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Combination of Non-invasive Brain Stimulation and Constraint Induced Movement Therapy in patients with Stroke: A Systematic Review and Meta-analysis

Auwal Abdullahi
The Hong Kong Polytechnic University - Rehabilitation Sciences
Hong Kong
Hong Kong

Thomson WL Wong,
The Hong Kong Polytechnic University - Rehabilitation Sciences
Hong Kong
Hong Kong

Tamaya Van Criekinge,
KU Leuven - Rehabilitation Sciences and Physiotherapy
Leuven, Flanders 3000
Belgium

Shamay SM Ng,
The Hong Kong Polytechnic University
Hong Kong
Hong Kong
*Corresponding Author
Email Address: shamay.ng@polyu.edu.hk

Abstract

Introduction: Constraint induced movement therapy (CIMT) and non-invasive brain stimulation (NIBS) are used to counteract learned non-use phenomenon and imbalance in interhemispheric inhibition following stroke. The aim of this study is to summarize the available evidence on the effects of combining NIBS with CIMT in patients with stroke.

Method: PubMED, Embase, Web of Science (WoS), PEDro, OTSeeker, and CENTRAL were searched for randomized controlled trials comparing the use of NIBS+CIMT with sham NIBS+CIMT. Data on variables such as time since stroke, and mean scores and standard

deviation on outcomes assessed such as motor function were extracted. Cochrane risks of bias assessment tool and PEDro scale were used to assess the risks of bias and methodological quality of the included studies.

Results: The results showed that, both NIBS+CIMT and sham NIBS+CIMT improved all outcomes post intervention and at follow-up. However, NIBS+CIMT is superior to sham NIBS+CIMT at improving level of motor impairment (SMD = 1.75, 95% CI = 0.49 to 3.01, P = 0.007) post intervention, and hand function (SMD = 1.21, 95% CI = 0.07 to 2.35, P = 0.04) at follow-up.

Conclusions: Addition of NIBS to CIMT seems to provide additional benefit to recovery of function following stroke.

Key words: Stroke, brain stimulation, learned non-use, interhemispheric inhibition, constraint induced movement therapy

1.0: Introduction

Stroke occurs as a result of abnormality in blood supply to the brain cells and tissues either from ischaemia or haemorrhage, which limits the supply of oxygen and other essential molecules and nutrients required for proper development, growth, survival and functions of the brain [1-2]. Consequently, the limitation in the supply of oxygen and the essential molecules and nutrients leads to impairment in the role the brain plays in the control of motor, sensory and cognitive functions [3-5].

For the impairment in the role the brain plays in the control of motor function, the process begins with cortical shock, which is a suppression of neural activity that occurs immediately after a stroke event [6]. Following the cortical shock, patients with stroke become unable or find it difficult to move their body parts, for instance the limbs. As such, after repeated failed attempts to move their body parts probably due to inadequacy of neural pathways which may lead to pain, fatigue or decreased motivation, the patients behaviourally learn not to use the limbs, a phenomenon known as the learned non-use [6-7]. Similarly, following a stroke, the unaffected hemisphere may exert inhibitory influence on the affected hemisphere, further strengthening the learned non-use phenomenon [8]. However, both learned non-use phenomenon and imbalance in interhemispheric inhibition can be reversed with the use of effective rehabilitation techniques.

Two major rehabilitation techniques used to reverse learned non-use and imbalance in interhemispheric inhibition are constraint induced movement therapy (CIMT) and non-invasive brain stimulation (NIBS). In CIMT, the unaffected limb is constrained using a sling or a mitt or glove so as to encourage or force repetitive use of the affected one [9-11]. In addition, a contract, known as the transfer package is also used to make the patients increase the use the affected limb in real life situations at home or outside clinic or the laboratory in order to increase the chances of recovery [12-13]. That way, the inhibitory influence of the unaffected hemisphere over the affected one and the learned non-use phenomenon will be reversed. Similarly, NIBS is a method of delivering electrical currents to the brain to help excite or inhibit neural activity [14]. It has been reported to increase and decrease neural activity in the motor cortex of the affected and unaffected hemispheres respectively [15]. That way, it may help in reversing imbalance in interhemispheric inhibition, and learned non-use.

There are two major techniques for NIBS: transcortical direct current stimulation (tCDs) and transmagnetic stimulation (TMS) [16]. The tCDs involves application of constant weak electrical currents of between 1 to 4 mA to the brain through the scalp for several minutes [17-20]. Its mechanisms of action consist of changes in membrane depolarization in the short-term, and neuroplastic changes associated with decreased GABA concentration, and increased BDNF levels in the long -terms [21-23]. On the other hand, TMS involves a continuous and an adjustable electrical current that is delivered to the brain through the scalp [24]. When the current is delivered at a low frequency, it is said to cause cortical inhibition; whereas, if it is delivered at a high frequency, it is said to cause cortical excitability [25]. In addition, the main mechanism through which TMS works is by causing membrane polarization shift, which in turn leads to changes in single-neuron, synaptic and network activity [26-28].

Thus, both CIMT and NIBS are effective at promoting recovery of function following stroke. However, in the recent decade, combination of these two techniques has become increasingly popular [29]. The rationale for combining the two techniques is to see whether addition of NIBS to CIMT will increase chances of recovery [29-31]. The aim of this systematic review and meta-analysis is to summarize the available evidence from the literature on the effects of combining NIBS with CIMT on outcomes after stroke.

2.0: Materials and Methods

The study is a systematic review and meta-analysis that was carried out using The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. The study was registered in PROSPERO (registration number, CRD42022354157).

2.1: Inclusion criteria for eligible studies

Only randomized controlled trials (RCT) comparing the use of a combination of NIBS and CIMTwith CIMT alone in patients with stroke who were 18 years old or older were included in the study.

2.2: Literature search

Search for the literature was carried out electronically in PubMED, Embase, Web of Science (WoS), PEDro, OTSeeker, and CENTRAL from their earliest dates to September 2022 using search strategies appropriate to the particular databases (see appendix) for the search strategy. Following this, reference lists of the included studies were manually screened for additional eligible studies. The search was carried out by one of the researchers (AA) and independently confirmed by another researcher (TVC).

2.3: Selection of studies and extraction of data

Two of the researchers (AA & TWLW) independently carried out selection of studies using Rayyan software (AA & TWLW) [32]. Studies that were obviously ineligible for inclusion based on their titles and abstracts, were excluded outright. When sufficient information was needed to include or exclude a study, the full text was read by the researchers. However, in case of any disagreement between the researchers on whether to include or exclude a study, one of the researchers (SSMN) was consulted to resolve the dispute.

For the data extraction, one of the researchers (AA) extracted information on the authors of the study, sample size, type of stroke, side affected, time since stroke, the NIBS and CIMT intensity and the duration used, mean age of the participants, and mean scores and standard deviation on outcomes assessed in the studies such as motor function, level of motor impairment, cortical

excitability and hand function post intervention and at follow-up. The extracted data was verified by the two of the researchers (TWLW & SSMN).

2.4: Assessment of risks of bias and methodological quality of the included studies

Risk of bias of the included studies was assessed using Cochrane risk of bias assessment tool. The tool assesses selection bias (random sequences generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and any other bias not covered in the previous items [33].

Methodological quality of the included studies was assessed using PEDro scale. The scale consists of 11 items with the first item assessing external validity of a study, and the remaining items assessing internal validity [34]. The items that assess internal validity are rated on a two-point scale, 0 and 1, which denote no and yes respectively to the questions in the items. Thus, the scale can have scores ranging from 0 to 10. When the total score obtained from scale ranges from zero to three or four to five or six to ten, the methodological quality is said to be low or moderate or high respectively [35-37].

The assessment of the risk of bias and methodological quality of the included studies were carried out by two of the researchers (AA & TWLW). In case of any disagreement, one of the researchers (SSMN) was consulted to resolve it.

2.5: Narrative and quantitative syntheses of the results of the included studies

For the narrative synthesis, the characteristics, risk of bias and methodological quality of the included studies were summarized and represented in a risk of bias graph and a summary figure, and a table respectively. For the quantitative synthesis, random effect model meta-analysis of the

mean and standard deviation of the scores on the outcomes of interest and the study sample size (for both the NIBS+CIMT and CIMT groups) post intervention and at follow-up was carried out. However, where studies provided median and interquartile range, the following formula was used to determine the mean value: Mean $=\frac{a+2m+b}{4}$ [where a = the smallest value (minimum), b = the largest value (maximum), and m = median] [38]. Similarly, the standard deviation was calculated by dividing the difference between the maximum and minimum values of the interquartile range (IQR) by 4. In addition, where studies provided standard error of mean (SEM) instead of standard deviation (SD), the following formula was used to convert it to SD: SD = SEM * ($\sqrt{n}$) (where n= sample size).

When percentage of variation across the studies due to heterogeneity (I^2) was between 50 and 90% at $P < 0.05$, it was considered that, there was significant heterogeneity between studies. The meta-analysis was carried out using Review Manager (RevMan), version 5.4.1 [39].

2.6: Interpretation of the of evidence

Interpretation of the evidence of the findings of the study was carried out using body of evidence matrix adapted from the Australian National Health and Medical Research Council's (NHMRC) evidence hierarchy [40].

3.0: Results

3.1: *Narrative synthesis*

3.1.1: Selection of eligible studies

Electronic search of the databases provided a total of 2755 studies; whereas manual search of the reference list of eligible studies provided one additional eligible study, bringing the studies to a total of 2756. Out of this number, only eight studies were eligible for inclusion in the study [41-

48]. In one of the studies, there are two experiments, 1 and 2 [42]. However, only experiment 2 was used in this study for fulfilling the inclusion criteria. In addition, one study was excluded for being a quasi-experimental study [29]. See Figure 1 for the details of the literature search and the selection of the studies.

3.1.2: Characteristics of the included studies

The included studies have a total sample size of 246 patients with stroke (range, 12 to 60), age range, 18 to 90 years and mean time since stroke range, 3 days to about 4 years. Out of this number, 85 were female and 134 had right sided hemiplegia. The type of stroke the patients had include both ischaemic and haemorrhagic stroke; however only six studies provided information on this [41-43, 45-46, 48]. These studies included 138 and 47 patients with ischaemic and haemorrhagic stroke respectively.

In some of the studies, the diagnosis of the stroke was carried out using computed tomography (CT) [46]; magnetic resonance imaging (MRI) [42-43]; and CT or MRI [41]. In addition, six studies, included participants with mild to moderate motor ability of the upper limb, demonstrated by at least 10˚ of active wrist dorsiflexion and extension of the metacarpophalangeal and interphalangeal joints [41, 45, 47-48]; or active extension of the paretic wrist against gravity; [44]; or the ability to grasp a washcloth from a table top, lift it up a few inches, and release it by using pinch method [46]. In contrast, one study included participants with mild to moderate and severe impairment in motor ability, demonstrated by having a trace movement at fingers, thumb or wrist, as well as those who were well recovered as long as they reported inadequate ability to use the paretic hand in daily life [43]. However, information on motor ability of the participants was not provided in one study [42].

Furthermore, some of the studies excluded participants with pacemaker or metal implant in the head [41-44, 46-47]; spasticity of grade 3 or more [44, 47]; any disorder or disability resulting in decreased mobility of the upper limb [42, 45, 47-48]; history of surgery or neurosurgery [44, 47]; history of significant alcohol or drug abuse [41-42]; coexistent neurological or psychiatric disease such as epilepsy [41-45, 47]; uncontrolled illness such as advanced liver, kidney, cardiac, or pulmonary diseases [42, 48]; excessive pain in the joints of the paretic limb [42, 44]; pregnancy [41, 45]; balance and walking impairment [48]; who use any neuro- or psychoactive medications [41-43]; and those who are unable to follow instructions or have cognitive deficit [42, 44, 46, 48].

Similarly, the included studies used different types of NIBS. Seven studies used transcortical direct stimulation (tCDs) [42-48]; whereas, one study used transmagnetic stimulation (TMS) [41].

Two studies used low intensity NIBS, 90% of the motor threshold and 0.7 mA respectively [41, 46]; four studies used moderate intensity NIBS [43-45, 48]; and two studies used high intensity NIBS, 2 mA [42, 47]. Duration of use of NIBS ranges between 9 mins to 2 hours in the studies that used tCDs [42-48]; while in the study that used TMS, 2000 stimulations per session were administered [41].

In seven studies, the participants received bilateral NIBS [42-48]. In three of these studies, the anode and the cathode electrodes were placed over the motor cortices of the ipsilesional and contralesional hemispheres respectively [42, 47-48]; while in four studies, they were placed on the ipsilesional motor cortex and contralesional supraorbital region respectively [43-46]. However, in one study, the participants received a unilateral NIBS with the anode electrode

placed over the ipsilesional motor cortex [41]. In addition, in one study, the participants received NIBS simultaneously with CIMT for 2 hours [43]; whereas, in all the other studies, the participants performed CIMT after the NIBS sessions.

For the CIMT protocol, modified CIMT (mCIMT) consisting of less than six hours of tasks practice was used in four studies [42-43, 46, 48]; whereas in the remaining four studies, a signature or traditional CIMT consisting of tasks practice of at least six hours per session was used [41, 44-45, 47]. For the constraint, most of the studies used it for 90% of the waking hours except in two studies where it was used for two and five hours per day respectively [43, 48].

The outcomes assessed in the studies include level of motor impairment, motor function, hand function, hand grip strength, arm muscle strength, activities of daily living (ADL), cortical excitability and interhemispheric inhibition. Although, both groups demonstrated improvement in most of the outcomes post intervention and at follow-up, NIBS+CIMT seems to be superior to sham NIBS+CIMT at improving motor function in three studies [45-47]; level of motor impairment in one study [47]; functional independence and spasticity in one study [46]; and interhemispheric imbalance in one study [42]. However, only NIBS+CIMT improved hand function and muscle power post intervention in one study [46].

In addition, adverse events following NIBS were reported in only four studies, discomfort in the scalp [41]; fatigue [43, 45]; and skin redness, headache and sleepiness [46]. See Table 1 for the details of the characteristics of the study participants.

3.1.3: Methodological quality and risks of bias of the included studies

All the included studies have either good or excellent methodological quality. Out of these studies, four have good methodological quality [43, 46-48]; and another four have excellent

methodological quality [41-42, 44-45]. See Table 2 for the details of the methodological quality assessment.

In addition, generally the studies have low risks of bias except in random sequence generation [41, 43, 46-47]; and allocation concealment in some of the studies [42-43, 47-48]. See Figure 2 and Figure 3 for the risks of bias graph and summary respectively.

3.2: *Quantitative synthesis*

All the eight studies were used for meta-analysis of post intervention results. However, in one of the studies, two different methods of NIBS were used (anodal stimulation of the primary motor cortex, and anodal stimulation of the premotor cortex) [46]. Consequently, these two modes were considered as separate arms in the meta-analysis. The result showed that, NIBS+CIMT was only superior to sham NIBS+CIMT at improving level of motor impairment (SMD = 1.75, 95% CI = 0.49 to 3.01, P = 0.007). However, there was significant heterogeneity between the included studies (I^2=91%, p=0.0001). See Figure 4 for the forest plot detailing the result.

At follow-up, only three studies assessed outcomes [41-42, 44]. The result showed that, NIBS+CIMT was only superior to sham NIBS+CIMT at improving hand function (SMD = 1.21, 95% CI = 0.07 to 2.35, P = 0.04). However, there was significant heterogeneity between the included studies (I^2=60%, p=0.01). See Figure 5 for the forest plot detailing the result.

4.0: Interpretation of the of evidence

Although there is heterogeneity between the included studies in the use of outcome measures and protocols of both NIBS and CIMT, the evidence seems to be excellent, satisfactorily consistent, excellently applicable, and generalizable and have substantial clinical impact. Therefore, the

body of evidence may be trusted to guide practice in most cases. See Table 3 for the body of the evidence matrix.

5.0: Discussion

The aim of this study is to determine the evidence on the effects of combining NIBS with CIMT on outcomes in patients with stroke. The results showed that, combining NIBS with CIMT improves motor function, level of motor impairment, hand function, hand grip strength, arm muscle strength, activities of daily living (ADL), cortical excitability and interhemispheric inhibition. However, it is only superior to CIMT alone at improving level of motor impairment post intervention; and hand function at follow-up. These findings are not surprising since CIMT alone has been reported to improve many outcomes post stroke [9-10, 49].

In addition, the tasks that are practiced during CIMT mimics natural daily life active movement unlike NIBS, which is in a way a passive form of rehabilitation. Active movement induces cortical activity higher than passive form of movement or treatment [50]. However, the superior effect demonstrated by NIBS+CIMT on hand function is worth noting. This is because, the cortical map contracts following stroke especially during later time post stroke [51]. In addition, the upper limb occupies a large area in the cortical homunculus [52-53]. Furthermore, the process of recovery following brain injury such as stroke, involves an extensive cortical rewiring [54]. Consequently, it was suggested that, use of sensorimotor stimulation can help expand cortical map size, which is an indication of improved motor control [49]. Thus, a technique such as NIBS that can help recruit the neurons in the somatosensory cortex is needed to aid with recovery especially in patients with chronic stroke.

Similarly, the findings seem to suggest that, it is better to stimulate both hemispheres during NIBS to help activate the ipsilesional motor cortex and inhibit the contralesional motor cortex [42-45, 48]. This is because following a stroke, there is decreased cortical activation in the ipsilesional hemisphere and as such, the contralesional hemisphere tends to inhibit the former in a process known as the interhemispheric inhibition [55]. Bilateral stimulation provides a better effect than unilateral stimulation [56-57].

Additionally, the sites for the stimulation and the order in which they are stimulated also seem to be important [58]. Consequently, anodal and cathodal stimulation of the premotor cortices of the affected and unaffected hemispheres respectively, and then followed by the stimulation of the primary motor cortices in similar manner, may be more appropriate since the two cortical areas play sequential roles in movement control. For instance, the premotor cortex receives direct inputs from the dorsolateral frontal cortex and posterior parietal cortex, processes the information, and then projects the output to the primary motor cortex for movement execution [59-60]. Thus, sequential stimulation of these two areas may help induce proper functional reorganization and recovery of function.

Moreover, the timing of the stimulation seems to also be important. As such, most of the included studies administered NIBS before CIMT. The rationale for this is that, administering NIBS before CIMT will help prime the motor cortex and prepare it for activity [61]. Accordingly, it has been argued that, the most effective way of administering NIBS with motor therapy is the interleaved method, whereby a short period of NIBS and then followed by a short period of motor therapy with the cycle repeating itself many times in like manner are given [62-63]. Therefore, it is important studies compare the use of this interleaved method with the one

that provides NIBS simultaneously with CIMT. That way, the most effective method may be determined.

Although, the level of evidence from the results of this study seems to be good, caution needs to be exercised in interpreting the results. This is because of the significant heterogeneity between the included studies especially as regards to the sample size and time since stroke [58]. Similarly, it has been argued that, potential effects of brain stimulation depend on many factors such as the assessment tools used, individual patients' neuroanatomical and neurophysiological differences and the type of additional therapy used [58, 64]. However, it has been argued that, intensity of stimulation does not necessarily affect outcome [65]. Thus, it is important clinicians and researchers consider these factors during practice and research involving a combination of NIBS with CIMT in patients with stroke.

Similarly, from the findings of the study, there are some reports of adverse events due to NIBS such as discomfort in the scalp where the electrodes were placed, fatigue, skin redness in the sites of stimulation, mild headache, and sleepiness. Notwithstanding, patients' experiences have shown that, NIBS is widely accepted by them [66]. Thus, the adverse events may not be major concerns after all. Furthermore, only three of the outcome measures used to assess the outcomes in the included studies are considered core measures that are required to be included in every stroke trial [67]. These outcome measures are upper extremity Fugl meyer motor assessment (UEFMA) used for assessing level of motor impairment, action research arm test (ARAT) used to assess motor function, and National Institute of Health stroke scale (NIHSS) used to assess stroke severity. The UEFMA was used in only five studies [43-44, 46-48]; the ARAT was used in only two studies [42, 48]; and the NIHSS was used in one study only [42]. Therefore, it is important future studies use the core measures recommended for stroke trials [67]. This is

because using such measures may provide more valid, reliable and generalizable findings that can be used by clinicians and researchers.

However, the findings of this systematic review and meta-analysis are not without limitations. One of the limitations of the study is the lack of access to the datasets of the included studies that we could use to verify the results of the individual studies. In addition, the conversion of the results of some of the studies we did from median to mean, from interquartile range to mean, and from standard error of mean to mean, could also affect the reliability of the results of the study.

6.0: Conclusion

Addition of NIBS to CIMT seems to provide additional benefit to recovery of function following stroke. However, significant heterogeneity between the included studies especially in terms of sample size and time since stroke, makes a definite conclusion difficult at the moment. Thus, it is important clinicians and researchers consider these factors during practice and research involving a combination of NIBS with CIMT in patients with stroke. In addition, more quality and consistent RCTs are needed to accurately determine the effects of combining NIBS and CIMT in patients with stroke.

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Figure Legends

Figure 1: The study flowchart

Figure 2: Risks of bias graph of the included studies

Figure 3: Summary of the risks of bias of the included

Figure 4: Comparisons of outcomes post intervention between NIBS+CIMT and sham NIBS+CIMT

Figure 5: Comparisons of outcomes at follow-up between NIBS+CIMT and sham NIBS+CIMT

Appendix 1

Search strategy used in PUBMED

(1) cerebrovascular accident*
(2) stroke*
(3) post-stroke*
(4) post stroke*
(5) brain injury*
(6) 1 OR 2 OR 3 OR 4 OR 5
(7) constraint-induced movement therapy*
(8) constraint induced movement therapy*
(9) CIMT*
(10) constraint induced therapy*
(11) CIT*
(12) modified constraint-induced therapy*
(13) modified constraint therapy*
(14) mCIMT*
(15) forced use*
(16) forced-use*
(17) 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
(18) brain stimulation*
(19) Transcortical direct current stimulation*
(20) tDCS*
(21) Transmagnetic stimulation*
(22) Repetitive Transmagnetic stimulation
(23) TMS
(24) rTMS
(25) 18 OR 19 OR 20 OR 21
(26) 6 AND 17 AND 22 OR 23 OR 24
(27) 6 AND 17 AND 26

Data availability statement

All data for this study has been included within the manuscript

Table 1: Characteristics of the included studies

References	N	*Stroke duration*	Mean age (years)	Intervention	Outcomes	Findings	Adverse events
Malcom et al. [41]	N=19; NIBS+CIMT (n=9, females=4); NIBS+CIMT (n=10, females=4)	3.8 ± 3.3 years; (NIBS+CIMT =3.9±3.1; sham NIBS+CIMT =3.8±3.7)	67 ± 6.8years; (NIBS+CIMT =68.4±8.4; sham NIBS+CIMT =65.7±5.1)	rTMS- Subjects in the NIBS+CIMT group received 2000 rTMS daily as 50 trains of 40 stimulations for ten consecutive weekdays, administered as 50 trains of 40 stimuli, at a frequency of 20 HZ, stimulus train duration of 2 secs, and inter-train interval of 28 secs. A figure-8 coil was placed over the motor cortex area of the affected hand. The stimulus intensity used was 90% of the motor threshold. The subjects in the sham NIBS+CIMT group received a sham rTMS for the same duration as the NIBS+CIMT group. Bothe groups received rTMS or sham rTMS before CIMT. CIMT-both groups received 7-hour CIMT and 5- hour daily home program for 10 consecutive days with constraint of the affected limb for 90% of the waking hours	Motor function (WMFT), quality and quantity of use of the limb in daily life (MAL), the ability to use the hand to grasp, transport, and release of small objects (BBT), cortical excitability (TMS).	All outcomes improved post intervention in both groups. However, there was no significant difference between groups in all the outcomes of interest.	Scalp discomfort in both groups
Di Lazzaro et al. [42]	N=20; NIBS+CIMT (n=10, females=4); sham NIBS+CIMT (n=10, females=3)	3.10±1.45 days; (NIBS+CIMT =3.1±1.80 days; sham NIBS+CIMT =3.1±1.10)	63.80±13.40 years; (NIBS+CIMT =60.80±16.13; sham NIBS+CIMT =68.80±9.95)	tCDs- the NIBS+CIMT group received 40 minutes (total charge of 4.8 C; fade-in/fade-out=10 seconds) tCDs each day before CIMT. The anode electrode of the tCDs was placed over the ipsilesional M1; while cathode electrode was placed over the contralesional M1. The parameters used were constant current of 2 mA intensity (current density of 0.5 A/m^2). The sham NIBS+CIMT group received tCDs for only 30 seconds, after which the device was turned off before CIMT. CIMT- both groups received laboratory-based CIMT, 1.5 hours per day for 5 days with constraint for 90% of the waking hours.	Severity of stroke (NIHSS), level of disability (mRS), quality and quantity of use of the limb in the daily life activities (MAL), motor function (ARAT), hand grip strength (hand dynamometer), manual dexterity (NHPT) and motor evoked potential (TMS).	All outcomes improved in both groups post intervention and at follow-up. However, NIBS+CIMT was superior to sham NIBS+CIMT at improving interhemispheric imbalance post intervention and at follow-up.	Not reported

Key: rTMS=repetitive transmagnetic stimulation, WMFT=Wolf motor function test, MAL=motor activity log, BBT=box and block test, tCDs=transcortical direct stimulation, JHFT=Jebsen Taylor hand function test, UEFMA=upper extremity Fugl Meyer motor assessment, MEP=motor evoked potential

Table 1: Characteristics of the included studies

References	N	*Stroke duration*	Mean age (years)	Intervention	Outcomes	Findings	Adverse events
Cunningham et al. [43]	N=12; NIBS+CIMT (n=6, females=2); sham NIBS+CIMT (n=6, females=2)	50.00±59.42 months; (NIBS+CIMT =63.33±81.27; sham NIBS+CIMT =36.67±27.14)	61.25±9.35; (NIBS+CIMT =63.67±8.31; sham NIBS+CIMT =58.83±10.46)	tCDs- the NIBS+CIMT group received tCDs at intensity of 1 mA for 2 hours simultaneously with CIMT. The anode electrode of the tCDs was placed over the ipsilesional M1; while cathode electrode was placed over the subraorbial area contralateral to the ipsilesional hemisphere. The sham NIBS+CIMT group received sham tCDs transiently for 30 to 60 seconds only. CIMT- both groups received 15 sessions of 2-hour laboratory-based CIMT over 5 weeks. Participants were asked to wear mitt to constraint the unaffected limb for 2 hours during performance of home exercises.	Level of motor impairment (UEFMA), manual dexterity (NHPT), quality and quantity of use of the limb in daily life (MAL) and cortical excitability, cortical map size and inter-hemispheric inhibition (TMS+fMRI+sEMG).	Only NIBS+CIMT improved level of motor impairment. However, there is no significant difference between groups in all the outcomes of interest. Similarly, there was increased in the ability of ipsilesional hemisphere to counteract inhibition by the contralesional hemisphere and increased cortical excitability in the contralesional hemisphere. However, there was no significant difference between groups	Fatigue in one patient
Rocha et al. [44]	N=21; Anodal NIBS+CIMT (n=7, females=1); cathodal NIBS+CIMT (n=7, females=2); sham NIBS+CIMT (n=7, females=3)	Anodal NIBS+CIMT =27.5±9.75 months; cathodal NIBS+CIMT =34.2±14.25 months; sham NIBS+CIMT =26.5±10.0 months	Anodal NIBS+CIMT =58.3±3.75; cathodal NIBS+CIMT =58.5±7.5; sham NIBS+CIMT =58.5±6.0	tCDs- Anodal NIBS+CIMT group received 13 mins of 1 mA tCDs with the anode electrode placed over the primary motor cortex of the affected hemisphere and the cathode electrode placed above the supra-orbital region. Similarly, the cathodal NIBS+CIMT received 9 mins of 1 mA tCDs with the cathode placed over M1 of the unaffected hemisphere and the anode above the supraorbital region. The sham NIBS+CIMT group received 13 mins of 1 mA sham tCDs with the anode electrode placed over the primary motor cortex of the affected hemisphere and the cathode placed above the supra-orbital region. Stimulation in all groups were carried out 3 times a week for 4 consecutive weeks before CIMT. CIMT- all groups received laboratory-based CIMT, 6 hours per day for 4 consecutive days. Constraint using sling was applied during daily activities, but was removed for 10 minutes every hour in order to perform stretching.	Level of motor impairment (UEFMA), quality and quantity of use of the limb in the daily life activities (MAL), and hand grip strength (hand dynamometer).	Only anodal NIBS+CIMT resulted in remarkable improvement in the level of motor impairment that attained meaningful clinical significance compared to sham group post intervention and at follow-up. However, there was no significant difference between groups in other outcomes.	Not reported

Key: tCDs=transcortical direct stimulation, NIHSS=National Institute of Health stroke scale,mRS=modified Rankin scale, MAL=motor activity log, ARAT=Action research arm test, NHPT=Nine Hole Peg test, TMS=Transmagnetic stimulation, UEFMA=upper extremity Fugl Meyer motor assessment, fMRI=Functionalmagnetic resonance imaging, sEMG=Surface Electromyography.

Table 1: Characteristics of the included studies

References	N	*Stroke duration*	Mean age (years)	Intervention	Outcomes	Findings	Adverse events
Figlewski et al. [45]	N=44; NIBS+CIMT (n=22, females=1); sham t NIBS+CIMT (n=22, females=7)	NIBS+CIMT =9.0±8.0 months; sham NIBS+CIMT =7.0±8.25 months	NIBS+CIMT =60.0±11.0; sham NIBS+CIMT =60.0±10.0	Both groups received 6-hour CIMT for 9 consecutive days with constraint for 90% of the waking hours after 1.5 mA Anodal tCDs and sham tCDs for 30 mins. In both groups, anode electrode placed over the primary motor cortex of the affected hemisphere and the cathode placed above the supra-orbital region. However, for the sham tCDs, the device was switched after 30 secs from the beginning of the treatment.	Motor function (WMFT), grip strength (precision dynamometer) and arm strength (lifting cuff weights)	All outcomes improved significantly post intervention in all groups. However, the NIBS+CIMT is superior to the sham NIBS+CIMT at improving motor function	Fatigue in 1 patient in the NIBS+CIMT group
Andrade et al. [46]	N=60: Anodal NIBS+CIMT (M1) (n=20, females=7); anodal NIBS+CIMT (PMC) (n=20, females=11); sham NIBS+CIMT (n=20, females=8)	Anodal NIBS+CIMT (M1) =1.78±1.75 months; anodal NIBS+CIMT (PMC)= 1.86±1.52 months; sham NIBS+CIMT =1.92±1.36 months	Anodal NIBS+CIMT (M1) =51.18±4.21; anodal NIBS+CIMT (PMC)=52.97±3.19; sham NIBS+CIMT =54.76±4.28	All groups received received 10 sessions (5 consecutive days for 2 weeks) of anodal tCDs or sham tCDs, with an intensity of 0.7 mA. In both the Anodal NIBS+CIMT (M1) and sham NIBS+CIMT, the anodal electrode was placed over M1; whereas, in the anodal NIBS+CIMT (PMC), it was placed over the PMC. However, the cathode electrode was placed over the supraorbital region in all groups. All the groups received CIMT immediately after stimulation for 3 hours per day with constraint for 90% of the waking hours during week days for 2 weeks	ADL (BI), level of motor impairment (UEFMA), shoulder abductors and elbow, wrist, fingers and thumb flexors spasticity, gross motor function (BBT), shoulder abductors, flexors, and extensors of the elbow, the wrist, the fingers, and the thumb muscle power (MRC) and adverse events (A tDCS side effects questionnaire)	Functional independence, spasticity and motor function improved post intervention in all groups. However, the anodal NIBS+CIMT (PMC) demonstrated a superior improvement in these outcomes. Gross motor function and muscle power improved only in anodal NIBS+CIMT (PMC) group.	skin redness under the site of stimulation, mild headache, and sleepiness
Ateia et al. [47]	N=40: NIBS+CIMT (n=20, females=5); sham NIBS+CIMT (n=20, females=6)	NIBS+CIMT =8.37±2.22 months; sham NIBS+CIMT=9.60±2.44 months	45-60 years NIBS+CIMT =53.05±5.69; sham NIBS+CIMT=54.30±5.03	All groups received 2 mA tCDs before 6-hour CIMT with constraint for 90% of the waking hours for 10 consecutive days. However, in the sham NIBS+CIMT, the stimulation was sham. In both groups, the anode electrode was placed over the ipsilesional motor area; while the cathode was placed over the contralateral motor area.	Muscle strength (MI), motor function (ARAT), and level of motor impairment (UEFMA)	All outcomes improved significantly in both groups. However, the NIBS+CIMT group is superior at improving all the outcomes	Not reported

Key: tCDs=transcortical direct stimulation, NIHSS=National Institute of Health stroke scale, mRS=modified Rankin scale, MAL=motor activity log, ARAT=Action research arm test, NHPT=Nine Hole Peg test, TMS=transmagnetic stimulation, WMFT=Wolf motor function test.

Table 1: Characteristics of the included studies

References	N	*Stroke duration*	Mean age (years)	Intervention	Outcomes	Findings	Adverse events
Kim [48]	N=30: NIBS+CIMT (females=8); sham NIBS+CIMT (females=7)	NIBS+CIMT = 12.13±1.84 months; sham NIBS+CIMT=10.93±1.94 months	20-90 years tCDs+CIMT =60.2±5.3; sham tCDs+CIMT=60.33±6.33	The NIBS+CIMT and the sham NIBS+CIMT received 1 mA of active and sham stimulation respectively for 20 minutes per day for 4 weeks. In both groups, the anodal electrode was placed over M1 of the affected hemisphere; whereas, the cathode electrode was placed over the M1 of the unaffected hemisphere. Following this, both groups received 30 mins CIMT per day, 5 times a week for 4 weeks with constraint using gloves for 5 hours per day during the period.	Level of motor impairment (UEFMA), quality and quantity of use of the limb in daily life (MAL) and actual use of the affected and the unaffected limb (accelerometer)	There was significant improvement in the outcomes of interest in both groups except in quality of use of the limb in daily life. However, there was no significant difference between groups in all the outcomes of interest.	Not reported

Key: tCDs=transcortical direct stimulation, M1=primary motor cortex, PMC=premotor cortex, BI=Barthel index, UEFMA= upper extremity Fugl Meyer motor assessment, MRC=Medical Research Council scale, MI=Motoricity index.

Table 2: Methodological quality of the included studies

Study	Eligibility criteria specified	Random allocation	Concealed allocation	Comparable subjects	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention to treat analysis	Between group comparison	Point estimation and variability	Total score
Malcom et al. [41]	Yes	1	1	1	1	1	0	1	1	1	1	9/10
Di Lazzaro et al. [42]	Yes	1	1	1	0	1	1	1	1	1	1	9/10
Cunningham et al. [43]	Yes	1	1	1	1	0	1	0	1	1	1	8/10
Rocha et al. [44]	Yes	1	1	1	1	1	1	1	1	1	1	10/10
Figlewski et al. [45]	Yes	1	1	1	1	1	1	0	1	1	1	9/10
Andrade et al. [46]	Yes	1	1	1	0	1	0	0	1	1	1	7/10
Ateia et al. [47]	Yes	1	0	1	1	0	0	0	1	1	1	6/110
Kim [48]	Yes	1	0	1	0	0	1	0	1	1	1	6/10

Table 3: Body of evidence matrix

Component	Grade	Comments
1. Evidence	A-Excellent Several Level II evidence	Quantity: a total of 8 studies Participants: 246 patients with stroke Level II studies: 8
2. Consistency	C-satisfactory	There is significant heterogeneity between studies, I^2>50%.
3. Clinical impact	B-Substantial	Five studies reported effect size (Malcom et al. [41]; Cunningham et al. [43]; Rocha et al. [44]; Andrade et al. [46]; Kim et al. [48])
4. Generalizability	A-Excellent	The studied population is the same as the target population (patients with stroke)
5. Applicability	A-Excellent	The evidence is applicable globally since the studies were carried out in 6 different countries (Brazil, Denmark, Egypt, Italy, South Korea and USA) in four different continents
Recommendation	B=Body of evidence can be trusted to guide practice in most cases	

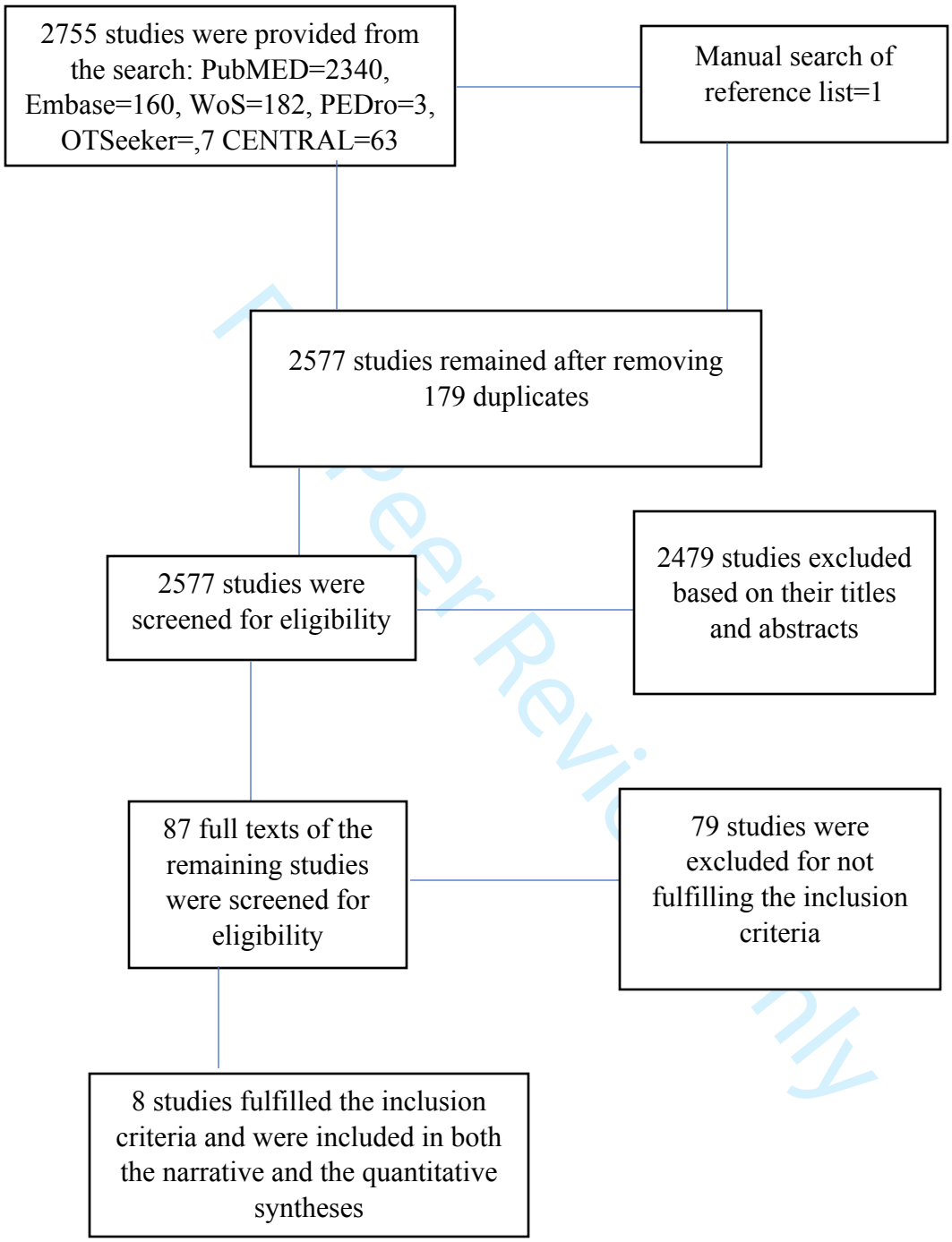

Figure 1: The study flowchart

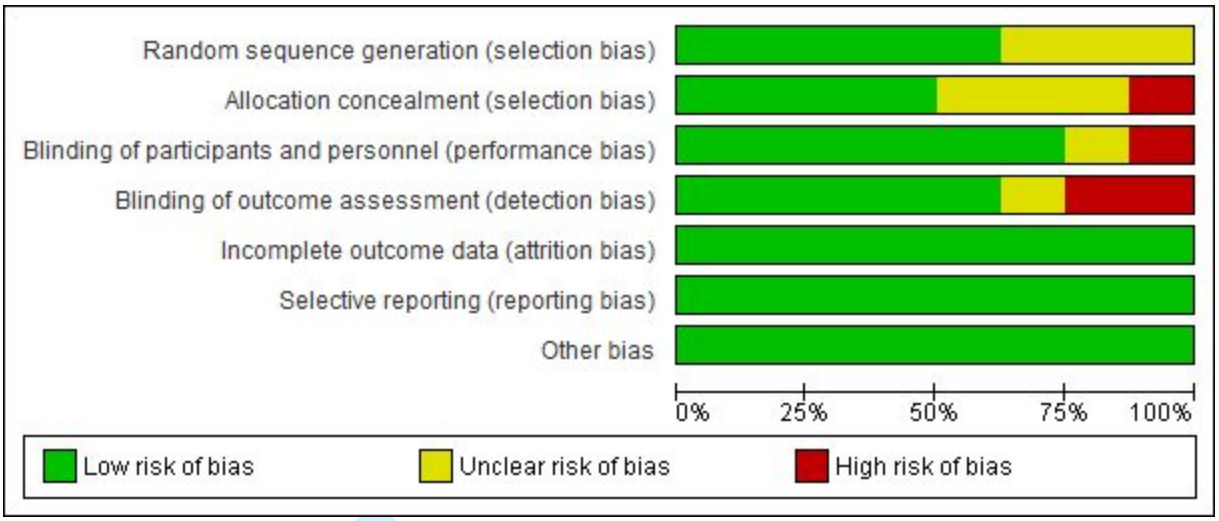

Figure 2: Risks of bias graph of the included studies

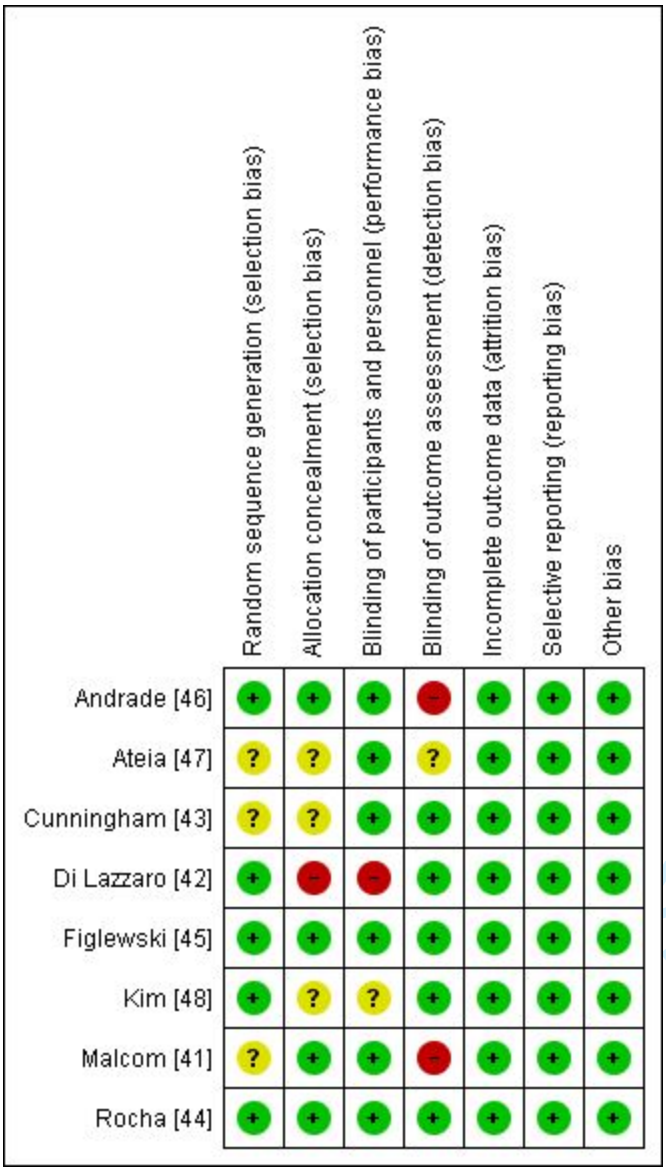

Figure 3: Summary of the risks of bias of the included

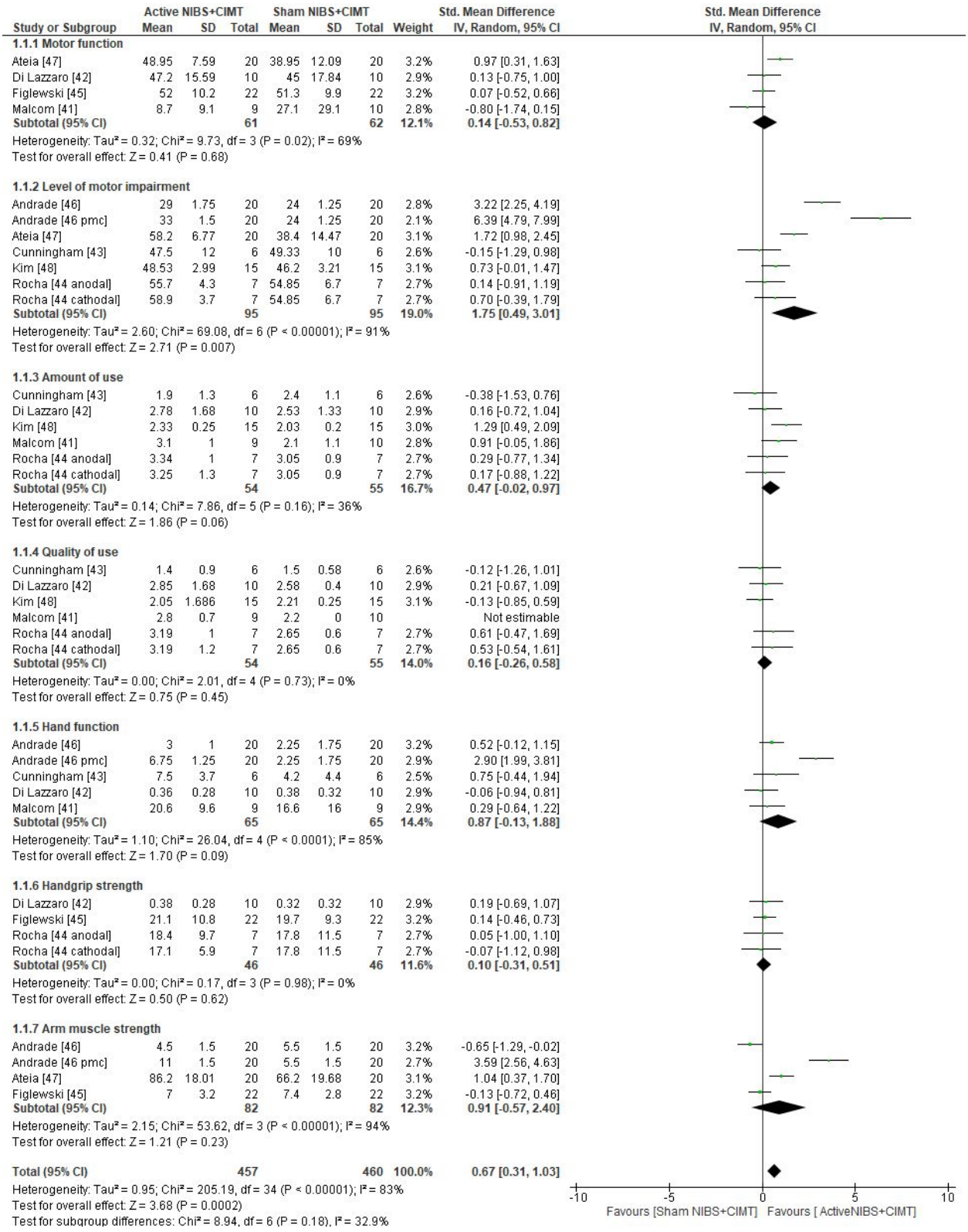

Figure 4: Comparisons of outcomes post intervention between NIBS+CIMT and sham NIBS+CIMT

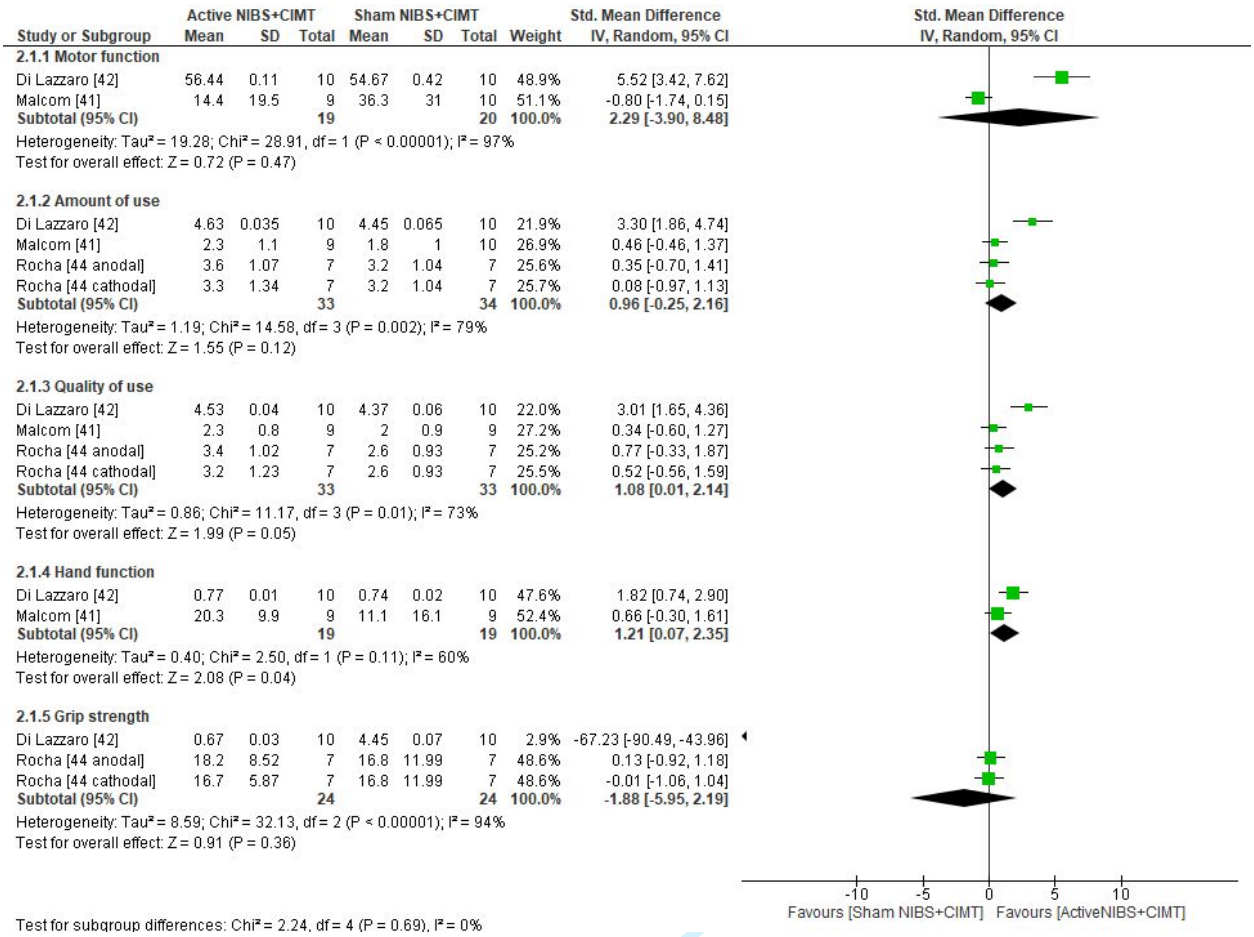

Figure 5: Comparisons of outcomes at follow-up between NIBS+CIMT and sham NIBS+CIMT

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 23
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 8
Study characteristics	17	Cite each included study and present its characteristics.	Page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 11-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 11-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 11-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 11-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
na	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 11-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 12-15
	23b	Discuss any limitations of the evidence included in the review.	Pages 12-15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 12-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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

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