patients with severe paresis, whereas treatment of moderate paresis was insignificant.

The different treatment effects of NMES toward improving ADL and functional motor abilities is consistent with a previous meta-analysis regarding FES[24] where the authors speculated that the difference was governed by the patient characteristics of their analysis, all being in the chronic stage, which is not the case for our analysis. We propose that this result could be explained by 1 or both of the 2 following reasons. First, there are strong indications in the literature that poststroke motor recovery occurs partly through behavioral compensation rather than a "true" physiological recovery per se.[65] Therapies using compensatory strategies are known to achieve functional goals sooner than therapies that do not allow for behavioral compensation.[65,66] The most frequently adopted measure of functional motor abilities in the studies included is the Action Research Arm Test,[67] which rates patients ability to perform tasks "normally" whereas the Barthel Index[68,69] evaluates to what degree tasks are performed independently, not normally, thus allowing use of compensatory strategies. Perhaps the apparent ability of NMES to improve ADL is underpinned by the test's acceptance of patients' preferred movement pattern, making them able to detect minor but important recovery improvements sooner. Second,

Table 2 Methodological quality assessment using PEDro score

Author	Random Allocation	Concealed Allocation	Baseline Comparability	Blinded Participants	Blinded Therapists	Blinded Assessors	Adequate Follow-up	Intention to Treat	Between-Group	Point Estimate & Variability	Total
Church et al[44]	1	1	1	0	0	1	1	1	1	1	8
Fletcher-Smith et al[45]	1	1	1	0	0	0	0	0	0	1	4
Gürcan et al[57]	1	0	1	0	0	0	1	0	1	1	5
Hochsprung et al[46]	1	0	1	0	0	1	0	0	0	1	4
Hsu et al[47]	1	0	1	0	0	0	0	1	1	1	5
Kim et al[48]	1	0	1	0	0	1	1	0	1	1	6
Lin et al[49]	1	0	1	0	0	0	0	0	1	1	4
Linn et al[50]	1	0	1	0	0	0	1	0	1	1	5
McDonnell et al[51]	1	1	1	1	0	1	1	0	1	1	8
Powell et al[52]	1	1	1	0	0	1	1	0	1	1	7
Rosewilliam et al[53]	1	1	1	0	0	1	0	1	1	1	7
Sahin et al[54]	1	1	1	0	0	0	1	0	1	1	6
Sonde et al[55]	1	0	1	0	0	0	0	0	1	1	4
Tan et al[58]	1	0	1	0	0	0	0	1	1	1	6
Wang et al[59]	1	0	1	0	0	1	1	0	1	1	6
Yan et al[60]	1	0	1	0	0	1	1	0	1	1	6
Yavuzer et al[61]	1	1	1	0	0	1	1	0	1	1	7
You et al[62]	1	0	1	0	0	1	1	0	1	1	6
Zheng et al[63]	1	0	1	0	0	1	0	1	1	1	6
Zhou et al[56]	1	1	1	0	0	1	0	0	1	1	6

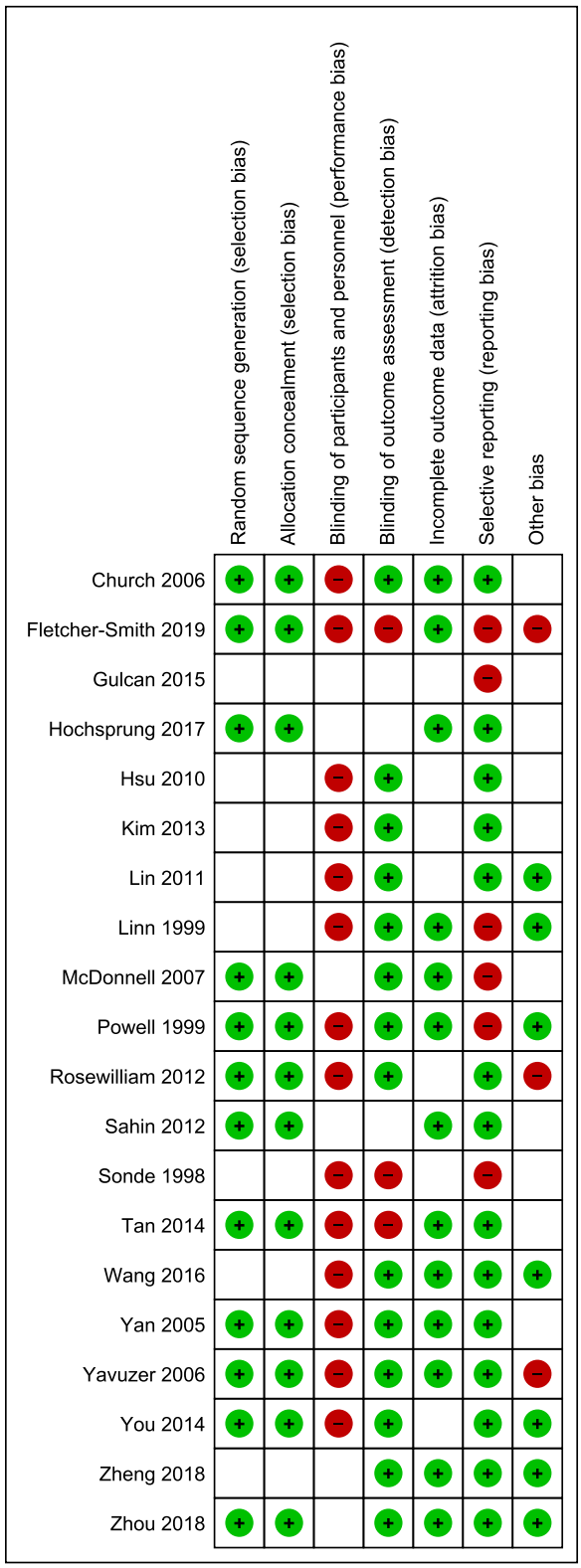

Fig 2 Cochrane risk of bias tool: risk of bias summary.

in the sensitivity analysis the study by Yavuzer et al was excluded, which resulted in a significant positive effect of NMES toward functional motor abilities, eliminating the apparent contrast regarding the effectiveness of NMES toward ADL and functional motor abilities, respectively. Yavuzer reported a significant difference in baseline mean walking velocity between the intervention and control groups, which might have influenced their results.

In line with earlier work,[70,71] our subgroup analysis revealed a positive effect of NMES toward ADL in the subacute stage, with no apparent effect in the chronic stage. This observation could possibly relate to the mechanisms underlying strength attenuation, initially because of a loss of descending motor drive, whereas decreased muscle cross sectional area, spasticity and long-term reduction of motor units secondary to inactivity govern later-stage strength reduction.[27,72] The subgroup analysis on paresis severity showed a positive effect of NMES in patients with severe paresis, with insignificant results in moderate paresis, which is in contrast to previous related work indicating a superior rehabilitation potential and prognosis in patients with paresis compared with patients with paralysis.[71,73] The positive effect in patients with severe paresis might be because of the feasibility of NMES in a patient population with limited capacity for voluntary training. These results, however, should be interpreted with caution because only half of the studies were included in this subgroup analysis because of poor data reporting.

Overall completeness and applicability of evidence

Our search identified a considerable number of studies applying NMES through triggering devices or applied during voluntary movement. Because this was not the focus of our review, these studies were excluded, and the present results are thus not generalizable throughout the entirety of the ES research domain. This narrow review question was chosen with the aim of guiding practitioners in the process of choosing between multiple different ES modalities. Even though 20 studies were included, the underlying evidence for NMES is not complete. Overall, the patients were similar regarding sex and age, and to strengthen our study, the differences in time since stroke and severity of paresis were addressed by the subgroup analyses, but because none or only a small number of studies included participants within the first week post stroke (acute stage), 6 months post stroke (chronic), or with mild paresis, we are unable to draw firm conclusions regarding the effectiveness of NMES in these patient populations. Furthermore, it appears that there are no universally agreed on stimulation parameters, and none of the included studies used the same stimulation protocol, with heterogeneity in parameters of importance such as stimulation channels, time per stimulation session, and the intervention duration. Although we exclusively included studies that produced muscle contractions through stimulation to minimize heterogeneity and strengthen our results, this was accomplished with different stimulation parameters, for example, Sonde et al[55] applied low frequencies of 1.7 Hz in pulse trains, whereas the majority of studies used relatively high frequencies (≥20Hz) in a cyclical pattern, thus contributing to the overall high degree of interstudy variability and thus equivocality of the evidence pertaining to NMES.

Comparison with previous reviews

Two previous systematic reviews[13,16] have examined the effect of NMES on activity measures post stroke; however,

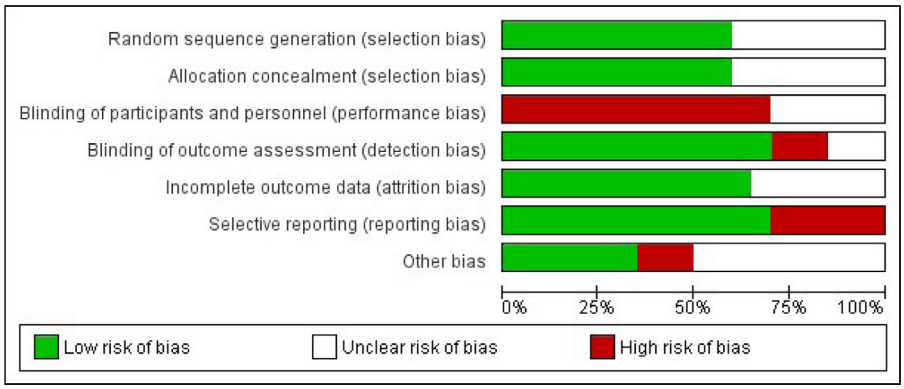

Fig 3 Cochrane risk of bias tool: risk of bias graph.

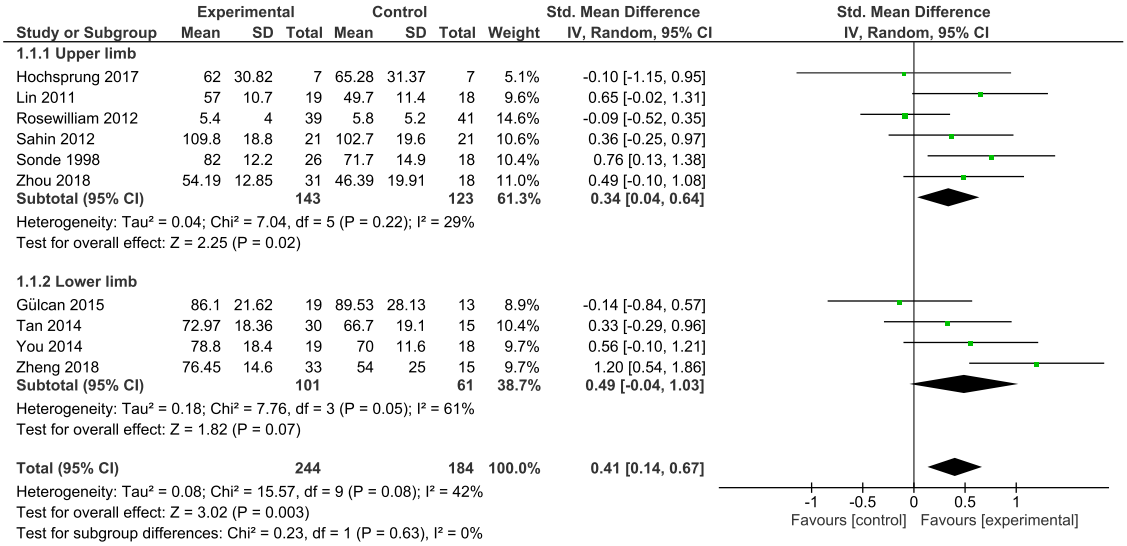

Fig 4 Effect of NMES on ADL: subgroup analysis on limb stimulation.

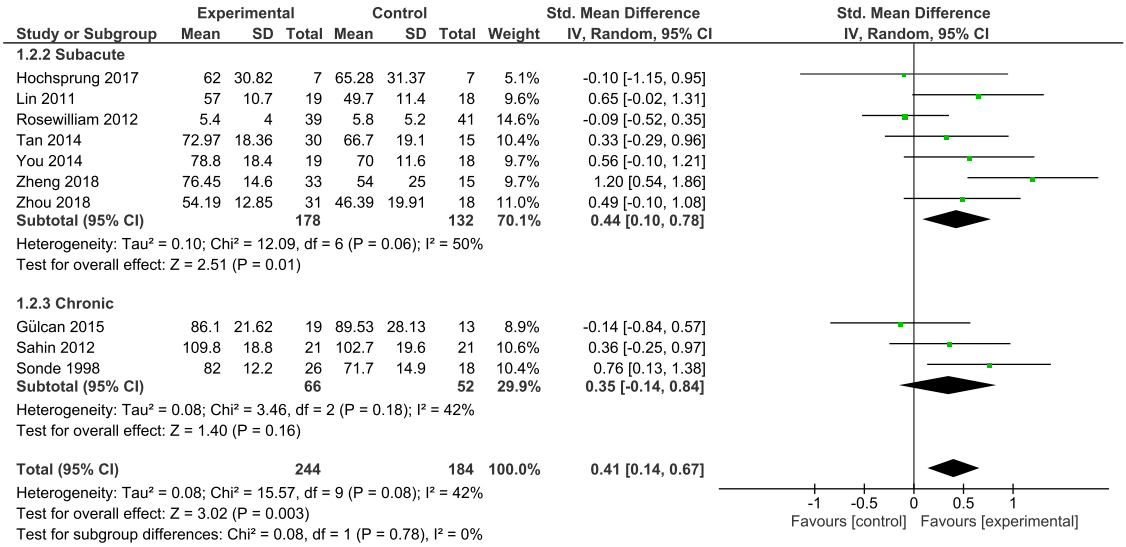

Fig 5 Effect of NMES on ADL: subgroup analysis on stage of stroke.

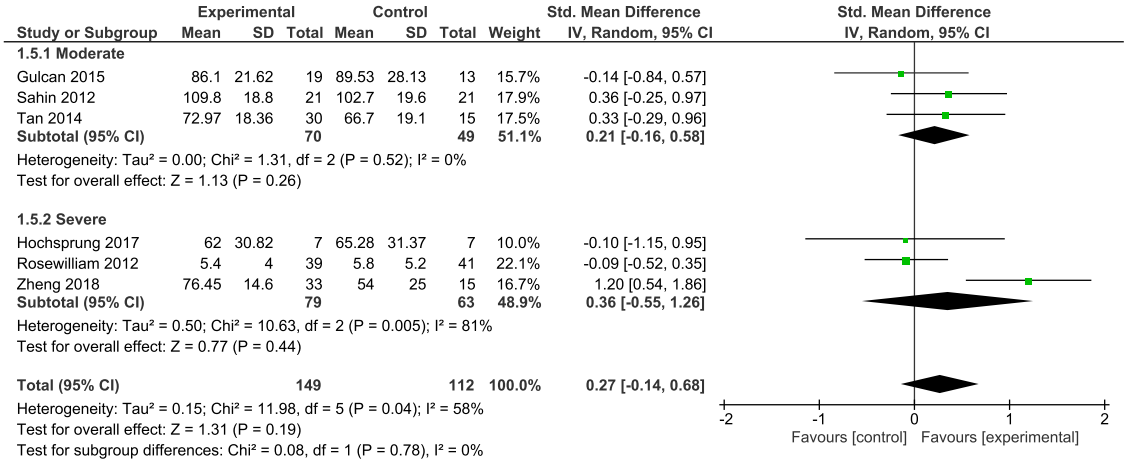

Fig 6 Effect of NMES on ADL: subgroup analysis on degree of paresis.

both including studies featuring EMG-triggered ES. De Kroon et al[13] analyzed motor control and functional motor abilities and identified 6 relevant trials overall, 2 with functional motor ability measures. Although a meta-analysis was not performed, it was concluded that a positive effect of NMES on motor control exists, but no conclusions were drawn concerning the effect on functional motor abilities. Nascimento et al[16] analyzed the effect of ES on strength and conducted a secondary analysis to delineate whether this improvement carried over to measures of activity, identifying 16 relevant trials with 6 including measures of activity. Meta-analysis showed that ES had a moderate positive effect on strength and a small to moderate positive effect on activity, with the benefits extending beyond the intervention period for both measures. Nascimento performed their systematic literature search in December 2012, including 3 trials also included in the present review. The present review identified 8 additional trials investigating activity from the same period and 9 trials published afterward, thus justifying an updated analysis.

Study limitations

The present review is associated with some limitations that should be kept in mind when interpreting the results. The mean PEDro score of 5.8 only represents fair quality. Both the PEDro score and CROB tool revealed high risk of bias concerning blinding, thus increasing the risk of performance bias, which is a perennial issue in ES studies[25] because of the nature of the intervention. Also, our protocol was not registered a priori, introducing the possibility of reporting bias. We identified studies for inclusion by searching across multiple medical and physiotherapy related databases, but we limited our search to English literature and no gray literature search was conducted. The extent of our search potentially confounded the pool of included studies; however, the Egger's test does not appear to be indicative of this being the case. Lastly, studies were only included if the sole difference between the intervention and control group was ES; therefore, the groups received the same amount of physical

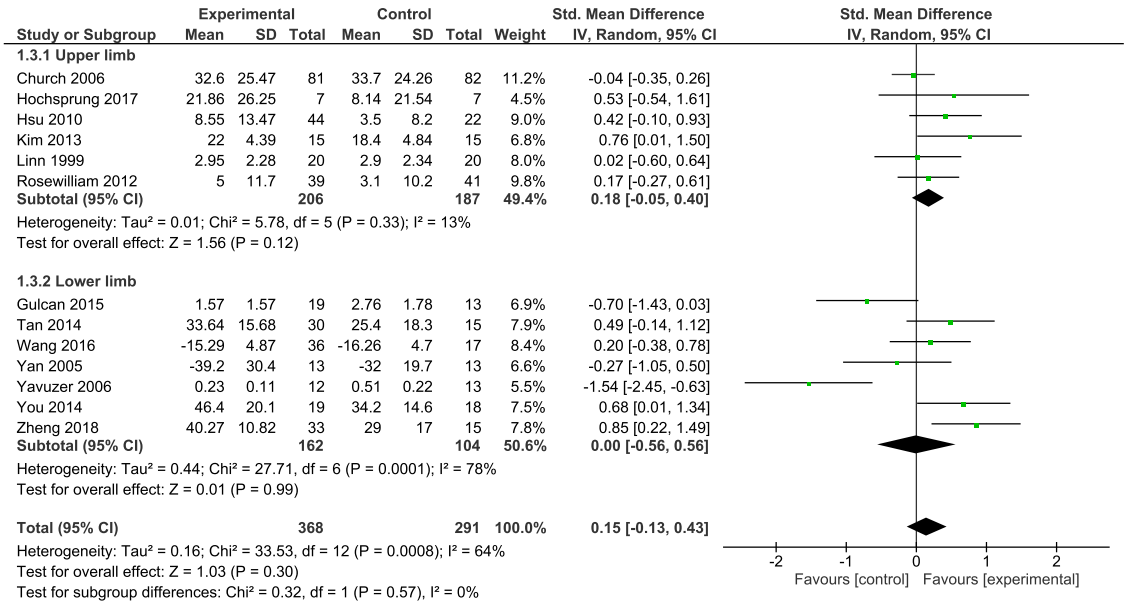

Fig 7 Effect of NMES on functional motor ability: subgroup analysis on limb stimulation.

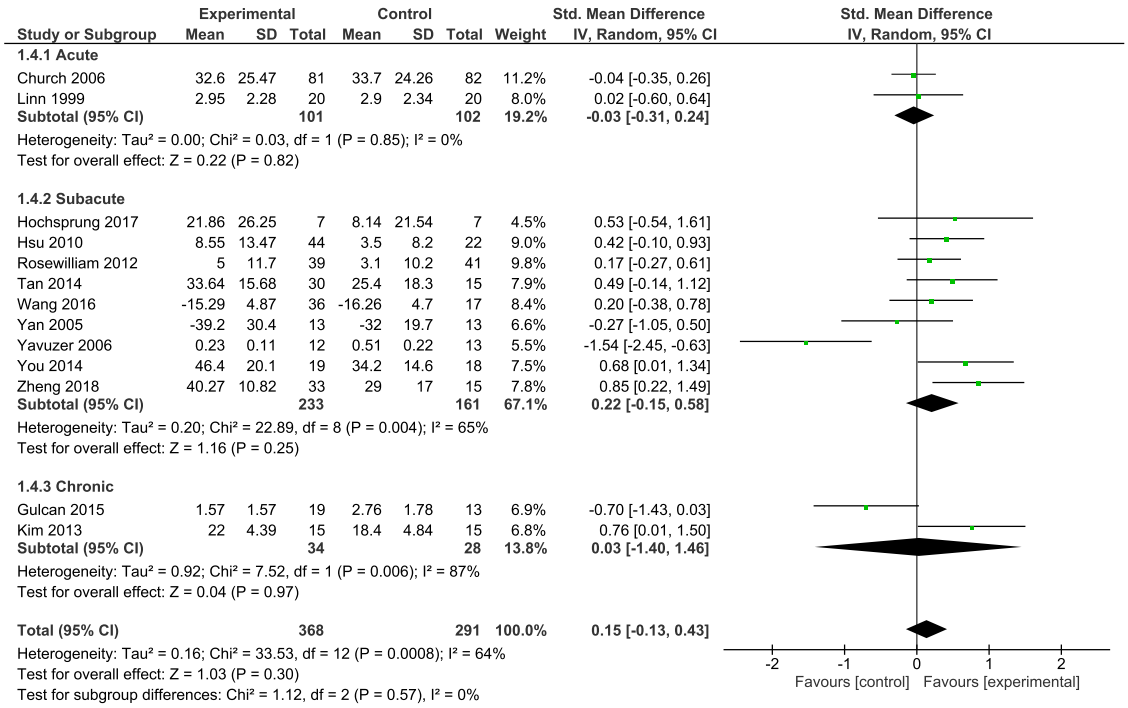

Fig 8 Effect of NMES on functional motor ability: subgroup analysis on stage of stroke.

training, but the intervention group additionally received stimulation outside formal sessions. Time in therapy is a robust predictor of recovery across different types of therapy[74] and is known to bias the results in favor of the group receiving more therapy.[75,74] Therefore, one could argue that our review question is inherently biased and our positive results toward NMES is a result of more therapy time. On the other hand, the sole effect of NMES was best disclosed by comparing it with nothing or placebo, and therefore our results indicate that NMES could be one of multiple ways to increase therapy time.

Conclusions

The results of the current systematic review and meta-analysis are indicative of a significant positive effect of NMES toward ADL function in the poststroke rehabilitation process, whereas the potential for improving functional motor ability appears to be less clear. Subgroup analysis indicated that NMES application in the subacute stage and targeted at the upper extremity is efficacious for ADL rehabilitation and that functional motor abilities can be positively affected in patients with severe paresis. Although the present results

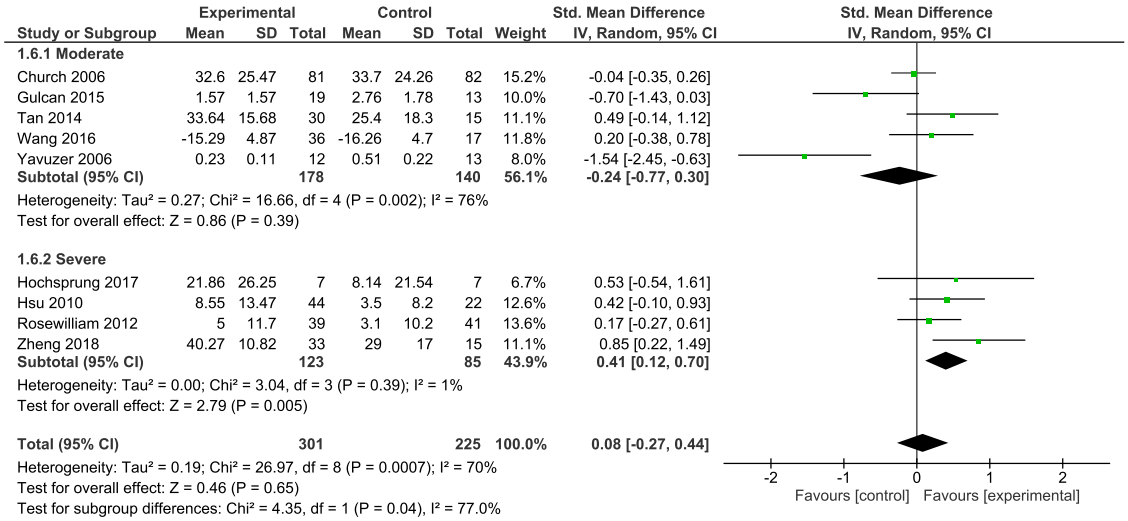

Fig 9 Effect of NMES on functional motor ability: subgroup analysis on degree of paresis.

are generally in favor of NMES in poststroke rehabilitation, the only fair mean methodological quality of the included trials should be kept in mind. Furthermore, one should be cognizant that the apparent benefits of NMES are in reference to nothing or placebo and not supplementary training, and the results could thus be somewhat influenced by the additional time devoted to these patients. Future studies comparing different therapeutic interventions applicable outside formal sessions to maximize total therapy time without extra rehabilitation resources for both patients and the health care system appear warranted.

Suppliers

a. Review Manager version 5.3; The Cochrane Collaboration.
b. RStudio version 1.4; RStudio Public Benefit Corporation.

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Appendix 1: Search Strategy PubMed, MEDLINE

1. Cerebrovascular disorders [MeSH]
2. Stroke* OR poststroke OR post-stroke OR CVA
3. cerebrovasc* OR cerebral vascular
4. cerebral OR cerebellar OR brain OR vertebrobasilar
5. infarct* OR ischemi* OR thrombos* OR thromboe* OR emboli* OR apoplexy
6. 4 AND 5
7. cerebral OR brain OR subarachnoid
8. haemorrhage OR hemorrhage OR haematoma OR hematoma
9. 7 AND 8
10. 1 OR 2 OR 3 OR 6 OR 9
11. Electric stimulation therapy [MeSH]
12. electric* stimulat* OR muscu* stimulat* OR muscle* stimulat*
13. neuromusc* stimulat* OR nerve stimulat* OR transcutaneous nerve stimulat*
14. transcutaneous muscu* stimulat* OR transcutaneous muscle* stimulat*
15. NMES OR FES OR TES OR TENS OR electrostimulat* OR electrotherap*
16. 11 OR 12 OR 13 OR 14 OR 15
17. Upper Extremity [MeSH]
18. upper limb OR upper extremit*
19. shoulder OR arm OR forearm OR wrist OR hand OR finger OR digit
20. 17 OR 18 OR 19
21. Lower Extremity [MeSH]
22. lower limb OR lower extremit*
23. leg OR hip OR thigh OR crus OR foot OR knee OR ankle OR toe OR gait
24. 21 OR 22 OR 23
25. 20 OR 24
26. 10 AND 16 AND 25
27. humans[mesh:noexp]
28. 26 AND 27
29. animals[mesh:noexp]
30. 28 NOT 29
31. migrain* OR epilep* OR myocard* OR headache* OR heart* OR parkinson*
32. 30 NOT 31

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