Suzana Bleckmann Reis

Associação de terapia robótica e estimulação cerebral não-invasiva na reabilitação do membro superior pós-acidente vascular cerebral: revisão sistemática e metanálise de ensaios clínicos randomizados

Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Mestre em Ciências

Programa de Neurologia

Orientador: Profa. Dra. Adriana Bastos Conforto

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To my father, Sergio Bleckmann,
who lives in heaven today,
with my Father, God.

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To God, who put all these people in my life.

It’s not about reaching the top of the word and knowing that you have won
It’s about climbing and feeling that the path strengthened you
(..)
Hold tight your son
Smile and hug your parents while they are still here
Because life is a bullet-train, pal
And we are just passengers about to leave

Ana Vilela

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Journal title abbreviations according to the List of Journals Indexed in Index Medicus.

SUMMARY

List of abbreviations

ARAT - Action Research Arm Test

atDCS – Anodal Transcranial Direct Current Stimulation

CI - Confidence interval

cTBS - Continuous Thetaburst Stimulation

ctDCS – Cathodal Transcranial Direct Current Stimulation

DALYs - Disability-adjusted life-years

ICF - International Classification of Functioning, Disability and Health

MAL - Motor Activity Log

MAS - Motor Assessment Scale

NIBS – Non-invasive brain stimulation

RT – Robotic Therapy

rTMS - Repetitive Transcranial Magnetic Stimulation

tACS – Transcranial Alternating Current Stimulation

tDCS – Transcranial Direct Current Stimulation

TMS – Transcranial Magnetic Stimulation

tRNS – Transcranial Random Noise Stimulation

WMFT - Wolf Motor Function Test

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Resumo

Reis SB. *Associação de terapia robótica e estimulação cerebral não-invasiva na reabilitação do membro superior pós-acidente vascular cerebral*: revisão sistemática e metanálise de ensaios clínicos randomizados [dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2020.

Introdução. A terapia robótica e a estimulação cerebral não invasiva são estratégias promissoras para a reabilitação pós-acidente vascular cerebral. *Objetivo.* Esta revisão sistemática e meta-análise objetiva avaliar a evidência da estimulação cerebral não invasiva associada à terapia robótica na melhora dos desfechos de estrutura/ função corporal e atividade do membro superior em sujeitos que sofreram acidente vascular cerebral. *Método.* Este estudo foi realizado de acordo com o protocolo PRISMA e previamente registrado na Plataforma PROSPERO (CRD42017054563). Sete bases de dados e literatura cinzenta foram sistematicamente consultadas por dois revisores, e 1176 registros foram acessados. Oito ensaios clínicos randomizados com desfechos de estrutura/ função corporal e atividade do membro superior foram incluídos. A análise de subgrupos foi realizada de acordo com a fase pós-acidente vascular cerebral; características do dispositivo robótico (i.e. suporte para o braço, articulações envolvidas, treino unimanual ou bimanual); paradigma da estimulação cerebral não invasiva; momento da estimulação cerebral e quantidade de sessões. O Software Grade-Pro foi utilizado para acessar a qualidade da evidência. *Resultados.* Um tamanho de efeito homogêneo não significativo foi encontrado tanto para o desfecho de estrutura e função corporal (diferença média 0.15, 95% CI -3.10 to 3.40; P = 0.93, I^2 = 0%) quanto para o desfecho de limitação da atividade (diferença média padronizada 0.03, 95% CI -0.28 to 0.33; P = 0.87, I^2 = 0%). *Conclusão.* De acordo com esta revisão sistemática e meta-análise, não há evidências de que a estimulação cerebral não

invasiva associada à terapia robótica melhore o desempenho motor e a atividade do membro superior em sujeitos que sofreram acidente vascular cerebral.

Descritores*:* Acidente vascular cerebral; Robótica; Extremidade superior; Estimulação transcraniana por corrente contínua; Estimulação magnética transcraniana; Metanálise.

Abstract

Reis SB. *Effects of robotic therapy associated with non-invasive brain stimulation on upper limb rehabilitation after stroke*: systematic review and meta-analysis of randomized clinical trials [dissertation]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2020.

Background. Robot-assisted therapy and non-invasive brain stimulation (NIBS) are promising strategies for stroke rehabilitation. *Objective.* This systematic review and meta-analysis aim to evaluate the evidence of NIBS as an add-on intervention to robotic therapy in order to improve outcomes of upper limb motor impairment or activity in subjects with stroke. *Methods.* This study was performed according to the PRISMA Protocol and was previously registered on the PROSPERO Platform (CRD42017054563). Seven databases and grey literature were systematically searched by two reviewers, and 1176 registers were accessed. Eight randomized clinical trials with outcome measures of upper limb body structure/ function or activity limitation were included. Subgroup analyses were performed according to: phase post-stroke; device characteristics (i.e. arm support, joints involved, unimanual or bimanual training); NIBS paradigm; timing of stimulation and number of sessions. The Grade-Pro Software was used to assess quality of the evidence. *Results.* A nonsignificant homogeneous summary effect size was found both for body structure function domain (mean difference 0.15, 95% CI -3.10 to 3.40; P = 0.93, I^2 = 0%) and activity limitation domain (standard mean difference 0.03, 95% CI -0.28 to 0.33; P = 0.87, I^2 = 0%). *Conclusions.* According to this systematic review and meta-analysis, there is a lack of evidence that NIBS, as an add-on intervention to RT, improves outcomes of upper limb motor impairments or activity in subjects with stroke.

Descriptors*:* Stroke; Robotics; Upper extremity; Transcranial direct current stimulation; Transcranial magnetic stimulation; Meta-analysis.

1. INTRODUCTION

According to the definition of the World Health Organization, stroke is as clinical syndrome that consists of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function persisting more than 24 hours or bringing on death with no other apparent cause than a vascular agent(1). The mean global lifetime risk of stroke increased from 22.8% in 1990 to 24.9% in 2016(2).

Stroke can be ischemic or haemorrhagic and lead to unilateral or bilateral motor/sensory impairments, aphasia, hemianopia, apraxia, ataxia, neglect and other neurologic deficits(3) Recovery is often incomplete and neurologic impairments are associated with restrictions in functional abilities and in participation in activities of daily living, work and leisure.

According to the approach of the International Classification of Functioning, Disability, and Health [ICF], functionality includes interaction of positive aspects among three different domains: body functions and structures; activity and participation; environmental and personal factors(4). All of these domains may be affected by stroke. In 2013, stroke was considered the third major cause of long-term disability, preceded only by ischemic heart disease and lower respiratory tract infections(5). In underdeveloped countries, where two-thirds of all strokes occur, DALYs (disability-adjusted life-years) lost are almost seven times greater than in developed countries(6-8). In Brazil, up to 61.5% of stroke survivors become dependent for performance of activities of daily living(9) and up to 70% of patients in working age do not return to work(10, 11).

Disability may impact quality of life, mental health and also pose significant economic burden. In the United States, the direct and indirect costs related to stroke in 2007 were estimated at US $ 40.9 billion. A total of US $ 25.2 billion were directed toward direct medical expenses such as hospital admission, outpatient care and home care(12).

Motor impairment after stroke typically affects about 80% of patients(13) and involves the upper limbs in more than 73% of them(14). Only 38% of individuals who present flaccid arm plegia after stroke recover dexterity to some extent, and only 11% achieve full functional recovery(14). Upper limb function is directly related to the satisfactory performance of self-care activities, leisure and labor(15). Upper limb function also impacts mental health(16) and perception of quality of life(17). In developed countries, even six months after lesion onset, two-thirds of survivors are unable to perform daily life activities using the paretic hand(18, 19). Upper limb function is directly related to the satisfactory performance of self-care activities, leisure and labor(15).

Outlining an individual treatment plan for improvement of upper limb function requires that the health professional understands goals of the patient and caregiver regarding impairments, activity limitation and level of participation(20). The identification of more effective interventions to enhance arm and hand function is a priority of neurorehabilitation research, reflected by an increasing number of randomized clinical trials(21). In systematic reviews, several techniques for upper limb rehabilitation have been identified, ranging from bilateral arm training to robotic therapy [RT](21).

In this context, RT is evolving rapidly(22). Robotic devices can move passive limbs, provide resistance or assistance to movement(23) of a single joint(24), or control of intersegmental coordination(25). Robotic devices may deliver or increase repetitive task training or task-specific training. RT may support motor learning, enhance motor control and strength.

A systematic review concluded that there is strong evidence for interventions favouring intensive high repetitive task-oriented and task-specific training in all phases poststroke(26). Intensity of practice and task-specific training are key elements of successful RT(26, 27). A Cochrane overview that synthetized systematic reviews concluded

that there is moderate-quality evidence of a beneficial effect of RT compared with any comparison intervention (other rehabilitation, placebo or no treatment) on measures of impairment (16 trials, 586 participants) and activities of daily living (13 trials, 552 participants)(21).

Different robotic devices are available for clinical practice and five have been more often used in clinical trials: MIME, BiManu Track, NeRebo, MIT Manus and InMotion Shoulder Elbow Robot(22) (Figure 1). These devices may target various joints (i.e. shoulder/elbow, elbow, elbow/wrist, wrist/hand, or the upper limb as a whole), apply forces (end-effector devices) or have robot axes aligned with anatomical axes of the subject (exoskeleton-type devices). They can provide different types of training (i.e. assistive, active, passive, passive-mirrored, active-assistive, corrective, path guidance, and resistive)(22, 28, 29).

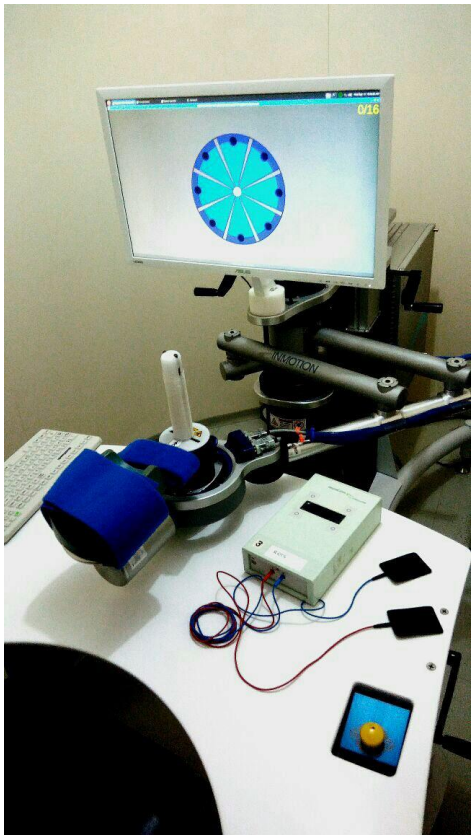

Figure 1. Example of robotic device: InMotion Shoulder Elbow Robot.

At the same time, NIBS has emerged as a potential add-on tool to rehabilitation interventions, by boosting adaptive plasticity mechanisms(30). NIBS is based on the principle of application of external stimuli to modify brain activity. One of the primary objectives of NIBS in stroke is to allow a given motor training intervention (such as RT) to have a similar effect when administered for a shorter period of time, or to have a greater effect when used for the same period of time. NIBS techniques include transcranial direct current stimulation [tDCS] and transcranial magnetic stimulation [TMS], among other interventions(31, 32).

TMS consists in the induction of electric current by the application of a magnetic pulse in the target region of the motor cortex through a coil (Figure 2). The electric current promotes neuronal depolarization. When magnetic pulses are administered rhythmically (repetitive TMS, rTMS), neuronal activity can be inhibited or excited. Effects may outlast the stimulation period. Usually, low-frequency rTMS (1 Hz), decreases excitability while high frequency rTMS (around 3 - 20 Hz) increases excitability but effects can vary according to baseline neuronal activity(33).

TDCS, on the other hand, does not lead to neuronal depolarization, but facilitates or hinders the depolarization of the cell membrane and consequently leads to increased or decreased excitability. In tDCS, a low-intensity electric current (variable from 1mA to 2mA) flows between two electrodes (cathode and anode) soaked in saline solution (Figure 3). For stimulation of the motor cortex, one electrode is placed on the skin, near the topography of the motor cortex, and another electrode can be placed over the supraorbital area. Similarly to rTMS, tDCS effects may last beyond the stimulation period.

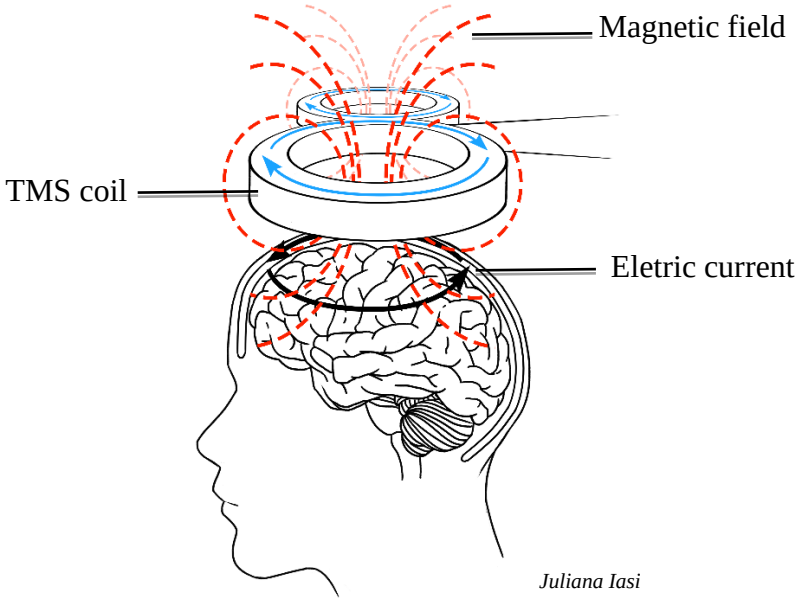

Figure 2. Transcranial magnetic stimulation. Electric currents are induced in the brain by a phenomenon of electromagnetic induction.

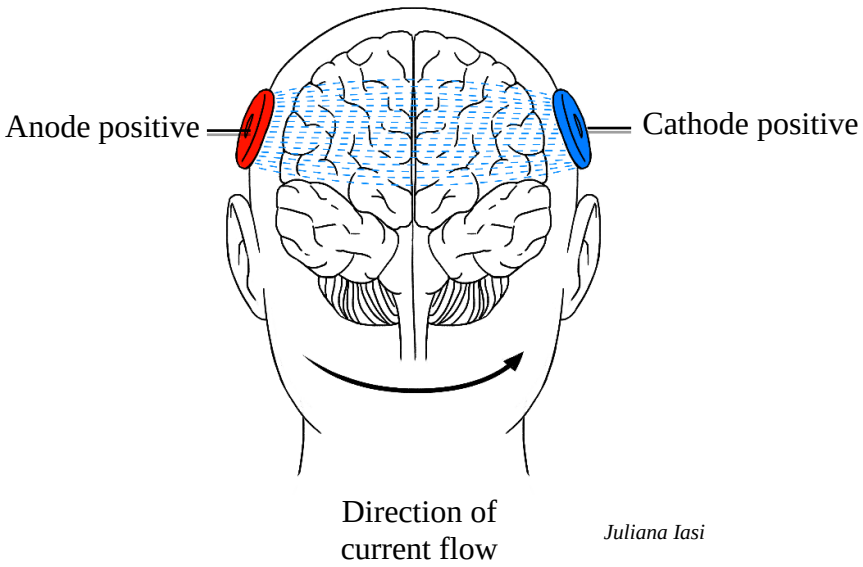

Figure 3. tDCS. Transcranial direct current stimulation increases or decreases cortical excitability modifying the membrane potential through two surface electrodes.

Transcranial alternating current stimulation [tACS] and transcranial random noise stimulation [tRNS] are two others NIBS methods(34). They deliver electrical stimuli with

different parameters from those delivered by tDCS. TACS may be applied in a wide frequency range(35), commonly over the cortex to deliver EEG-like frequency currents (0.1–80 Hz)(34). When applied in the EEG range, it is possible that tACS entrains with or synchronizes neuronal networks, targeting the membrane excitability of neurons more selectively(35). For plasticity studies using a frequency range of 1-5kHz, cortical excitability of the primary motor cortex (M1) is increased(36). In tRNS, a normally distributed random level of current generated with a frequency spectrum between 0.1 and 640 Hz at a sampling rate of 1280 samples per second. The frequency spectrum is comparable to "white noise"(37). Similarly to tACS, tRNS can modulate cortical excitability(34).

In this context, several studies support the idea that the association of NIBS with other interventions may lead to further benefits on upper limb impairments or function(38, 39). Yet, despite the exponential increase in studies about NIBS as an add-on therapy for upper limb rehabilitation after stroke(40), meta-analyses disagree on its effectiveness(21, 41-44).

Specifically, in regard to the association between NIBS and RT to improve upper limb function, the first randomized clinical trials were published in 2011(45, 46). Since then, other studies that used different outcomes, devices, protocols and NIBS parameters also reported results of the association of NIBS and RT.

This systematic review and meta-analysis aim to evaluate the evidence of the association of RT and NIBS for upper limb rehabilitation in stroke. We analyzed randomized clinical trials that compared the association of RT and active NIBS or sham for the improvement of upper limb motor recovery on body function and structure (impairment) as well as on activity and participation (disability) according to the ICF(20).

2.1. Motor recovery after stroke

For motor-related abilities, functional gains tend to follow the level of recovery of movement skills(47) so that upper limb motor control runs in parallel with the level of independence for activities of daily living. In general, three phenomena underlie motor recovery: restitution, compensation and substitution(47).

Restitution includes events such as reduction of edema, absorption of heme products in hemorrhagic stroke, restauration of ionic currents and axonal transport(47). Recovery associated with restitution of function is more prominent within the first weeks after the injury.

Compensatory strategies comprise the adequacy of the patient's impairment to the environmental demand, for instance by increasing the time or effort employed in a particular task, adjusting intentions or selecting new goals, modifying the environment or using assistive devices such as functional orthoses or neuroprostheses(47).

Substitution includes the reorganization of neural networks in order to perform functions that were lost or disrupted by the injury. It is associated, therefore, with motor learning and changes in synaptic efficacy(47). Motor recovery by substitution can be enhanced by external stimuli such as assistive modalities of motor training, neuromuscular or musculoskeletal interventions, and may occur through the acquisition, retention or adaptation of motor skills(48).

The science of neurorehabilitation flourished in the last decades, along with increased knowledge about neuronal plasticity. There is evidence that neural networks may reorganize(49). After a brain lesion such as stroke, perilesional or remote cortical areas can undergo changes to facilitate motor performance and learning(49, 50). The reorganization of neural networks is more prominent within the early stages after stroke but can occur still in the chronic phase (after 6 months post-injury)(51-53). One of the goals of

neurorehabilitation is to maximally take advantage from the capacity of the brain to adaptively reorganize(54) in order to facilitate recovery of function, activity and participation.

The knowledge about the role of the affected and non-affected hemispheres in motor recovery has been expanded by assessing the behavioural consequences of inhibition of each hemisphere before and after motor tasks. Using rTMS as a tool to transiently inhibit neuronal excitability, it has been demonstrated that inhibition of the motor cortex of the affected, but not of the unaffected hemisphere, may decrease motor performance of the paretic hand in some patients with mild hand paresis in the chronic phase after stroke(55). Additionally, excessive inhibition of the motor cortex of the affected hemisphere by the unaffected hemisphere may compromise the generation of voluntary movement by the paretic hand(56). These results suggest that the loss of balance between the two hemispheres and increased activity in the unaffected hemisphere may be a maladaptive type of neural plasticity that can compromise motor performance in a subset of subjects after stroke. This concept is known as the hypothesis of interhemispheric imbalance (Figure 4).

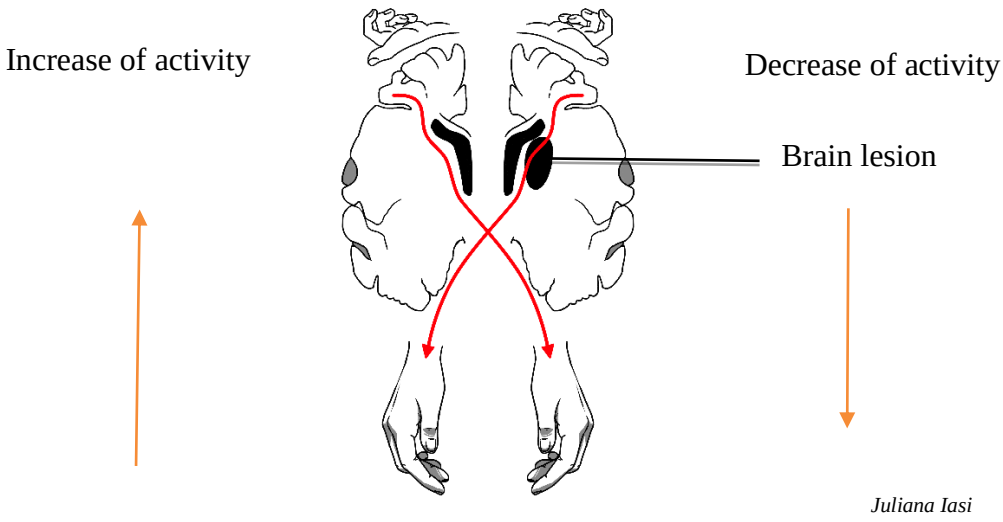

Figure 4. Theory of interhemispheric imbalance after stroke. The loss of balance between the two hemispheres and increased activity in the unaffected hemisphere may compromise motor performance.

Traditional rehabilitation interventions, qualified as “bottom-up” approaches, such as motor training aim to modify stimuli at the peripheral level that influence the central nervous system and lead to changes in behaviour(57). “Top-down” approaches, such as NIBS, act directly on the central nervous system to improve behaviour(57). As an add-on intervention to “bottom-up” approaches, NIBS can potentially be applied with the goal of adjusting inter-hemispheric imbalance after brain injuries and hence, facilitate the rehabilitation process. (Figure 5).

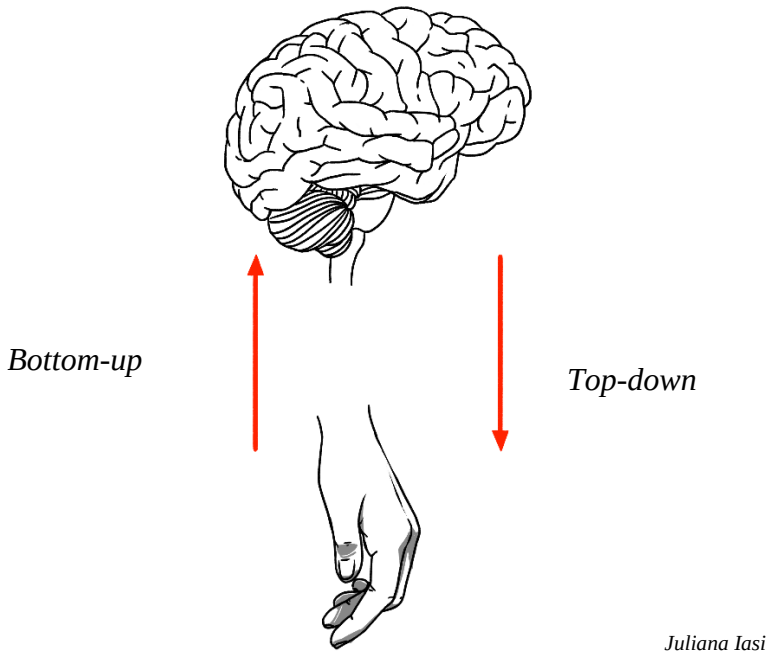

Figure 5. “Bottom-up” and “top-down” rehabilitation approaches.

The variability of available techniques and the heterogeneity of subjects represent opportunities and challenges for rehabilitation based on scientific evidence.

2.2. Robotic Therapy

Even though each robotic device employs a different paradigm of movement training, in general RT rests on principles of rehabilitation that indicate benefits of intensive repetition of movements, providing feedback on performance and increasing the input of somatosensory information from the paretic limb to the central nervous system(58-64). Computational models of motor learning of the task of moving the upper limb to reach an object suggest that the central nervous system plans these movements in outer space(65, 66) with the location and target initially coded as vectors in respect to fixation, and subsequently subtracted to produce an intentional motion vector in a centralized coordinate system in the hand. The internal maps, or, internal models, are the responsible to convert this vector into motor commands. Once an internal template is learned, it can be remembered at a future date. The relearning is then faster and more complete than the original learning. This phenomenon is called consolidation(65-69). There is evidence that, during the learning process, motor memories are initially stored in the primary motor cortex. Subsequently, they are transferred to the premotor and parietal cortices, where they are consolidated and stabilized during sleep (for a review, see Ebajemito et al, 2016)(70).

Research and development efforts in the area of rehabilitation robotics were initiated in the 70's(25). In 2010, a landmark multicenter, randomized controlled trial (Veterans Administration, VA study) showed benefits of upper limb RT compared to traditional therapy(71). This trial included 127 patients with moderate-to-severe upper-limb impairment, six months or more after stroke, randomly assigned to either intensive robot-assisted therapy, intensive comparison therapy, or usual care. During 12 weeks, the RT group received 36 sessions with a planar shoulder-and-elbow robotic device, an antigravity shoulder and grasp-hand device and a wrist robot device, consecutively along 3-week blocks. The intensive comparison therapy group received conventional rehabilitative

techniques matching robot-assisted therapy in intensity, type and schedule of movements. The usual care group received medical management, clinic visits as needed, and in some cases rehabilitation services not dictated by a protocol.

The study concluded that the RT group improved significantly more in performance in the Fugl-Meyer Assessment Scale (upper limb) and in the Wolf Motor Function Test after 36 weeks than the usual care group. Differences in motor gains between the RT and intensive comparison therapy groups were not statistically significant. No serious adverse events were reported.

Concerns about the cost-effectiveness of RT have been raised, given the costs of the robotic equipment. RT enables a therapist to simultaneously supervise multiple robots and patients while performing a large number of repetitions of movements. It has been argued that the cost per session of RT is lower compared to intensive training administered by many therapists. Furthermore, In the VA study, patients who underwent RT used fewer health services in general, resulting in a lower average cost in relation to an intensive training group(72). The reasons underlying this finding were not clearly determined.

The effectiveness of RT according to systematic reviews may vary according to the outcome analysed. The ICF can be used to describe whether treatment aimed to reduce impairments, increase activity or participation(21). Systematic reviews that addressed effects of RT on body structure and function according to the ICF concluded that this intervention leads to statistically significant but small improvements in motor control of the upper limbs, compared to conventional therapy(22, 73, 74). Indeed, the overall effects do not exceed the values of the minimal clinical important differences of Fugl-Meyer Assessment scores(22). Regarding muscle strength, the magnitude of the effect is considered medium(74). Only shoulder/elbow devices seem to be beneficial(22). There is

still no evidence of benefit of RT over conventional therapy to improve muscle tone(22, 73, 74).

In regard to effects of activity according to the ICF, systematic reviews disagree about RT benefits. Veerbeek et al. 2016 (22), Lo et al, 2017(75) and Bertani et al. 2017(73) concluded that RT is just as effective as conventional training for activities of daily living, whereas a Cochrane review of 2018, that included 24 studies with a total of 957 participants, concluded that RT improved activities of daily living scores over any other intervention(23).

According to guidelines of the American Heart Association/American Stroke Association(76), RT provides some benefit for upper limb motor ability and participation, but it remains to be determined whether it is more beneficial than dose-matched conventional therapy. According to the guidelines, RT is "reasonable to consider to deliver more intensive practice for subjects with moderate to severe upper limb paresis"(76).

Evidence is lacking about mechanisms underlying RT and about benefits of this treatment, when initiated early after stroke(22). Also, there is a need for interventions that can boost effects of RT. NIBS is a candidate intervention to attain this goal.

2.3. Models for non-invasive brain stimulation (NIBS) as add-on therapies in stroke

Many of the studies about the benefit of excitation or inhibition of a particular cortical area in neurorehabilitation have been based on the hypothesis of inter-hemispheric imbalance. NIBS could be applied to either increase excitability of the motor cortex of the ipsilesional hemisphere, decrease excitability of the motor cortex of the contralateral hemisphere, or both (56, 77), in order to restore inter-hemispheric balance and thus enhance upper limb performance.

Several articles have been published using NIBS to facilitate adaptive processes of brain plasticity, improve upper limb performance or motor learning according to the hypothesis of interhemispheric imbalance. However, the effectiveness of this approach is still uncertain, according to conflicting conclusions of systematic reviews(41, 42, 78-80).

The effectiveness of increasing the excitability of the affected hemisphere with facilitatory rTMS or suppressing the unaffected hemisphere using inhibitory rTMS to improve motor function after stroke is a matter of debate(79). A review including 19 trials involving a total of 588 participants did not find statistically significant effects of rTMS on motor function or the Barthel Index score(41). The heterogeneity across studies, the lack of randomised controlled trials, the small sample sizes and the lack of studies in the subacute stage post-stroke limit conclusions(79).

Likewise, results of studies implementing tDCS to modulate motor excitability have been highly variable(80). A systematic review and meta-analysis, for example, including 17 studies with 468 participants concluded that tDCS and motor practice positively facilitate long-term motor learning in individuals with stroke(78). A network meta-analysis including 26 studies with 754 participants found that there is no evidence that tDCS improves arm function, measured by the Fugl-Meyer upper extremity assessment, however the intervention may enhance capacity to perform activities of daily living(42). A Cochrane systematic review included nine studies with 396 participants and concluded that, when only studies with good methodological quality were included in the analysis, tDCS does not improve performance of activities of daily living(81).

TDCS has some practical advantages over rTMS in clinical research. It is considered a simpler and safer technique(82, 83). Blinding of participants is more reliable by the administration of sham tDCS than sham rTMS, because active tDCS does not cause

sensations in the subject other than slight tingling in the scalp, whereas, depending on the intensity of stimulation of the motor cortex, active rTMS can evoke visible movements.

One of the reasons of the discrepancies in studies that employed rTMS or tDCS to improve motor performance or recovery is a flaw in the premise of imbalance in interhemispheric inhibition as a universal mechanism of maladaptive plasticity in stroke. Under a number of circumstances, the hypothesis of inter-hemispheric imbalance does not seem to apply. In patients with severe post-stroke upper limb impairments, the unaffected hemisphere may be relevant for recovery and motor performance(84-86). Also, inhibition of the unaffected hemisphere at an early stage after stroke could worsen motor performance of the paretic hand if the activity of the unaffected hemisphere is beneficial, rather than maladaptive. This hypothesis is known as the vicariation model, according to which activity in residual networks substitutes those functions lost by damaged areas(40).

However, both hypotheses – interhemispheric imbalance and vicariation – may be too simplistic and not sufficient to explain recovery in all patients(40). The bimodal balance–recovery model combines these two hypotheses into a single model, introducing a new parameter – the structural reserve - which describes the extent to which neural pathways and neural tissue preserved by the lesion contribute to recovery in an individual patient. The amount of structural reserve determines whether interhemispheric imbalance dominates over vicariation: if the structural reserve is high, the interhemispheric competition model can predict recovery better than the vicariation model. The latter is more useful in predicting recovery in patients with little structural reserve(40). Thus, the bimodal balance model could better enable NIBS to be tailored to the specific needs of an individual patient.

2.4. State of art and gaps in knowledge

Within the past decade, the possibility of associating NIBS with intensive motor training, represented by RT, has progressively raised more interest. A narrative review on the effects of tDCS coupled with RT in post stroke upper limb rehabilitation(30) included eight studies and highlighted the large variability in the characteristics of enrolled patients and the lack of a standardized intervention protocol. The main sources of variability underscored by the review were: subjects' characteristics such as phase post stroke, type of stroke, lesion site; NIBS intervention, such as, bi or unilateral stimulation, excitation or inhibition, stimulation parameters, electrode size; and RT principles, such as bi- or unimanual training and support offered to the arm. However, until now, a systematic review and meta-analysis about effects of NIBS in association with RT on measures of body structure/function and activity limitation according to the ICF had not been performed.

3. OBJECTIVE

This systematic review and meta-analysis aims to evaluate the evidence of NIBS as an add-on intervention to robotic therapy in order to improve outcomes of upper limb motor impairment or activity in subjects with stroke.

4.1. Ethics and registration

This study was performed according to the PRISMA Protocol(87) and was approved by the Research Ethics Committee of USP Medical School on March, 2017 (nº 0085/17) (Supplementary Material 1). The protocol was properly registered on the PROSPERO Platform (CRD42017054563) (Supplementary Material 2).

4.2. Search Strategy

Seven scientific databases were systematically searched: MEDLINE (Medical Literature Analysis and Retrieval System Online; through the PubMed interface); EMBASE (Excerpt Medical Database); Cochrane Central Register of Controlled Trials (CENTRAL); LILACS (Latin American & Caribbean Health Sciences Literature; through the Virtual Health Library - Bireme interface); CINAHL (Cumulative Index to Nursing and Allied Health Literature through the EBSCO interface); DORIS (Database of Research in Stroke) and PEDro (Physiotherapy Evidence Database). The articles were manually retrieved. In addition, the following online archives of theses or trial registers were searched: Clinical Trials; Digital Library of Theses and Dissertations of São Paulo University; DORIS; Digital Brazilian Library of Theses and Dissertations; Public Domain Portal; CAPES (Coordination for the Improvement of Higher Education Personnel) Thesis and Dissertation Bank.

The following key words were used: stroke, robot, transcranial direct current stimulation and transcranial magnetic current stimulation. The term “upper limb” was not selected in order to avoid missing studies that involved both lower and upper extremities. The term “transcranial direct current stimulation” and “transcranial magnetic current stimulation” were used instead of “non-invasive brain stimulation”, because 1. “non-invasive brain stimulation” is not registered as a controlled vocabulary term; and 2. When the key word “transcranial direct current stimulation” is exploded, records of “transcranial

alternating current stimulation" and "random noise stimulation" are automatically detected. For databases without the option of "exploding" terms, the key words "transcranial alternating current stimulation" and "random noise stimulation" were also used. Whenever possible, the filter "random" was used. The full search strategy can be found in Supplementary Material – Table 1. No publication data, or language restrictions were imposed. The search included all studies published until July, 2019.

Table 1. Full Search Strategy

Database	Search Strategy
CINAHAL EMBASE MEDLINE	**1.**(Stroke) OR (Strokes) OR (Apoplexy) OR (CVA) OR (CVAs) OR (Cerebrovascular Accident) OR (Cerebrovascular Accidents) OR (Vascular Accident, Brain) OR (Vascular Accidents, Brain) **2.**(Robot*) OR (Exoskeletons Device) OR (Exoskeleton Devices) **3.**(Transcranial Direct Current Stimulation) OR (tDCS) OR (Transcranial Random Noise Stimulation) OR (Transcranial Alternating Current Stimulation) OR (Transcranial Electrical Stimulation) OR (Transcranial Electrical Stimulations) OR (Electric Stimulation Therapy) OR (Therapeutic Electrical Stimulation) OR (Therapeutic Electric Stimulation) OR (Electrical Stimulation Therapy) OR (Electrotherapy) OR (Interferential Current Electrotherapy) OR (Transcranial Magnetic Stimulation) OR (Transcranial Magnetic Stimulations) OR (Magnet*) **4.**1 AND 2 AND 3 + filter "random" (if disponible)
COCHRANE	**1.**MeSH descriptor: [Stroke] explode all trees **2.**MeSH descriptor: [Robotics] explode all trees **3.**MeSH descriptor: [Transcranial Direct Current Stimulation] explode all trees **4.**MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees **5.**#3 or #4 **6.** #1 and #2 and #5
LILACS PEDro DORIS GRAY LITERATURE	**1.**(stroke) AND (robot*) **2.**(robot*) AND (transcranial direct current stimulation) **3.**(robot*) AND (transcranial random noise stimulation) **4.**(robot*) AND (transcranial alternating current stimulation) **5.**(robot*) AND (transcranial magnetic stimulation) **6.**(stroke) AND (transcranial direct current stimulation) **7.**(stroke) AND (transcranial random noise stimulation) **8.**(stroke) AND (transcranial alternating current stimulation) **9.**(stroke) AND (transcranial magnetic stimulation)

4.3. Study Selection

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were independently assessed by two reviewers who read the full-text articles and selected studies according to the inclusion and exclusion criteria. Disagreements between the two reviewers were resolved by consensus.

4.4. Eligibility Criteria

Types of studies: Randomized clinical trials with parallel or crossover design were included. Authors were contacted to provide missing data of abstracts and non-published studies.

Types of participants: People with upper limb paresis due to stroke were included. No restrictions were imposed regarding: age, residual upper limb motor-function, time since last stroke, type of stroke or history of previous strokes. Studies that included subjects with cerebellar strokes or strokes in cerebellar pathways were not included.

Types of interventions: Trials that added active NIBS before, during or after RT in order to improve upper limb outcomes were included. Four types of NIBS were assessed: tDCS, transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and TMS.

Types of controls: RT associated with sham NIBS or RT alone.

Types of outcome measures: Upper limb performance measured by the main standard scales for the ICF Body Structure/ Body Function domain (for instance, Fugl-Meyer Assessment Scale - FMA, Ashworth or modified Ashworth scale, force and range of motion) or Activity level (for instance, Wolf Motor Function Test [WMFT], Action Research Arm Test [ARAT], Motor Activity Log [MAL], Box and Blocks Test [BBT],

Jebsen-Taylor Hand Function Test [JTHFT], Nine Hole Peg Test [NHPT], and Motor Assessment Scale [MAS](88).

4.5. Data extraction

Data were extracted from the records to a standard form by two reviewers. Disagreements were resolved by consensus. If information was missing/unclear in manuscripts, their authors were contacted. In case of crossover studies, only data of the first intervention were extracted for metanalyses.

If more than one outcome was assessed to measure body function/ structure, the priority for analysis was the Fugl-Meyer according to recommendations of the measurement working group of the Stroke Recovery and Rehabilitation Roundtable (89). To measure activity limitation, priority of analysis was given to the ARAT according to recommendations of the same panel(89). If these scales were not present in the study, the choice of outcome was based on the most frequent outcomes across the selected studies.

4.6. Methodological Quality

Risks of bias were assessed independently by two reviewers. Disagreements were settled by consensus and no consultation with a third reviewer was necessary. If there was a lack of, or unclear information, authors were asked for clarification, or requests were made for the provision of the missing information.

The following domains were assessed for each study: randomization(90); concealment allocation(90); blinding of outcome assessment(90); blinding of participants and personnel(90); description or implicit intention-to-treat analysis; extent of loss(91); sample homogeneity (similarity between characteristics data of active and control group); sample representativeness (absence or presence of exclusion criteria others than the usually

present on RT or NIBS trials in general); presence of description of sample calculation; information regarding early cessation of trials; and selective reporting(90). For each domain, the study was classified as having high, low or unclear risk of bias.

The classification of bias was not used as a criterion to exclude studies from a possible meta-analysis but was used for analysis of quality of the evidence according to GRADE -pro GDT (Grading of Recommendations Assessment, Development and Evaluation)(87), by a GRADE Evidence Profile across the domains study design, risk of bias, inconsistency, indirectness and imprecision. The domain risk of bias was classified prioritizing randomization, allocation, blinding and extent of loss. Others domains contributed with the percentage of high or unclear risk of bias (i.e. <50% not serious; 50% to 75%, serious; >75%, very serious). The domain inconsistency was classified according to I^2 of metanalysis (<50% not serious; 50% to 75%, serious; >75%, very serious). The domain imprecision was classified according to the Z test for overall effect (<50% not serious; 50% to 75%, serious; >75%, very serious).

The quality was stated as high (further research is very unlikely to change our confidence in the estimate of the effect), moderate (further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate), low (further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of the effect)(87).

4.7. Quantitative data Analysis

For studies in which the same scale was used to evaluate the outcome (i.e. Fugl-Meyer for *Body Structure/ Function*), the number of participants in each group, mean scores and standard deviations after interventions in the active and control groups were

analysed in RevMan 5.3. (Review Manager 5.3). For the Fugl-Meyer, a higher score was regarded as positive. The mean difference was established in individual studies by calculating the difference between the means of the active and control groups.

For types of outcomes assessed with different scales (i.e. *Activity Limitation*) measures of post and pre-intervention of each subject were assessed after contacting the authors and requesting individual data. The individual relative difference between post and pre- intervention (post-pre/pre) was calculated for each subject. The mean and standard deviations of relative differences in active and control groups were analysed in RevMan 5.3. In individuals who presented a baseline score of 0, the relative difference was also considered to be 0. We opted for this approach because none of the individuals who scored 0 at baseline presented a post-pre-difference above the Minimal Detectable Changes of the respective scale.

For scales in which a lower score was regarded as positive compared to a higher score, the mean was multiplied for -1. The standard mean difference was established in individual studies by calculating the difference between the means of the active and control groups.

The summary effect size was calculated by the average of the mean difference or standard mean difference of individual studies with the corresponding 95% confidence interval [CI]. Heterogeneity among studies was assessed by I^2. In case of statistical heterogeneity, defined as an $I^2 \geq 50\%$, a random-effect model was applied, while a fixed-effect model was applied for $I^2 < 50\%$ (92). All analyses were performed using RevMan 5.3. and P values ≤ 0.05 were considered statistically significant.

In addition, the following subgroup analyses were conducted(22, 30, 93, 94):

- *according to subjects´ characteristics:* phase post stroke (acute, 1-7 days; early subacute, > 7 days-3 months; late subacute, 3-6 months; chronic, > 6 months)(95).
- *according to robotic device characteristics*: arm support (end-effector or exoskeleton)(28); joints involved (shoulder; elbow; wrist; hand); and unimanual or bimanual training.
- *according to NIBS characteristics:* NIBS paradigm (aiming to increase or decrease cortical excitability); timing of stimulation (pre, post or during RT).
- *According to general characteristics:* number of sessions (1 -6; 7-12; 13-24; 25-36)(71).

5.1. Search results

At the last search in July 2019, a total of 1266 records were identified from databases, grey literature and hand-search. After removing duplicates, 1176 articles were identified and 14 abstracts were selected for full-text reading. The study selection process is represented in Figure 6, according to the PRISMA Flow diagram(87).

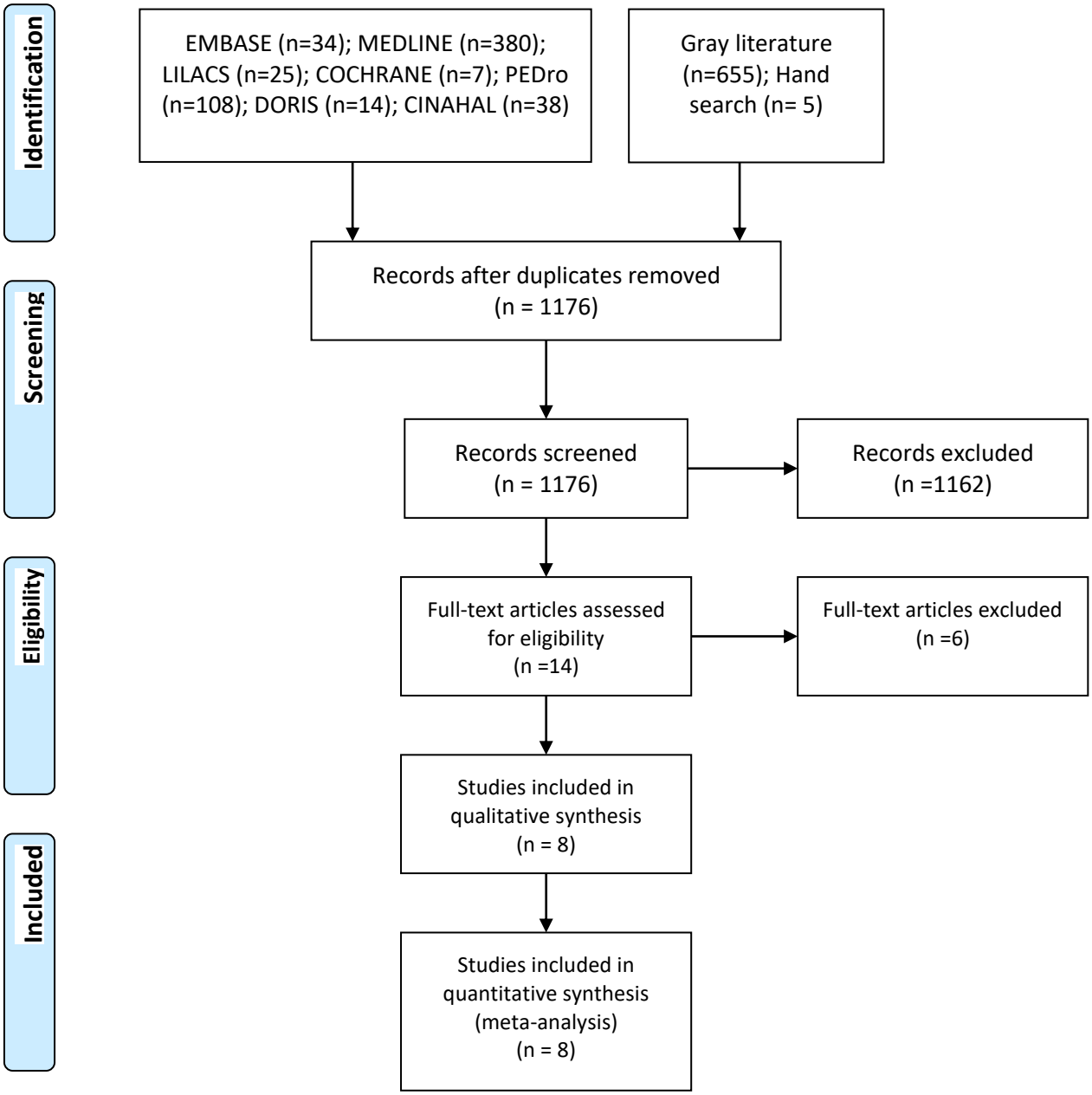

Figure 6. Study selection process: flow diagram.

At the end of the selection, six trials were excluded due to the following reasons: two did not attempt criteria for control groups(93, 96); three did not use standard clinical scales as outcome measures(46, 94, 97); and one did not attempt criteria for control groups and did not use standard clinical scales as outcome measures(98).

5.2. Characteristics of the trials

Characteristics of the participants in the trials selected for the systematic review and meta-analysis are shown in Table 2 and characteristics of the interventions are shown in Table 3. One study(45) applied three different interventions (sham tDCS; anodal tDCS; cathodal tDCS) and, in this review, was divided in two (*Hesse et al,2011*- A – anodal stimulation and *Hesse et al,2011- C* – cathodal stimulation). Thus, considering *Hesse et al, 2011* as two different trials for statistical analyses, the review included 9 trials, with a total of 324 participants (161, active; 163, control).

The robot devices used in the studies were: InMotion2; MitManus; BiManu Track; ReoGo; Armeo®Spring and REAplan robot. Their characteristics are shown in Table 4.

Table 2. Characteristics of the participants of the studies included in the meta-analysis

Study	N (sex)	Age Mean (SD)	Months/weeks /days post-stroke Mean (SD)	Motor basal Impairment FMA Mean (SD)	Type of Stroke	Affected Hemisphere	Site of the lesion
	Active (M/F) Control (M/F)	Active Control	Active Control	Active Control	Active Control	Active Control	Active Control
Ang et al., 2015	10 (6/4)	52.1(11.7)	1052(722) D	35.3 (7.8)	6 I / 4 H	5 L / 5 R	1 C / 9 SubC
	9 (8/1)	56.3(9.5)	1021(465) D	32.6 (8.1)	7 I / 2 H	6 L / 3 R	0 C / 9 SubC
Dehem et al., 2018	11(7/4)	62.73 (8.0)	17.47 (15.8) Mo	-	7 I / 4 H	6 L / 5 R	3 C / 8 SubC
	10 (8/2)	58.1 (10.8)	58.5 (75.5) Mo	-	8 I / 2 H	5 L / 5 R	4 C / 6 SubC
Di Lazzaro et al., 2016	8 (4/4)	57.9(12.4)	63.3(72) Mo	14.5 (2.4)	8 I / 0 H	NR	NR
	9 (4/5)	56.8(9.6)	61.3 (44.2) Mo	12.6 (2.2)	9 I / 0 H	NR	NR
Edwards et al., 2019	41 (25/16)	*(see footnote)	*(see footnote)	*(see footnote)	41 I	41 R	26 C / 15 SubC
	41 (25/16)	*(see footnote)	*(see footnote)	*(see footnote)	41 I	41 R	27 C / 14 SubC
Hesse et al., 2011 - A	32 (20/12)	63.9(10.5)	3.4(1.8) W	7.8 (3.8)	32 I / 0 H	18 L / 14 R	NR
	32 (21/11)	65.6(10.3)	3.8(1.5) W	8.2 (4.4)	32 I / 0 H	16 L / 16 R	NR
Hesse et al., 2011 - C	32 (18/14)	65.4(8.6)	3.8(1.4) W	7.9 (3.4)	32 I / 0 H	17 L / 14 R	NR
	32 (21/11)	65.6(10.3)	3.8(1.5) W	8.2 (4.4)	32 I / 0 H	16 L / 16 R	NR

continue

Table 2. Characteristics of the participants of the studies included in the meta-analysis. Continuation.

Study	N (sex)	Age (SD) Mean	Months / weeks /days Poststroke Mean (SD)	Motor basal Impairment FMA Mean (SD)	Type of Stroke	Affected Hemisphere	Site of the lesion
	Active (M/F) Control (M/F)	Active Control	Active Control	Active Control	Active Control	Active Control	Active Control
Maxfield et al., 2011	9 (6/3)	60.4(16.3)	55.3 (42.2) Mo	33.4 (16.3)	4 I / 3 H / 2 unk	3 L / 6 R	0 C/ 5 SubC / 4 C + SubC
	9 (6/3)	59.1(10.9)	50.8 (15.1) Mo	22.2 (18.2)	8 I / 0 H / 1 unk	7 L/ 2 R	0 C / 3 SubC / 6 C +SubC
Straudi et al., 2016	12 (5/7)	52.7 (16.0)	40.7 (35.1) W	24.1(16.6)	10 I /2 H	9 L / 3 R	9 C / 3 SubC
	11 (7/4)	64.3 (9.7)	78.2 (61.9) W	21.4 (13.2)	9 I / 2 H	6 L / 5 R	5 C / 6 SubC
Triccas et al., 2015	11 (6/5)	64.7 (9.2)	22.1 (31.2) Mo	24.9 (16.0)	9 I / 2 H	6 L / 5 R	3 C / 7 SubC / 1 unk
	11 (7/4)	62.5 (14.3)	13.4 (16.3) Mo	37.1 (1.,6)	9 I / 2 H	5 L / 6 R	4 C/ 6 SubC / 1 C +SubC

Abbreviations: C = Cortical, D = days, F = female, H = Hemorrhagic, I = Ischemic, M = male, L = Left, Mo = months, NR = not reported, R = Right, SD = standard deviation, SubC = Subcortical, Unk = Unknown, W = weeks

* Edward et al., 2019 provided median [interquartile range] of continuous variables: Age - 70.0 [64.0,77.0] active, 66.0 [61.0,73.0] control; Days poststroke - 654.0 [365.0,1445.0] active, 1201.0 [425.0,1693.0] control; Motor basal impairment (FMA) - 22.0 [9.0,42.0] active; 22.0 [11.0,43.0] control.

conclusion

Table 3. Interventions reported in the meta-analysis

Study	Robotic Device	NIBS	Therapy Protocol	Outcome Measure	
				Body function and Structure	Activity limitation
Ang et al., 2015	MIT Manus	bilateral tDCS	10 sessions of 20 minutes of bilateral tDCS (active or sham), followed by 1h RT session (MI-BCI) during 2 weeks.	FMA	-
Dehem et al., 2018	REAplan robot	bilateral tDCS	1 session of 20 minutes of bilateral tDCS (active or sham), during the 20 minutes of RT.	-	BB
Di Lazzaro et al., 2016	InMotion2 (commercial version MIT-Manus)	theta burst	10 sessions of inhibitory cTBS on affected hemisphere (active or sham), followed by 960 movements (active assistive) of RT, during 2 weeks.	FMA	-
Edwards et al., 2019	MIT Manus	anodal tDCS	36 sessions of 20 minutes of anodal tDCS (active or sham), followed by ~1h RT session (1024 movement repetitions), during 12 weeks.	FMA	WMFT
Hesse et al., 2011 - A	Bi-Manu Track	anodal tDCS	30 sessions of anodal tDCS (active or sham), during the first 20 minutes of RT (400 movements); plus conventional therapy (physical and occupational therapy), during 6 weeks.	FMA	BB

continue

Table 3. Interventions reported in the meta-analysis. Continuation.

Study	Robotic Device	NIBS	Therapy Protocol	Outcome Measure	
				Body function and Structure	Activity limitation
Hesse et al., 2011 - C	Bi-Manu Track	cathodal tDCS	30 sessions of anodal tDCS (active or sham), during the first 20 minutes of RT (400 movements); plus conventional therapy (physical and occupational therapy), during 6 weeks.	FMA	-
Maxfield et al., 2011	ReoGo	anodal tDCS	22 sessions of anodal tDCS (active or sham) during the first 20 of 60 minutes of RT, during 2,5 weeks.	FMA	WMFT
Straudi et al., 2016	ReoGo	bilateral tDCS	10 sessions of bilateral tDCS (active or sham), during the 30 minutes of RT for 2 weeks.	FMA	BB
Triccas et al., 2015	Armeo®Spring	anodal tDCS	18 sessions of anodal tDCS (active or sham), during the first 25 of 75 minutes of RT during 8 weeks.	FMA	ARAT

Abbreviations: ARAT = Action Research Arm Test, BB = Box and Blocks Test, FMA = Fugl Meyer Assessment, MI-BCI = Motor Imagery - Brain Computer Interface, SD = standard deviation, WMFT = Wolf Motor Function Test.

conclusion

Table 4. Characteristics of the robotic devices.

Robot device	Arm- support	Joint involved	Degrees of freedom	Training modalities[1]
MitManus[2]	end-effector	shoulder/elbow	2D	Assistive, Active, Passive, Active-assistive, Corrective, Path guidance, Resistive, Movement perturbation
		wrist	3D	
InMotion[2]	end-effector	shoulder/elbow	2D	Assistive, Active, Passive, Active-assistive, Corrective, Path guidance, Resistive, Movement perturbation
BiManu Track	end-effector	wrist /hand	2D	Passive-mirrored, Active-passive-mirrored
ReoGo	end-effector	shoulder/elbow	3D	Active, Passive, Path guidance, Resistive
Armeo®Spring	exoskeleton	whole-arm	3D	Active
REAplan robot	end-effector	shoulder/elbow	2D	Assistive, Active, Passive, Active-assistive

[1]The protocol used on the included studies not necessarily employed all these training modalities**.**

[2] InMotion is the commercial version of the MIT-Manus. This brand of device presents others versions that include wrist/hand joints. Ang et al., 2015 and Di Lazzaro et al., 2016 only used shoulder/elbow version, whereas Edwards et al., 2019 employed both shoulder/elbow and wrist version.

5.3. Methodological Quality

The assessment of risk of bias is shown in Figure 7.

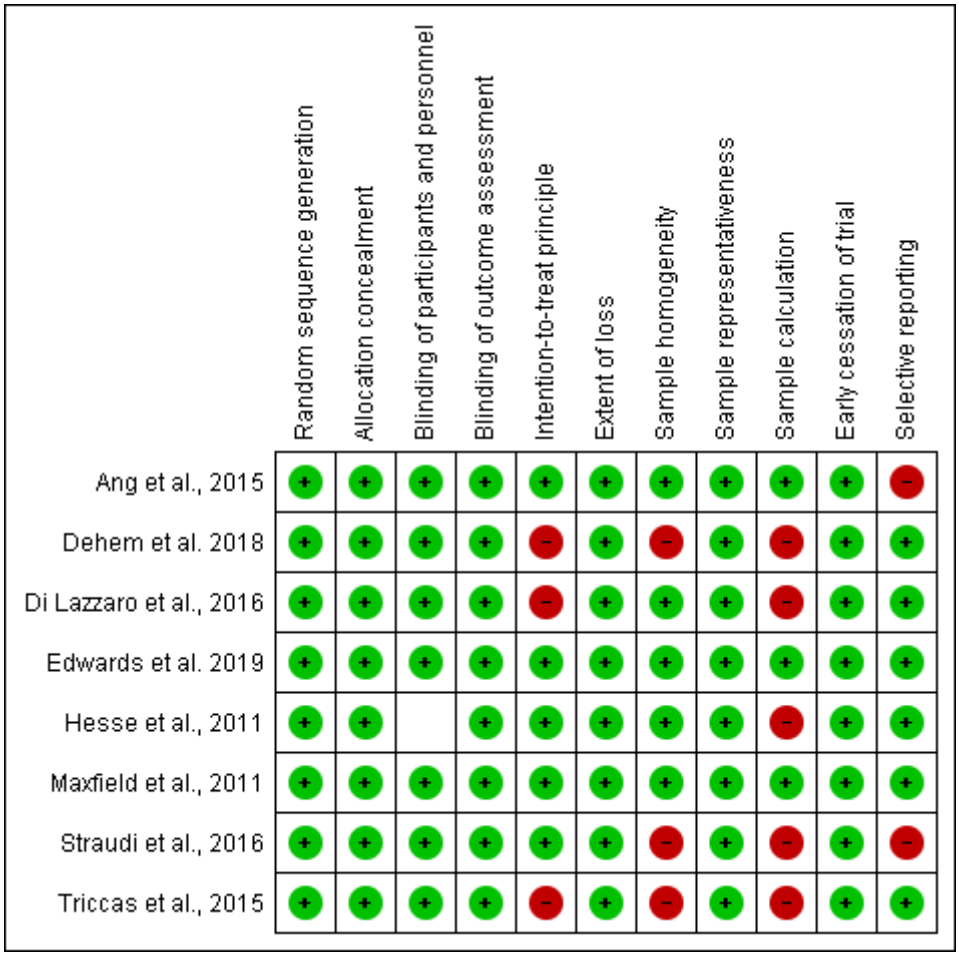

Figure 7. Risk of bias: domains assessed for each study. Green signal = low risk of bias; red signal = high risk of bias; no signal = risk of bias unclear.

5.4. Main analysis

5.4.1. Body structure/function

Seven of the included studies(38, 45, 99-103) chose the Fugl-Meyer Assessment scale as an outcome measure of body structure/function. Overall, a nonsignificant homogeneous summary effect size (mean difference 0.15, 95% CI -3.10 to 3.40; P = 0.93, I^2 = 0%) was found (Figure 8).

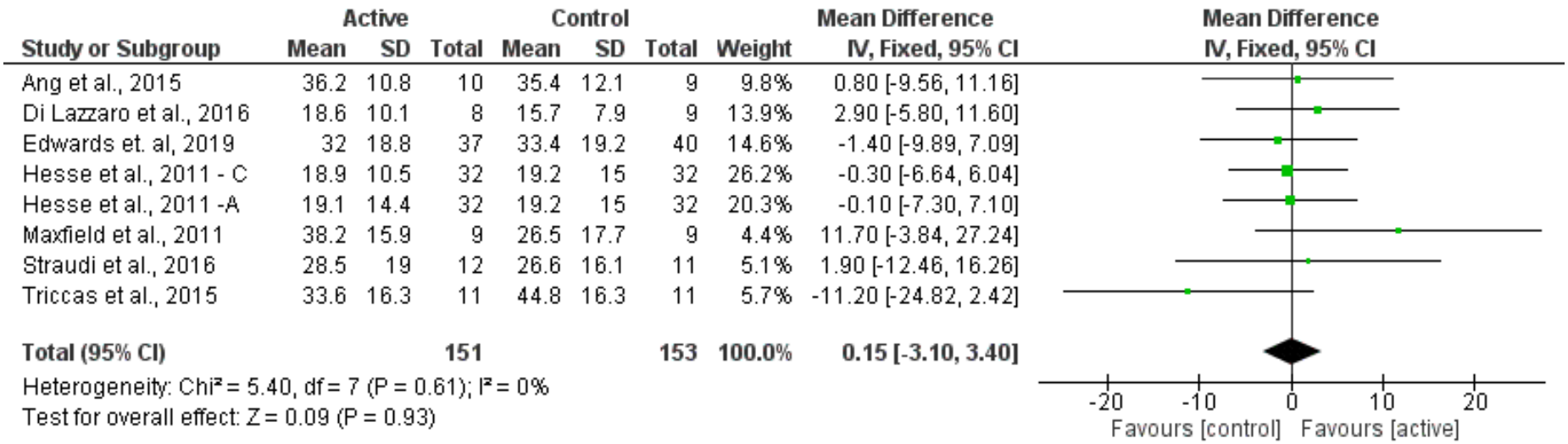

Figure 8. Forest plot of all trials comparing RT associated with NIBS (active) versus RT associated with sham NIBS (control) for body structure / function outcomes. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.4.2. Activity limitation

Six of the included studies(45, 100-104) evaluated eligible scales of activity limitation: ARAT(103), BB(45, 102, 104), MAL(102), and WMFT(100, 101). Of the two studies that assessed the WMFT, one reported the WMFT-Time score (time required to complete the tasks: a lower score was regarded as positive compared to a higher score)(101). The other study described the WMFT-FAS score (Functional Ability Scale: a higher score was regarded as positive compared to a lower score)(100). Data from Hesse et al. (2011) were not available. Therefore, results of 5 studies(100-104) were analysed.

Overall, a nonsignificant homogeneous summary effect size (standard mean difference 0.03, 95% CI -0.28 to 0.33; P = 0.87, I^2 = 0%) was found (Figure 9).

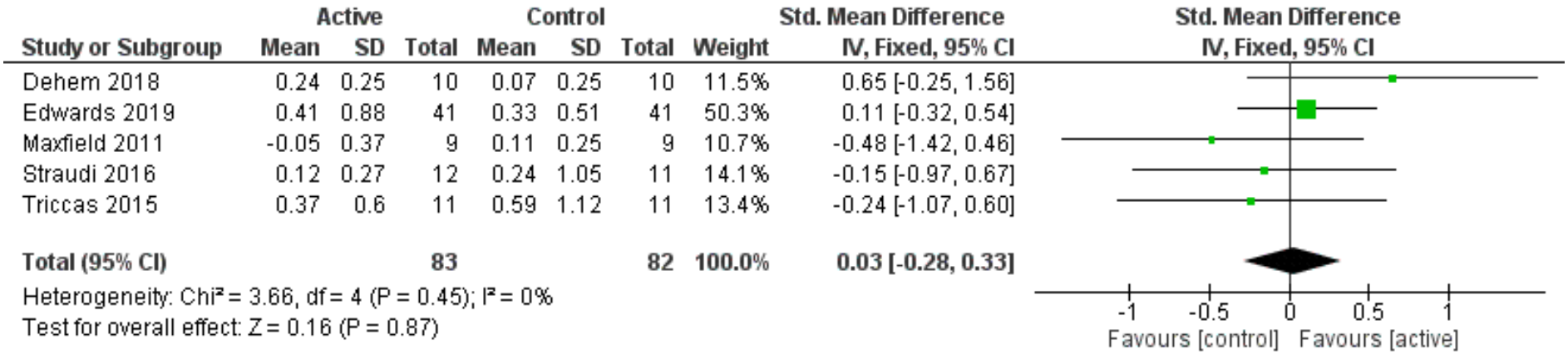

Figure 9. Forest plot of trials comparing RT associated with NIBS (active) versus RT associated with sham NIBS (control) for activity limitation outcomes. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5. Subgroups analyses

Subgroups analyses are shown in Table 5.

Table 5. Paradigms of studies included in subgroup analyses.

Study	Subjects	Robot Device			NIBS		General
	Phase Post Stroke	Arm support	Joints Involved	Unimanual or Bimanual training	NIBS paradigm	Timing of Stimulation	Number of sessions
Ang et al., 2015	Chronic	end-effector	Shoulder / elbow	unimanual	bilateral anodal and cathodal tDCS	Before RT	7-12
Dehem et al., 2018	Chronic	end-effector	Shoulder / elbow	unimanual	bilateral anodal and cathodal tDCS	During RT	1-6
Di Lazzaro et al., 2016	Chronic	end-effector	Shoulder / elbow	unimanual	cTBS on affected hemisphere	Before RT	7-12
Edwards et al., 2019	Chronic	end-effector	Whole arm	unimanual	atDCS on affected hemisphere	Before RT	25-36
Hesse et al., 2011 -A	Subacute	end-effector	Wrist / hand	bimanual	atDCS on affected hemisphere	During RT	25-36
Hesse et al., 2011 - C	Subacute	end-effector	Wrist / hand	bimanual	ctDCS on unaffected hemisphere	During RT	25-36
Maxfield et al., 2011	Chronic	end-effector	Shoulder / elbow	unimanual	atDCS on affected hemisphere	During RT	13 -24
Straudi et al., 2016	Chronic, Subacute	end-effector	Shoulder / elbow	unimanual	bilateral anodal and cathodal tDCS	During RT	7-12
Triccas et al., 2015	Chronic, Subacute	exoskeleton	Whole arm	unimanual	atDCS on affected hemisphere	During RT	13 -24

5.5.1. Phase post-stroke

Five trials(38, 99-101, 104) only recruited participants in the chronic phase post-stroke; one trial(45) only recruited participants in the subacute phase and two, in both phases(102, 103).

Body structure / body function - Nonsignificant homogeneous summary effect sizes were found for the chronic (mean difference 1.18, 95% CI -3.13 to 5.50; P = 0.59, I^2 = 0%) and subacute (mean difference -1.60, 95% CI -6.14 to 2.94; P = 0.49, I^2 = 36%) phases (Figure 10).

Activity limitation - Nonsignificant homogeneous summary effect sizes were found for participants in the chronic (standard mean difference 0.10, 95% CI -0.23 to 0.43; P = 0.56, I^2 = 30%) and subacute phases (standard mean difference -0.28, 95% CI -1.14 to 0.59; P = 0.53, I^2 = 0%) (Figure 11).

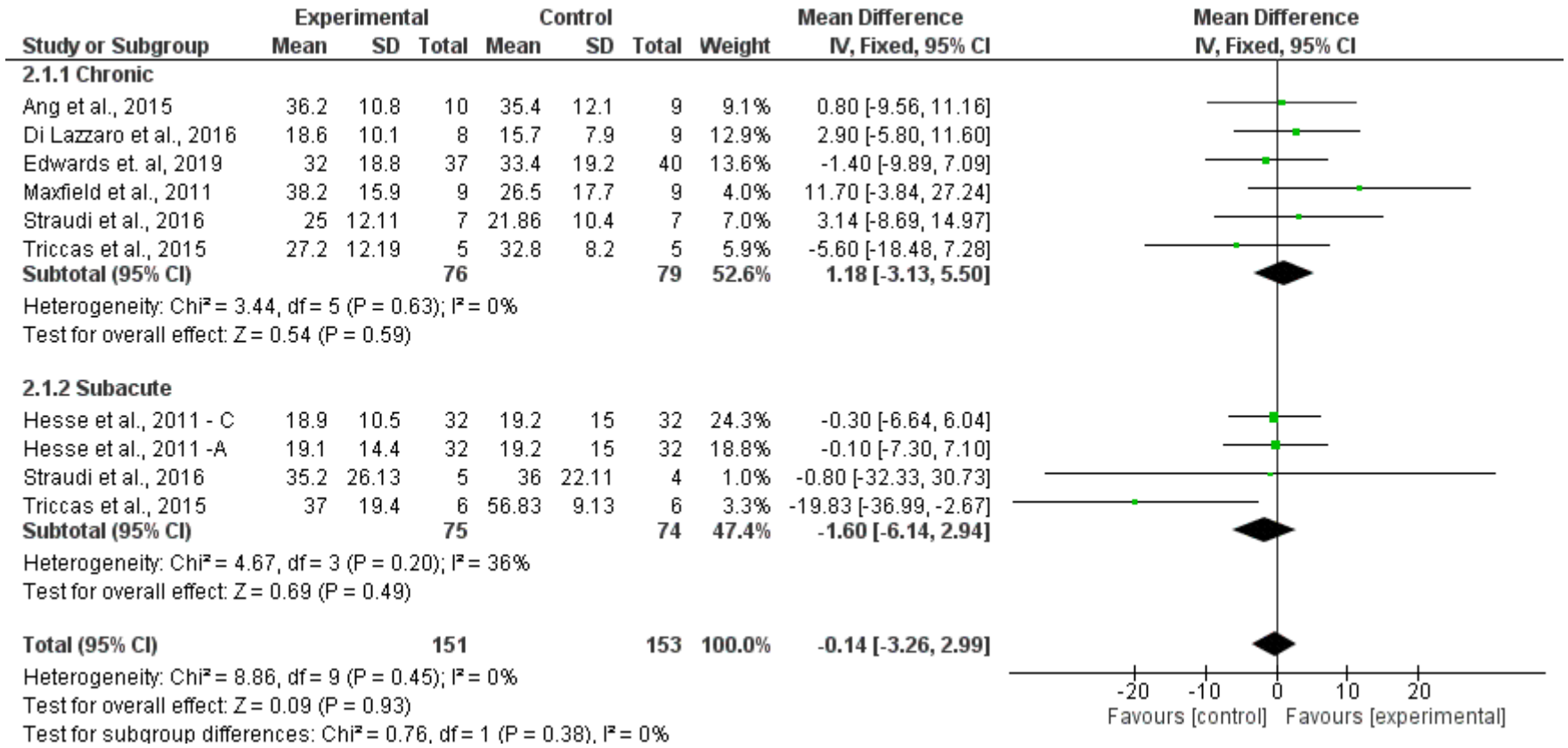

Figure 10. Forest plot for *body structure/function* outcome measures by *phase post stroke* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

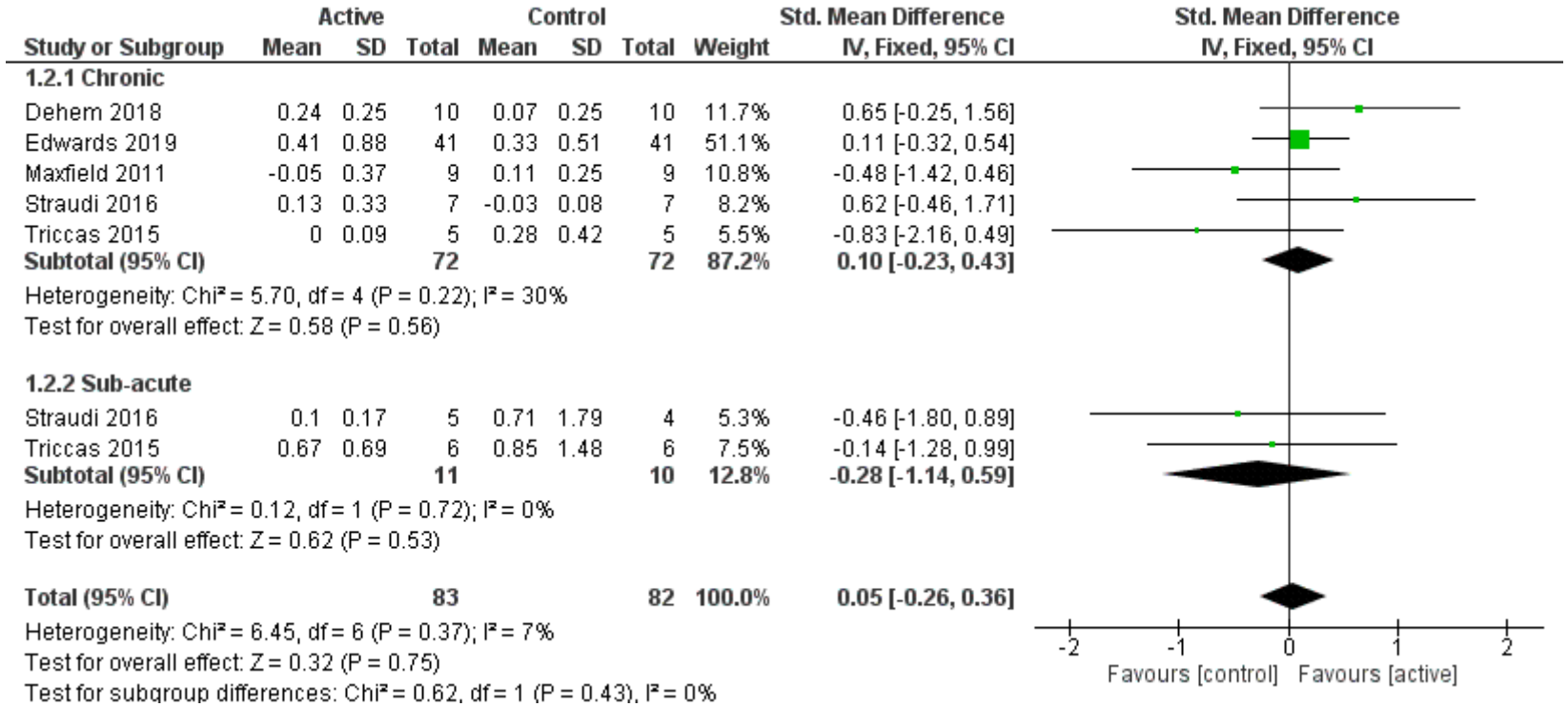

Figure 11. Forest plot for *activity limitation* outcome measures by *phase post stroke* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.2. Arm Support

Seven trials employed end-effector devices(38, 45, 99-102, 104); and one trial employed an exoskeleton device(103).

Body structure/body function - Nonsignificant homogeneous summary effect sizes were found for end-effector (mean difference 0.83, 95% CI -2.51 to 4.18; P =0.62, I^2 = 0%) and exoskeleton (mean difference -11.20, 95% CI -24.82 to 2.42; P = 0.11) devices (Figure 12).

Activity limitation - Nonsignificant homogeneous summary effect sizes were found for end-effector (standard mean difference 0.07, 95% CI -0.26 to 0.40; P= 0.69, I^2 = 7%) and exoskeleton (standard mean difference -0.24, 95% CI -1.07 to 0.60; P = 0.58) devices (Figure 13).

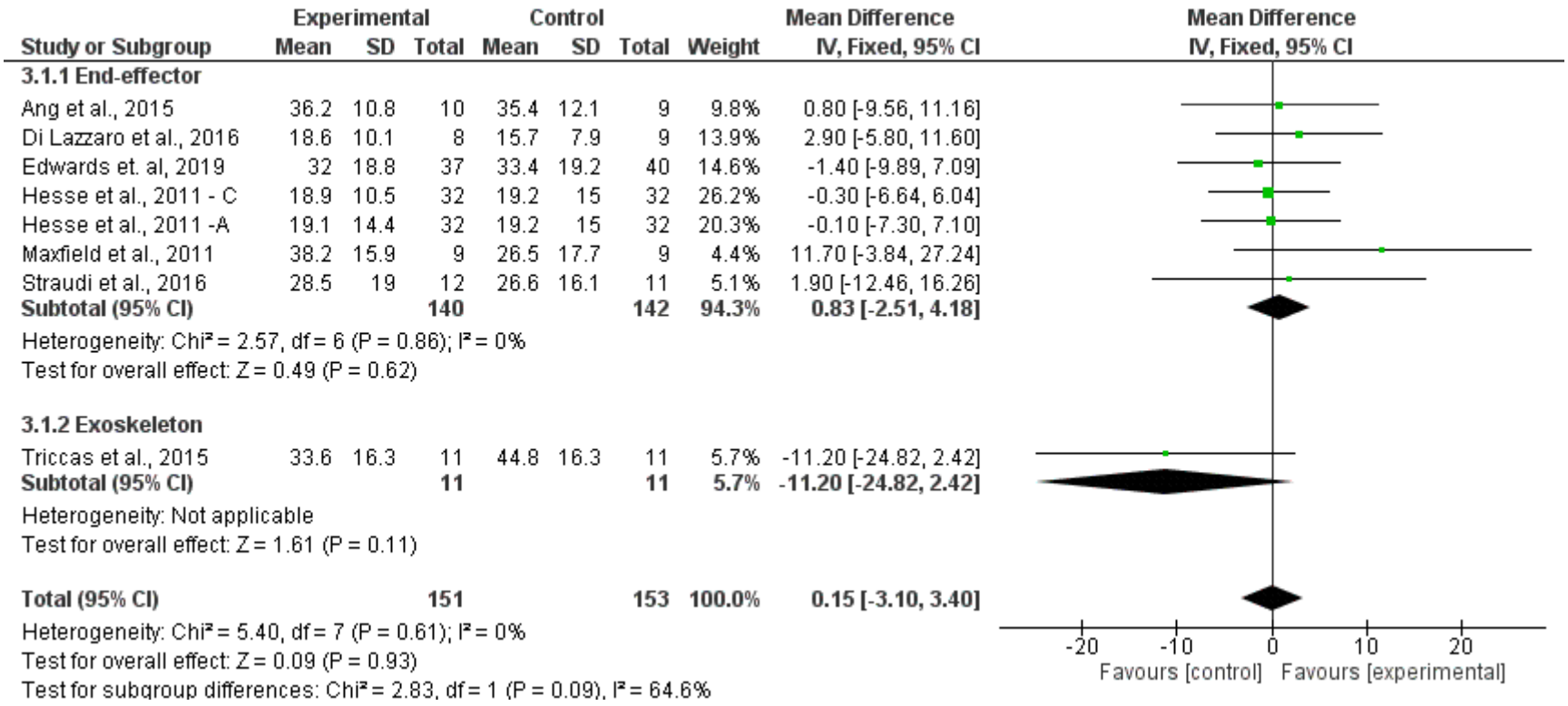

Figure 12. Forest plot for *body structure/ function* outcome measures by *arm support* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

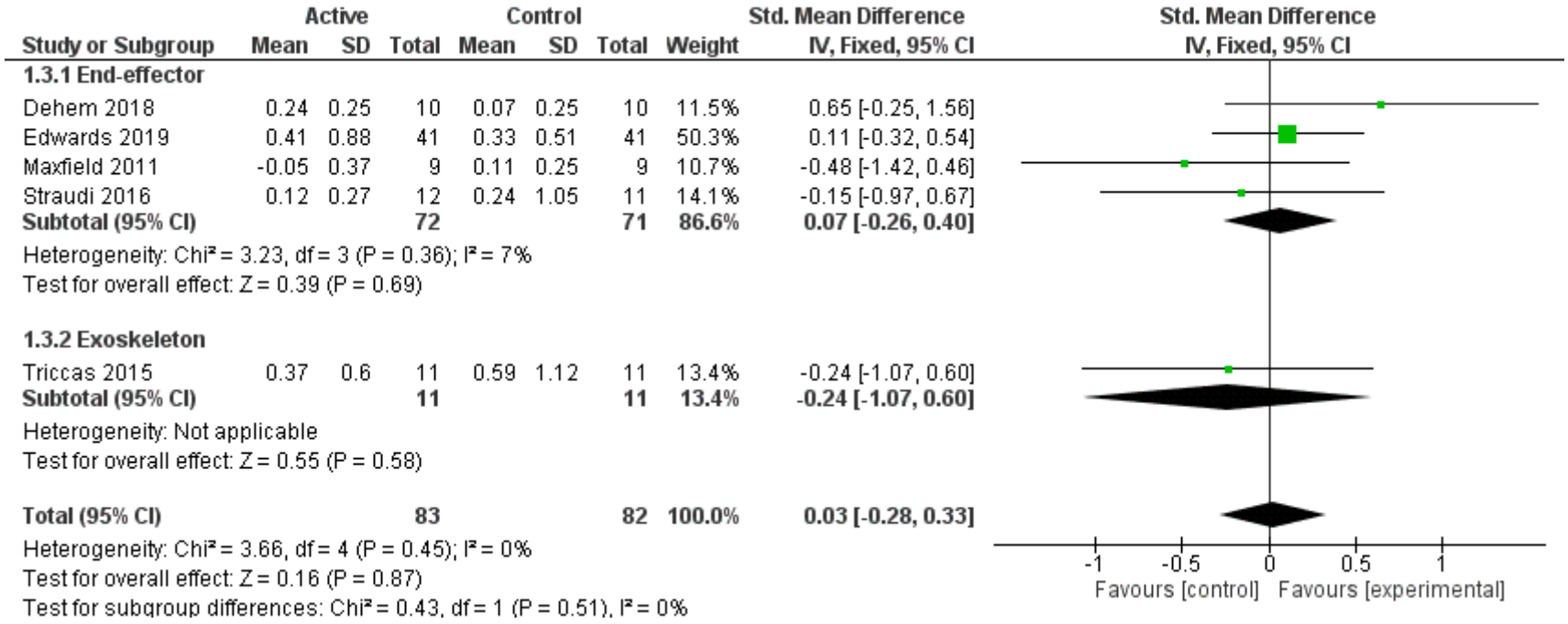

Figure 13. Forest plot for *activity limitation* outcome measures by *arm support* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.3. Joints involved.

Five trials employed robotic devices that involve only shoulder/ elbow movements: MitManus(99); REAplan Robot(104); InMotion 2(38) and ReoGo(101, 102). One trial employed a robotic device that involved only wrist movements: BiManu Track(45). One trial tested a robotic device that involves whole arm movements: Armeo®Spring(103). One trial alternated between two versions of the same device - MitManus *planar* robot, for shoulder/ elbow, and MitManus *wrist* robot, for wrist (100); therefore, this trial was analysed as part of the *whole arm* subgroup.

Body structure / body function - Nonsignificant homogeneous summary effect size were found for the comparisons involving robots with only shoulder/ elbow movements (mean difference 3.28, 95% CI -2.35 to 8.91; P = 0.25, I^2 = 0%), robots with wrist movements only (mean difference -0.21, 95% CI -4.97 to 4.55; P = 0.93, I^2 = 0%) and robots with whole arm movements (mean difference -4.14, 95% CI -11.35 to 3.06; P = 0.26, I^2 = 30%) (Figure 14).

Activity limitation - Nonsignificant homogeneous summary effect size were found for the comparison involving robots with only shoulder/ elbow movements (standard mean difference 0.01, 95% CI -0.50 to 0.52; P = 0.98, I^2 = 36) and for the comparison involving robots with whole arm movements (standard mean difference -0.04, 95% CI -0.35 to 0.42; P = 0.85; I^2= 0%) (Figure 15).

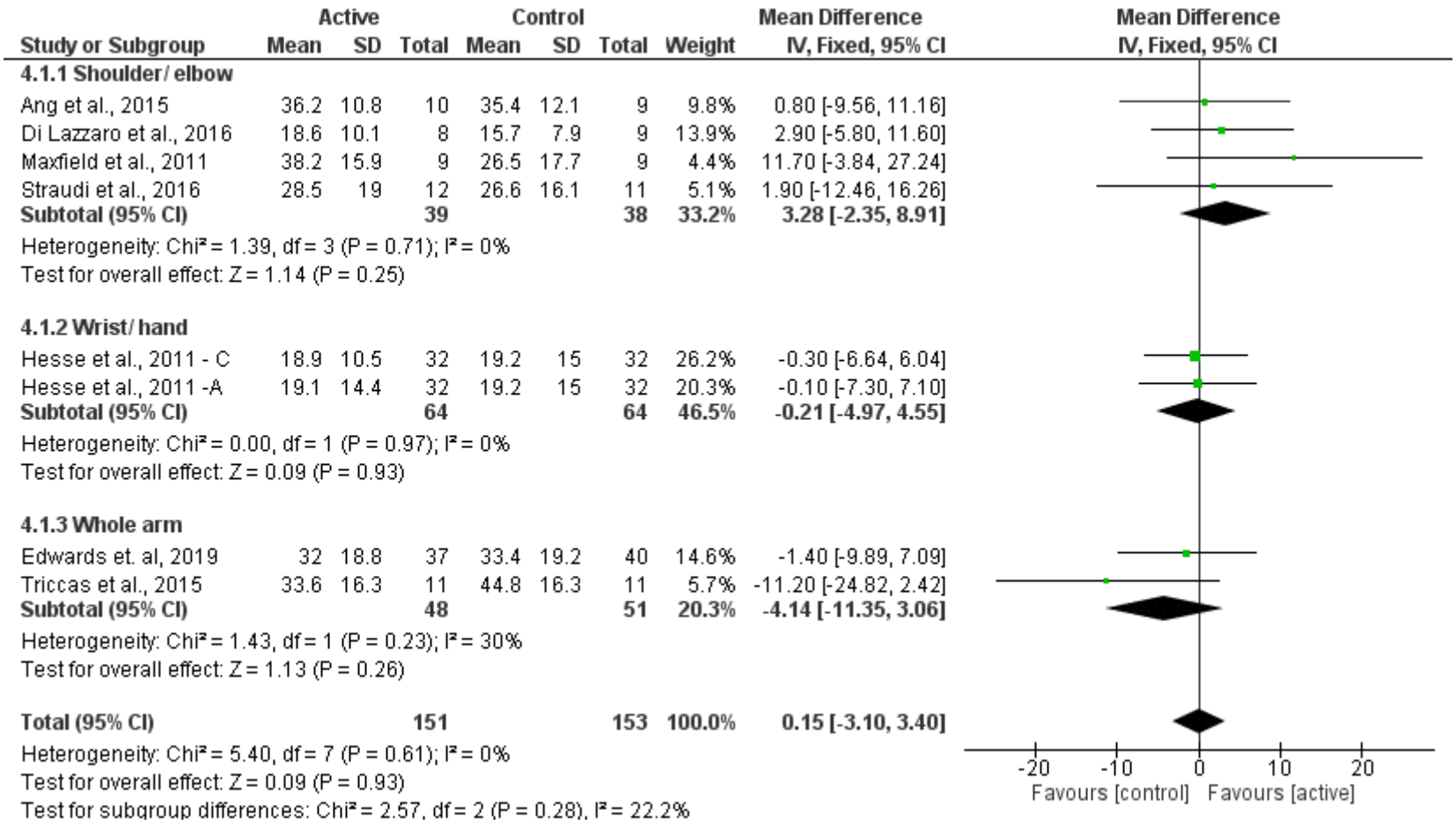

Figure 14. Forest plot for *body structure/ function* outcome measures by *joints involved* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

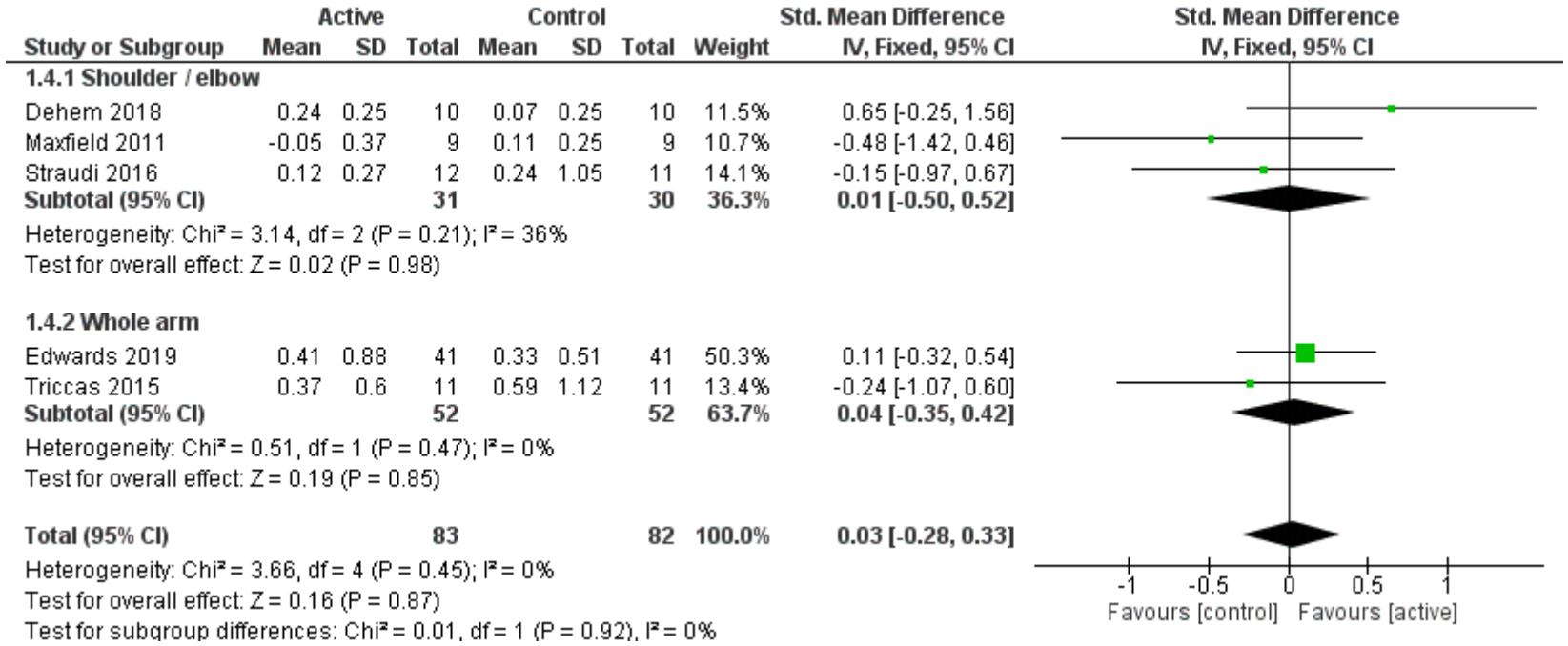

Figure 15. Forest plot for *activity limitation* outcome measures by *joints involved* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.4. Unimanual or bimanual training.

Only one trial(45) employed a robotic device with bimanual training. The results of this trial were split according to the intervention performed: Hesse et a. 2011-A (anodal tDCS) and Hesse et al. -C (cathodal tDCS).

Body structure / body function - For unimanual (mean difference 0.47, 95% CI -3.97 to 4.90; P = 0.84, I^2 = 7%) and bimanual (mean difference -0.21, 95% CI -4.97 to 4.55; P = 0.93, I^2 = 0%) training, nonsignificant homogeneous summary effect sizes were found (Figure 16).

Activity limitation - A nonsignificant homogeneous summary effect size (standard mean difference 0.03, 95% CI -0.28 to 0.33; P = 0.87, I^2 = 0%) was found (Figure 17).

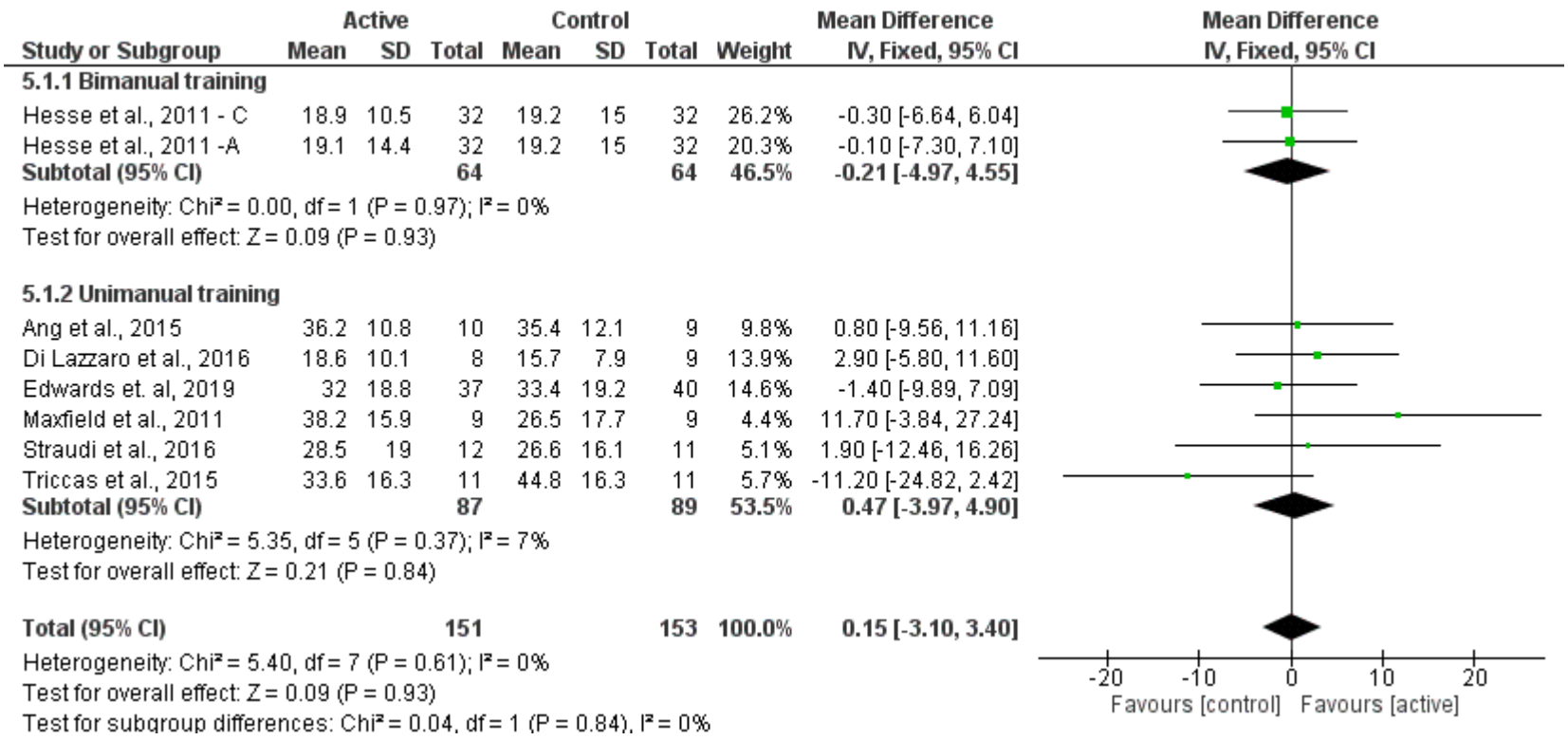

Figure 16. Forest plot for *body structure/function* outcome measure by *unimanual or bimanual training* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

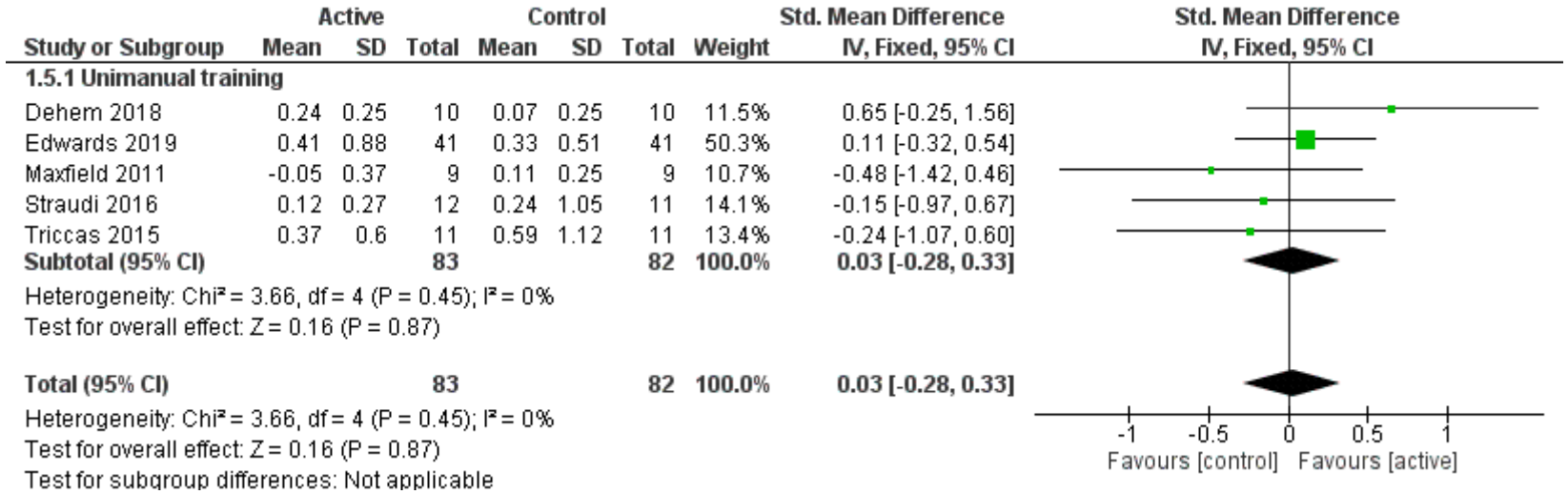

Figure 17. Forest plot for *activity limitation* outcome measure by *unimanual or bimanual training* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.5. NIBS paradigm

Three studies used anodal tDCS [atDCS] to improve cortical excitability of the affected hemisphere(100, 101, 103); three studies placed the tDCS anode over the affected hemisphere and the cathode over the unaffected hemisphere(99, 102, 104); and one study used atDCS and cathodal tDCS [ctDCS] in different groups(45). Only a proof-of-principle trial used continuous thetaburst stimulation [cTBS], a specific paradigm of repetitive TMS(38), to induce long-term depression-like changes in the affected hemisphere.

Body structure / body function - For atDCS, a nonsignificant heterogeneous summary effect size (mean difference -0.78, 95% CI -5.62 to 4.06; P = 0.75, I^2 = 37%) was found. For ctDCS, a nonsignificant SES (mean difference -0.30 95% CI -6.64 to 6.04; P = 0.93) was found. For bilateral anodal and cathodal tDCS, a nonsignificant homogeneous summary effect size (mean difference 1.18, 95% CI -7.22 to 9.58; P = 0.78, I^2 = 0%) was found. For cTBS of the affected hemisphere, a nonsignificant SES (mean difference 2.90, 95% CI -5.80 to 11.60; P = 0.51) was found (Figure 18).

Activity limitation - For atDCS of the affected hemisphere, a nonsignificant homogeneous summary effect size was found (standard mean difference -0.04, 95% CI -0.39 to 0.32; P = 0.84, I^2 = 0%). For bilateral anodal and cathodal tDCS, a nonsignificant homogeneous summary effect size was found (standard mean difference -0.21, 95% CI -0.40 to 0.82; P = 0.50, I^2=40%) (Figure 19).

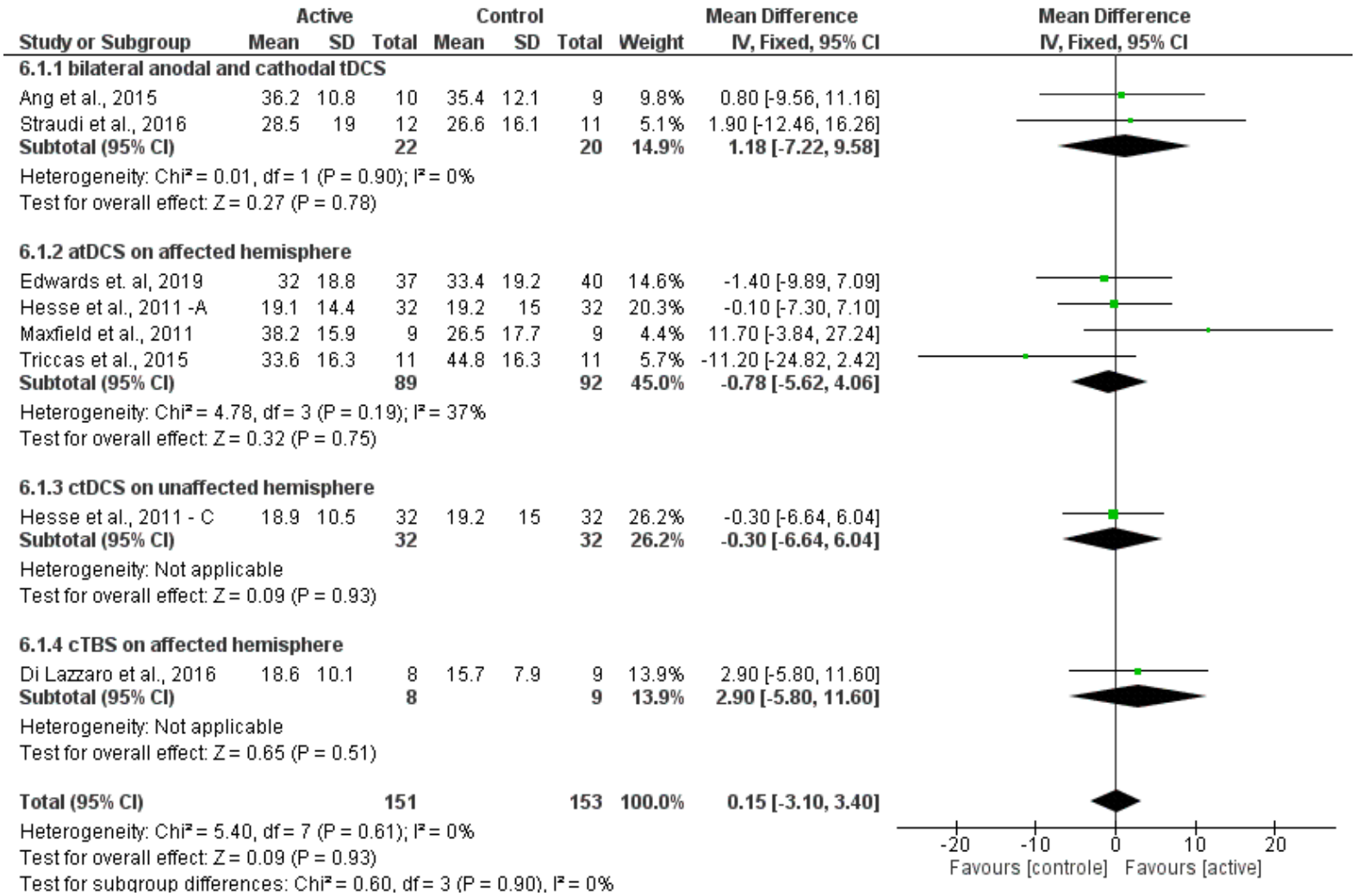

Figure 18. Forest plot for *body structure/function* outcome measures by *NIBS paradigm* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

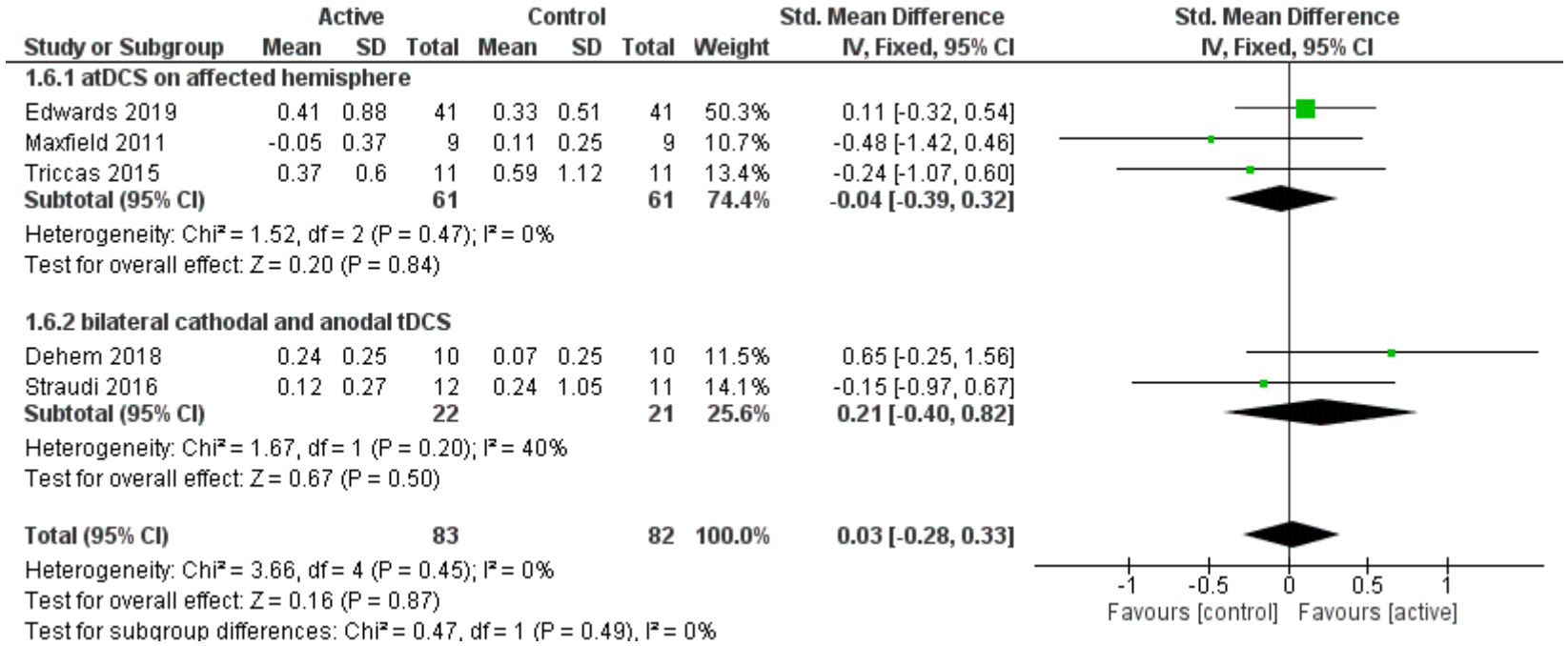

Figure 19. Forest plot for *activity limitation* outcome measures by *NIBS paradigm* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.6. Timing of stimulation

Five studies applied NIBS during the first 20 to 30 minutes of RT(45, 101-104) and three, before RT(38, 99, 100).

Body structure / body function - Nonsignificant homogeneous summary effect size were found for NIBS applied during RT (mean difference -0.21, 95% CI -4.34 to 3.93; P = 0.92, I^2 = 17%) and for NIBS applied before RT (mean difference 0.72, 95% CI -4.52 to 5.97; P = 0.79, I^2 = 0%) (Figure 20).

Activity limitation - Nonsignificant homogeneous summary effect sizes were found for both NIBS applied during RT (standard mean difference -0.06, 95% CI -0.50 to 0.38; P = 0.79, I^2 = 11%) and before RT (standard mean difference 0.11; 95% CI -0.32 to 0.54; P = 0.62) (Figure 21).

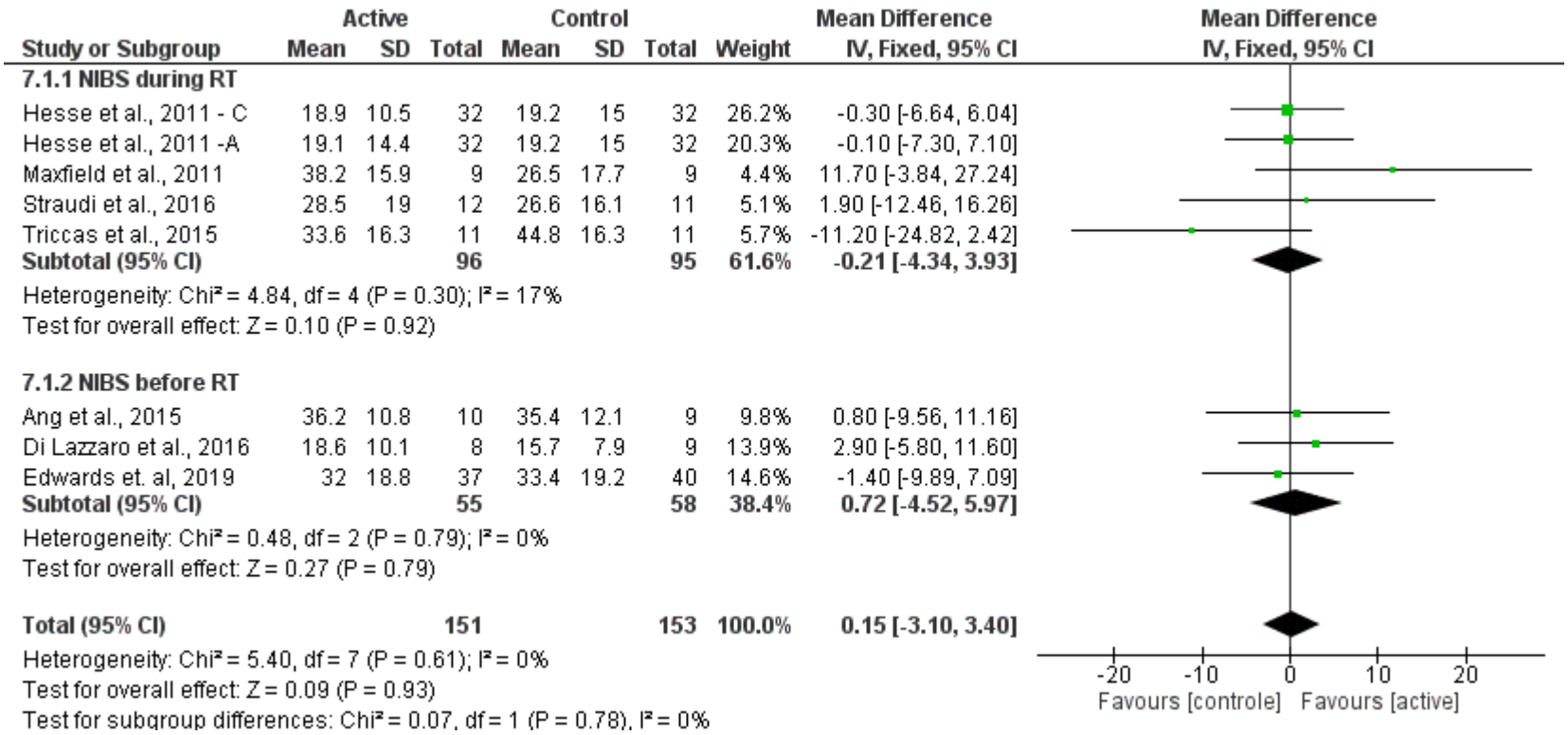

Figure 20. Forest plot for *body structure/function* outcome measures by *timing of stimulation* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

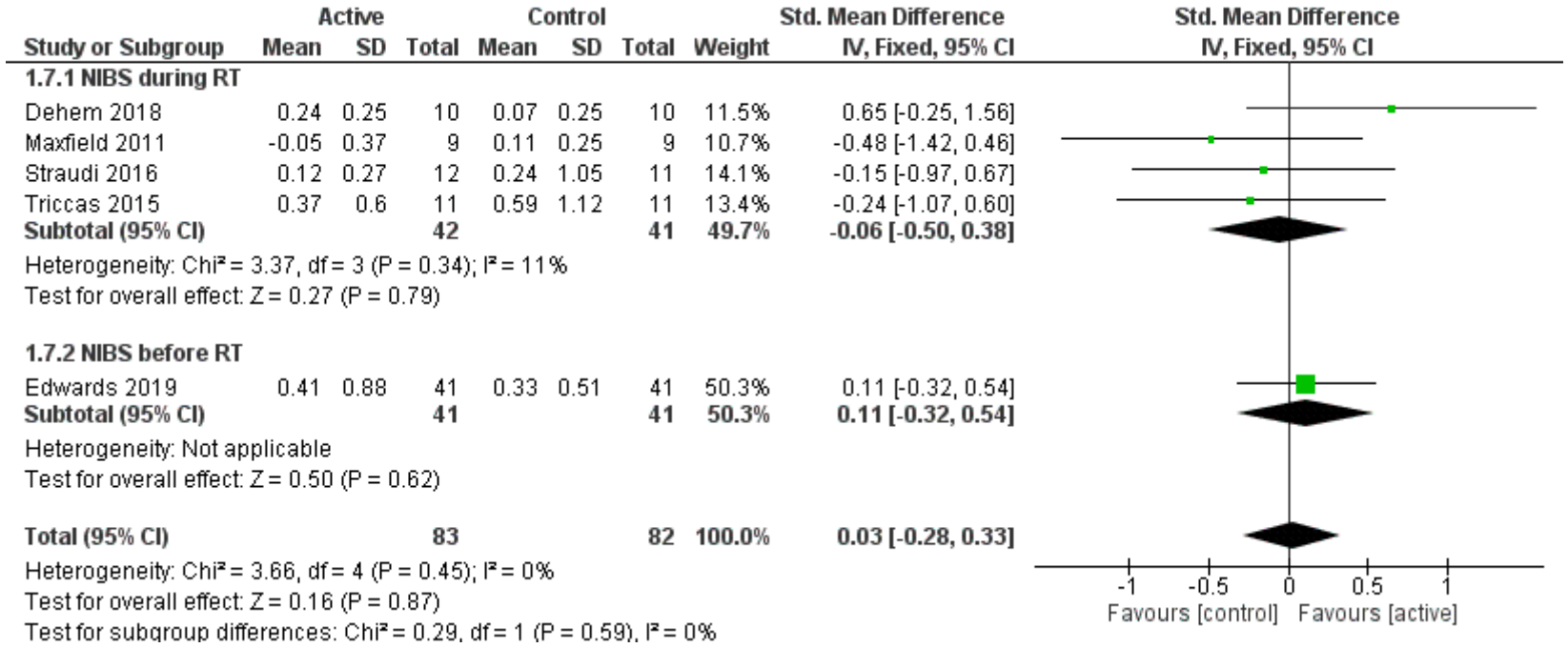

Figure 21. Forest plot for *activity limitation* outcome measures by *timing of stimulation* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.5.7. Number of sessions

In one cross-over trial with one active and one sham session of treatment, the results of the first session were included in the analysis(104). The following trials had a parallel design: in three trials, 7 to 12 sessions of treatment were performed(38, 99, 102); in two, from 13 to 24 sessions(101, 103) and in other two, from 25 to 36 sessions(45, 100).

Body structure / body function - Nonsignificant homogeneous summary effect sizes were found for trials in which 7 to 12 sessions (mean difference 2.01, 95% CI -4.03 to 8.05; P = 0.51, I^2 = 0%), and from 25 to 36 sessions (mean difference -0.50, 95% CI -4.65 to 3.66; P = 0.81, I^2 = 0%). A nonsignificant heterogeneous summary effect size was fond for trials with 13 to 24 sessions (mean difference -0.07, 95% CI -22.50 to 22.36; P = 1.00, I^2 = 79%) (Figure 22).

Activity limitation – Nonsignificant homogeneous summary effect sizes were found for the first session of the cross-over trial (standard mean difference 0.65, 95% CI -0.25 to 1.56; P =0.16); for trials with 7 to 12 sessions (standard mean difference -0.15, 95% CI -0.97 to 0.67; P = 0.71), 13-24 sessions (standard mean difference -0.35, 95% CI -0.97 to 0.28; P = 0.28, I^2 = 0%) and 25-36 sessions (standard mean difference 0.11; 95% CI -0.32 to 0.54; P = 0.62 (Figure 23).

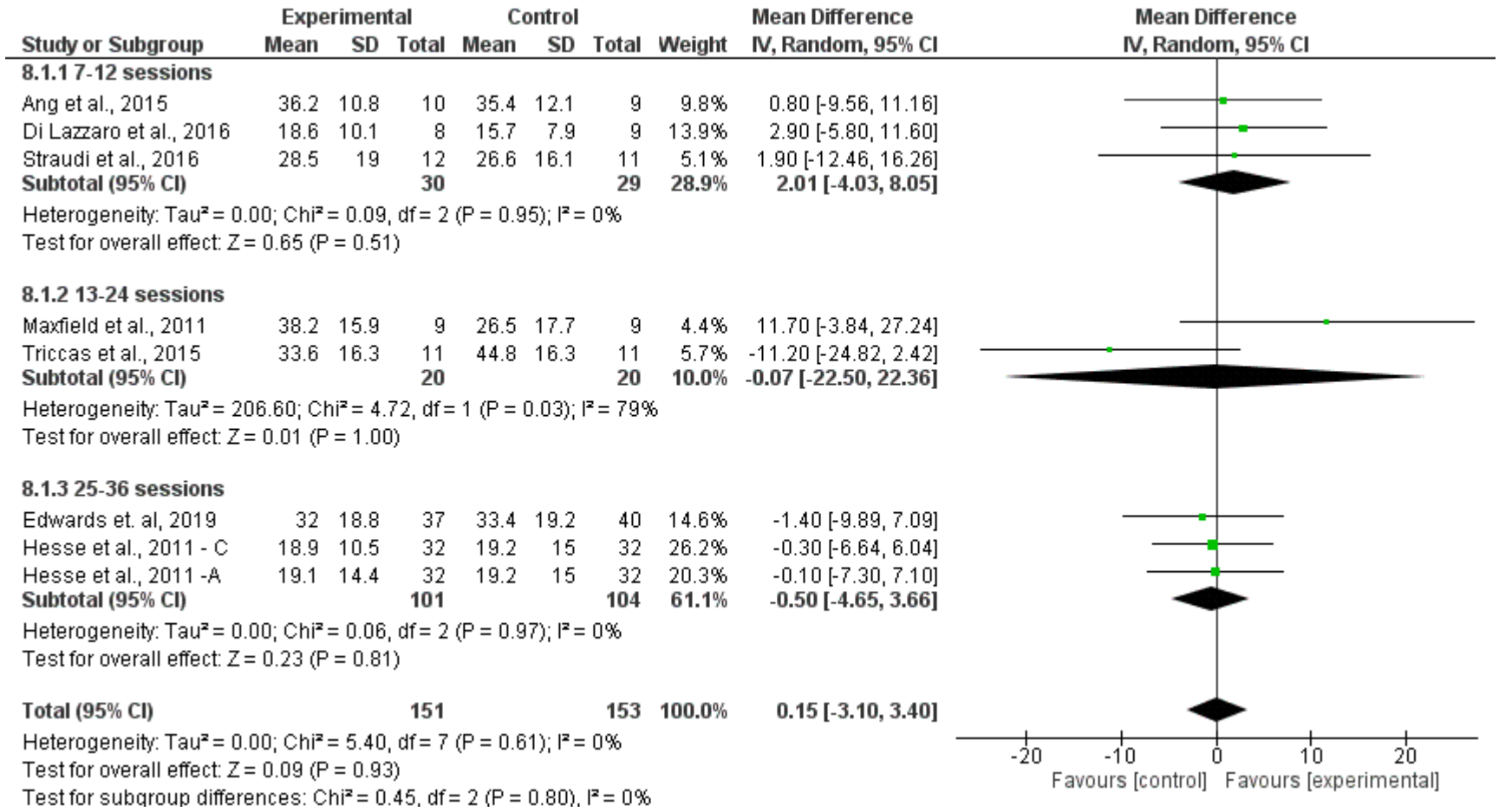

Figure 22. Forest plot for *body structure/function* outcome measures by *number of sessions* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

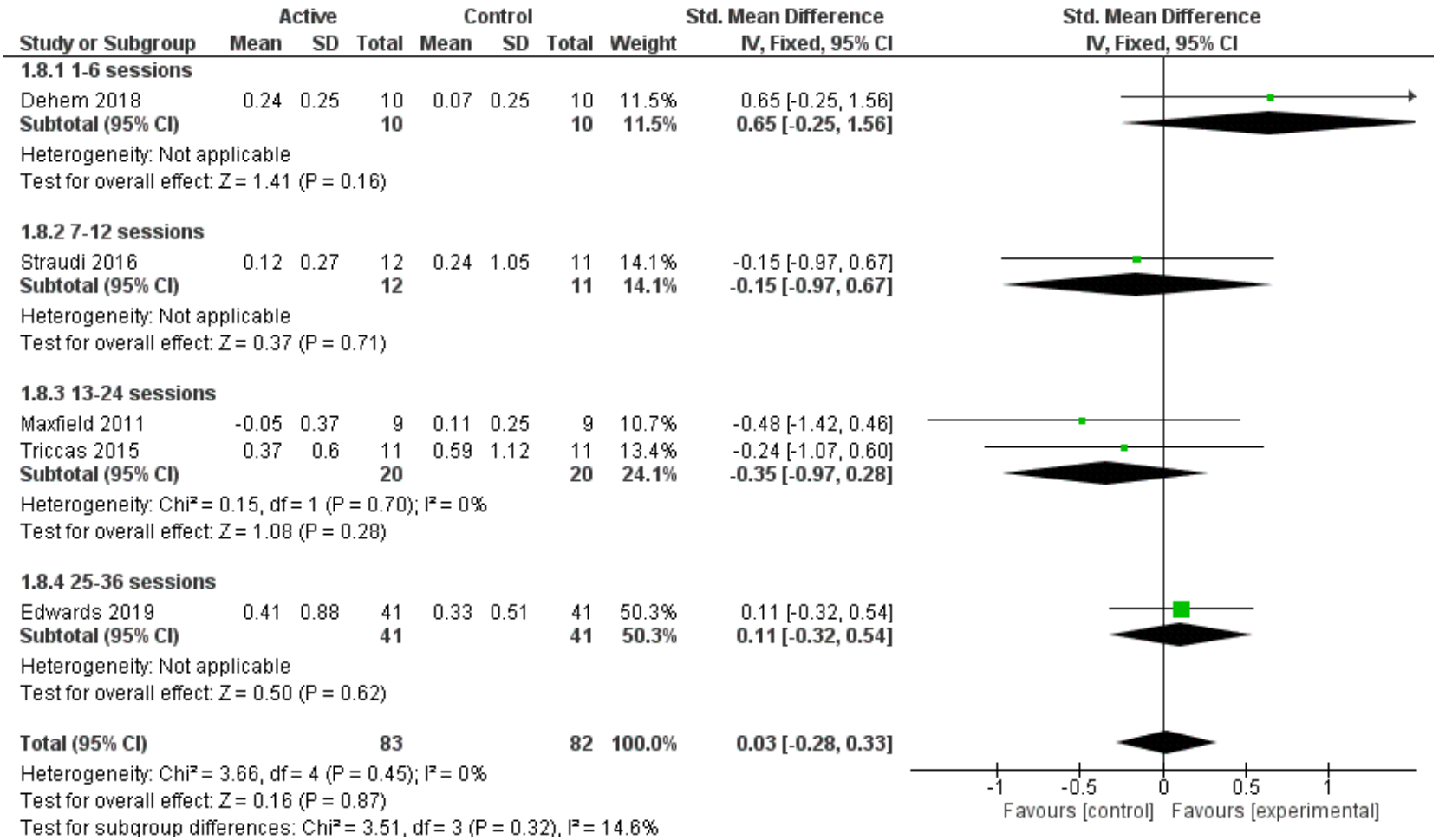

Figure 23. Forest plot for *activity limitation* outcome measures by *number of sessions* subgroups. CI = Confidence interval; IV = inverse variance; SD = Standard Deviation.

5.6. Quality of the evidence

An Evidence Profile was performed on GRADE -pro GDT. Quality was considered high for both *body structure/function* and *activity limitation* outcome measures, suggesting that further research is very unlikely to change the confidence in the estimate of the effect with the paradigms employed in these studies(87) (Table 6). However, quality of the evidence ranged from very low to high scores according to subgroup analyses (Table 7).

Table 6. Quality of the evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIBS + RT**	**sham NIBS + RT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Body Structure/Function												
8	randomised trials	not serious	not serious	not serious	not serious	none	151	153	-	MD 0.15 higher (-3.1 lower to 3.4 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Activity Limitation												
5	randomised trials	not serious	not serious	not serious	not serious	none	83	82	-	SMD 0.03 higher (-0.28 lower to 0.33 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviation: CI: Confidence interval; MD: Mean difference; SMD: Standardized mean difference

Table 7. Summary of the quality of evidence for different subgroups according to outcome measures.

Subgroup	*Body structure/function*	*Activity Limitation*
Phase post stroke – Chronic	MODERATE	MODERATE
Phase post stroke - Subacute	MODERATE	LOW
Arm support - End-effector	HIGH	HIGH
Arm support – Exoskeleton	VERY LOW	LOW
Joints involved - Shoulder / elbow	LOW	HIGH
Joints involved - Wrist/ hand	HIGH	NR
Joints involved - Whole arm	LOW	HIGH
Upper limb involved - Bimanual training	HIGH	NR
Upper limb involved - Unimanual training	HIGH	HIGH
NIBS paradigm - atDCS of affected hemisphere	HIGH	HIGH
NIBS paradigm - bilateral cathodal and anodal tDCS	HIGH	LOW
NIBS paradigm - ctDCS on unaffected hemisphere	HIGH	NR
NIBS paradigm - cTBS on affected hemisphere	MODERATE	NR
Timing of stimulation - NIBS during RT	HIGH	HIGH
Timing of stimulation - NIBS before RT	HIGH	MODERATE
Number of sessions - 1-6 sessions	NR	VERY LOW
Number of sessions - 7-12 sessions	MODERATE	MODERATE
Number of sessions - 13-24 sessions	LOW	LOW
Number of sessions - 25-36 sessions	HIGH	MODERATE

Abbreviation: NR = not reported

A total of 324 subjects were included in this meta-analysis, and there was no statistical heterogeneity in the results. Overall, the quality of the evidence was high. Despite the increase in the number of clinical trials that assessed NIBS as an add-on intervention of RT over the past years, there is no evidence to support the hypothesis that effects of RT on outcomes of body structure and function or on outcomes of activity limitation can be enhanced by NIBS. This conclusion is in line with the conclusion of a previous narrative review(30). Despite the lack of statistical heterogeneity, however, the NIBS paradigms and motor training protocols were very diverse across studies.

Four different NIBS paradigms were employed in the included studies and all, except one, were based on the hypothesis of interhemispheric competition model. This hypothesis seems not to apply to subjects with stroke with different levels of impairment(40, 105) or lesion location(106). Other variables that raise concerns about the potential of NIBS as a therapeutic tool are inter and intra-subject variability that can be caused by individual brain anatomy, level of ongoing cortical activity, muscle pre-contraction, subject attentional focus, and even menstrual cycle and circadian rhythms(107). Neuronavigated NIBS and EEG monitoring of stimulation effects in real time may be useful to decrease variability of effects(107). In order to select patients for clinical trials or proof-of-principle studies involving NIBS and motor training, understanding of mechanisms and biomarkers of responsiveness may be key to enhance the probability of success(108).

The need to tailor NIBS interventions to particular characteristics has been underscored by the negative results of the NICHE study, the largest clinical trial to date in which low-frequency rTMS was administered to the unaffected hemisphere of subjects in the chronic phase after stroke with the goal of down-regulating excessive inhibition of the affected hemisphere, prior to sessions of motor training(109). Another plausible

explanation of the negative results of the NICHE trial as well as those of this meta-analysis is a ceiling effect: the impact of high-intensity motor practice on improvement of performance may exceed the magnitude of NIBS effects.

Alternatively, the association of NIBS and RT may have effects on retention of improved motor performance rather on immediate effects of motor training. Results of a trial that randomized 164 patients to active or sham atDCS of the motor cortex of the affected hemisphere prior to RT(100), included in this review, contradict this hypothesis. After 36 sessions of treatment, the benefits of RT were unchanged by add-on atDCS. However, at 6 months post, the percentage of "responders" (improvement in FM >5 points) was significant greater in the control group than in the active group. Finally, it is necessary to consider that NIBS objectives may not only be to enhance effects of training, but also to yield comparable results of a training intervention when administered for a shorter period of time. No studies addressing this issue were identified.

Another point that deserves attention is that an optimal training RT paradigm to be associated with NIBS has not yet been determined. Giaccobe et al (2013) demonstrated that a single session of tDCS can enhance effects of motor training when applied immediately prior to RT but not during or after this intervention. Also, alternating sessions between proximal and distal joints seems to be a more efficient strategy to improve upper limb motor performance than isolated block sessions of proximal and distal joints(100, 110). It remains to be determined if this result also applies to NIBS + robotic training because no head-to-head comparisons of different paradigms of training associated with the same NIBS intervention were found. Finally, the role of robotic bimanual training remains to be clarified. This intervention may enhance the output to the paretic limb in some individuals with stroke(111) but we only included in this review one study that applied this approach(45).

Clinical trials that test a large number of combinations of NIBS and training paradigms may be challenging due to resource and time constraints. Kinematic measurements are sensitive and correlate well with clinical assessment in subjects with stroke(112). Therefore, proof-of-principle studies that assess responsiveness to different paradigms may inform the design of larger clinical trials.

None of the studies included in this meta-analysis chose outcomes of activity limitation as primary endpoints, and only one study assessed the ARAT(103), an outcome recommended by the Stroke Recovery and Rehabilitation Roundtable(89). Future studies may include this outcome measure as performed in the RATULS (Robot Assisted Training for the Upper Limb after Stroke) study(110). No significant changes were reported for the ARAT in RATULS(110), a trial in which RT was not associated with functional training. On the other hand, a smaller trial compared RT training (n = 22) with RT associated with therapist-assisted functional training (n=23) and found significant improvement on activity limitation favouring the experimental group(113). Overall, these results suggest that changes in measures of body structure and function or activity limitation may vary according to the specific model of motor training. It is possible that translation-to-task interventions as add-on therapies to RT are required to ameliorate activity limitation. In trials that plan to address the possibility of boosting the effect of RT by adding NIBS to enhance activity, inclusion of translation-to-task interventions should be considered.

Limitations

The number of included studies in this systematic review was relatively low but the sample size (n=324) was greater than those reported in other meta-analyses about effects of specific rehabilitation interventions in stroke. For instance, a meta-analysis(114) evaluated the effectiveness of a combination of NIBS and virtual reality included 213 individuals.

The present review did not explore some others possible subgroups that would probably interfere at motor and functional recovery, due to lack of sufficient individual data about baseline motor impairment, type of stroke, site of lesion and training intensity measured by the number of repetitions performed per session.

Summary of findings and remaining gaps

This systematic review found no evidence that NIBS, as an add-on intervention to RT, improves outcomes of upper limb motor impairments or activity in subjects with stroke. Overall, but not in subgroup analyses, the quality of this evidence was considered high for both outcomes. The greatest gaps of information are: use of exoskeleton robotic device and training concomitant of the whole joints of the arm for motor impairments; training with patients in a subacute phase post stroke; use of exoskeleton devices; bimanual motor training and motor training involving distal joints for activity limitation.

It is advisable to consider performance of proof-of-principle studies involving NIBS and different motor training paradigms, in order to better understand mechanisms underlying these interventions, as well as biomarkers of responsiveness. Furthermore, it is critical to assess effects of translation to task training as a complement for NIBS and RT, in order to enhance performance of activities of daily living.

According to this systematic review and meta-analysis, there is a lack of evidence that NIBS, as an add-on intervention to RT, improves outcomes of upper limb motor function or activity in subjects with stroke.

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Supplementary Materials

1. Approval of Research Ethics Committee of USP Medical School . March, 2017 (nº0085/17)

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COMITÊ DE ÉTICA EM PESQUISA

APROVAÇÃO

O Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, em sessão de 22/03/2017, **APROVOU** o Protocolo de Pesquisa nº **0085/17** intitulado**: "ASSOCIAÇÃO DE TERAPIA ROBÓTICA E ESTIMULAÇÃO CEREBRAL NÃO-INVASIVA NA REABILITAÇÃO DO MEMBRO SUPERIOR PÓS-AVC: REVISÃO SISTEMÁTICA E METANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS."** apresentado pelo **Departamento de NEUROLOGIA**

Cabe ao pesquisador elaborar e apresentar ao CEP-FMUSP, os relatórios parciais e final sobre a pesquisa (Resolução do Conselho Nacional de Saúde nº 466/12, inciso IX.2, letra "c").

Pesquisador (a) Responsável: Adriana Bastos Conforto
Pesquisador (a) Executante: Suzana Bleckmann Reis

CEP-FMUSP, 22 de Março de 2017.

Profa. Dra. Maria Aparecida Azevedo Koike Folgueira
Coordenador
Comitê de Ética em Pesquisa

Comitê de Ética em Pesquisa da Faculdade de Medicina

2. Protocol registered on the PROSPERO Platform (CRD42017054563).

Systematic review

This record cannot be edited because it is being assessed by the editorial team

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The effects of robotic therapy associated with non-invasive brain stimulation on upper limb rehabilitation after stroke:
systematic review and meta-analysis of randomized clinical trials

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

02/01/2017

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/03/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes

Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Suzana Reis

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Dra Suzana

7. * Named contact email.

Give the electronic mail address of the named contact.

suzana.reis@ymail.com

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information

Give the full postal address for the named contact.

255 Ovídeo Pires de Campos St. 5th Floor/5080

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+55 11 2661-7955

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Sao Paulo General Hospital

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Professor Adriana Conforto. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo/Fundação Faculdade de Medicina

Professor Wanderley Bernardo. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo/Fundação Faculdade de Medicina Ms Suzana Reis.

Mr Carlos Oshiro.

Hermano Igo Krebs. MIT, Boston, MA, US

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

The University of Sao Paulo General Hospital is the sponsor for the research, and where it will be carried out. No funding has, however, been received for this study.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The objective of this review and meta-analysis is to evaluate the evidence for the efficacy of robotic therapy associated with non-invasive brain stimulation for upper limb rehabilitation after stroke.

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period).
Do NOT enter the full search strategy (it may be provided as a link or attachment.)

Seven scientific databases will be systematically searched: MEDLINE (Medical Literature Analysis and Retrieval System Online; through the PubMed interface); EMBASE (Excerpt Medical Database); The Cochrane Central Register of
Controlled Trials (CENTRAL); LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde; through the Biblioteca Virtual em Saúde interface); CINAHL (Cumulative Index to Nursing and Allied Health Literature; through the EBSCO interface); DORIS (Database of Research in Stroke) and PEDro (the Physiotherapy Evidence Database).

In addition, a handsearch will be done by scanning the reference lists of articles, consulting experts in the field and searching non-published studies from the following online archives of theses and online trials registers: ClinicalTrials; Biblioteca Digital de Teses e Dissertações da USP; Doris; Biblioteca Brasileira Digital de Teses e Dissertações; Portal Domínio Público; Banco de Teses & Dissertações CAPES.

The following key words will be used: stroke, robot, and transcranial direct current stimulation.

The term “upper limb” was not selected in order to avoid missing studies that involve both lower and upper extremities. The term “tDCS” will be used instead of “NIBS”, because 1. NIBS is not registered as a controlled vocabulary term; and 2. We noticed that when the key word “tDCS” is exploded, records of tACS, RNS and TMS are automatically detected, and in databases which do not give the option to “explode” terms, the key words tACS, RNS and TMS will be used.

Thereby, as a general search strategy, combinations of these key words will be applied, according to the availability of each database; and, whenever possible, the filter “random” will be used.

The full search strategy can be found in the attached PDF document (link provided below).

No publication data, or language restrictions will be imposed.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.

Do NOT provide links to your search results.

https://www.crd.york.ac.uk/PROSPEROFILES/54563_STRATEGY_20170008.pdf

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Stroke. Upper limb rehabilitation.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients with upper limb paresis due to stroke will be included. No restrictions will be imposed regarding: age, residual upper limb motor-function, time since last stroke, type of stroke or history of previous strokes. Cerebellar strokes or strokes in cerebellar pathways will not be included, except in relation to irrelevant parts of the sample for which the data has been separately reported.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Trials that consider the association of robotic therapy and NIBS for the improvement of upper limb motor performance.

Robotics will be defined as “The application of electronic computerized control systems to mechanical devices designed to perform human function […].” (PubMed [MEDLINE], MeSH database, 2005); and NIBS will be defined considering the most used forms of tES (tDCS; tACS; RNS) and TMS.

All of the protocols associating these two interventions as rehabilitation tools will be included. Studies using robotic devices and TMS only as an evaluation tool for kinetic and kinematic analyses or for cortical excitability will not be included.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Trials that consider as control groups: robot-assisted therapy associated with sham NIBS; robot-assisted therapy associated with usual care; or robot-assisted therapy alone.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Randomized clinical trials with parallel design. Abstracts and finalized but non-published studies will be included if they present sufficient effect measures, or authors will be contacted and asked to provide any missing data. Cluster or crossover trials will not be included.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The motor performance of the upper limb measured using standard scales, such as the Fugl-Meyer assessment scale; the Wolf motor function test; the Ashworth scale; the action research arm test; the motor activity log; the box and blocks test; the nine hole peg test; the motor assessment scale; and the Jebsen Taylor hand test.

Timing and effect measures

Post-intervention mean and standard deviation data will be extracted from each study.

If more than one effect measure is present, the choice of scale (given in full above) to be used will be determined as follows: 1. FM; 2. WMFT; 3. Ashworth; 4. ARAT; 5. MAL; 6. BBT; 7. NHPT; 8. MAS; and 9. JTHT. The choice of timing will be determined in the following manner: 1. From the 25th session; 2. from the 19th to the 24th session; 3. from the 13th to the 18th session; 4. up to the 12th session.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

None.

Timing and effect

measures None.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two reviewers to identify studies that potentially meet the inclusion criteria. In case

of disagreement, the issue will be resolved by consensus. If consensus is not possible, a third reviewer will be consulted.

Reading of the full-text articles will be done by the same two reviewers, and studies will be selected according to the inclusion and exclusion criteria. Disagreements between the two reviewers will again be resolved by consensus, with the involvement of a third reviewer if required.

Data will be extracted from the records to a specific extraction form by two reviewers. Disagreements will be resolved by consensus, and if consensus is not possible, a third reviewer will be consulted. If more than one record of the same study is identified, the data will be compiled once in the extraction form. If inconsistencies across reports are identified, or, if there is a lack of, or unclear information, authors will be asked for clarification, or requests will be made for the provision of the missing information. A maximum of three emails will be sent in an attempt to gain contact.

The following information will be extracted from each study:

a) Population characteristics:

Age, gender, history of previous strokes, time since last stroke (acute, sub-acute, chronic), type of stroke, affected hemisphere, site of the lesion, stroke severity, handedness.

b) Intervention characteristics:

General: intervention design; number and frequency of sessions; number in each group.

Non-invasive brain stimulation: sort of NIBS, protocol used (including parameters of stimulation and the type equipment used); device used; application duration, timing of application (online; offline).

Robot-therapy: device used; joints targeted (shoulder/elbow; wrist/hand); bimanual or unimanual approach; principle of the device (exoskeletal or end-effector); amount of movement per session.

Outcome measures: mean and standard deviation post-intervention in the scale being used.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

Publication bias will be assessed independendly by two reviewers. Disagreements will be settled by consensus. If consensus is not possible, a third reviewer will be consulted. If inconsistencies are identified, or, if there is a lack of, or unclear information, authors will be asked for clarification or to request that the missing information is provided. A maximum of three emails will sent in an attempt to gain contact.

The following domains will be assessed for each study: randomization; concealment allocation; blinding; intention-to-treat principle; extent of loss; sample homogeneity; sample representativeness; sample calculation; and information regarding early cessation of trials. For each domain, the study will be classified as high risk of bias; low risk of bias; or unclear risk of bias.

Classification of bias will not be used as a criterion on which to exclude studies from a possible meta-analysis, but studies classified as high risk of bias or unclear will be analyzed in subgroups, and will be included in an evidence quality analysis using GRADEpro GDT.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

The effect measures (mean and standard deviations) will be entered into RevMan 5.1. (Review Manager 5.1) and a forest plot, funnel plot, heterogeneity assessment and standardized mean difference calculation will be

conducted. In addition, 95% confidence intervals will be determined, random effects modelling will be conducted, and the Mantel-Haenszel method applied.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

The intention is to conduct subgroup meta-analyses for the following: risk of bias; joints involved (shoulder; elbow; wrist; hand); time since the last stroke (acute; sub-acute; chronic); unimanual or bimanual approach; NIBS principle (increasing or decreasing of cortical excitability); timing of stimulation (online; offline).

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review. Type of review

Cost effectiveness	No
Diagnostic	No
Epidemiologic	No
Individual patient data (IPD) meta-analysis	No
Intervention	No
Meta-analysis	Yes
Methodology	No
Narrative synthesis	No
Network meta-analysis	No
Pre-clinical	No
Prevention	No
Prognostic	No
Prospective meta-analysis (PMA)	No
Review of reviews	No
Service delivery	No
Synthesis of qualitative studies	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	No

Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	No
Child health	No
Complementary therapies	No
Crime and justice	No
Dental	No
Digestive system	No
Ear, nose and throat	No
Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	No
International development	No
Mental health and behavioural conditions	No
Musculoskeletal	No
Neurological	No
Nursing	No
Obstetrics and gynaecology	No
Oral health	No
Palliative care	No
Perioperative care	No

Physiotherapy	No
Pregnancy and childbirth	No
Public health (including social determinants of health)	No
Rehabilitation	No
Respiratory disorders	No
Service delivery	No
Skin disorders	No
Social care	No
Surgery	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	No
Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

On completion of the review, a paper will be submitted to a leading journal in the field.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use. Systematic review

Meta-analysis

Stroke

Rehabilitation

Upper limbs

Robotic

Non-invasive brain stimulation

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.