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Influence of Sensory Re-training on Cortical Reorganization in Peripheral Neuropathy: A Systematic Review

Running Title: Cortical Reorganization After Sensory Re-training

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ABSTRACT

This study systematically reviewed the literature about sensory re-training effect in comparison to other rehabilitative techniques on cortical reorganization in patients with peripheral neuropathic pain. After performing an electronic search, risk of bias was assessed using the revised Cochrane Risk of Bias Tool for randomized controlled trials and the Risk of Bias in Non-Randomized Studies-of Interventions for non-randomized studies of intervention. The strength of conclusion was determined using the evidence-based guideline development approach. Limited evidence indicates a higher increase in cortical inhibition and a higher reduction in cortical activation during a motor task of the affected hemisphere after graded motor imagery compared to wait-list. Higher reductions in map volume (total excitability of the cortical representation) of the affected hemisphere after peripheral electrical stimulation (PES) were observed when compared to transcranial direct current stimulation(tDCS) or to sham treatment with limited evidence. No other differences in cortical excitability and representation of the affected and non-affected hemisphere were observed when comparing mirror therapy with sham therapy or tDCS, PES with sham therapy or tDCS, and graded motor imagery with wait-list. Graded motor imagery and PES result in higher cortical excitability reductions of the affected hemisphere compared to wait-list, tDCS and sham treatment, respectively.

Keywords: mirror movement therapy, transcranial magnetic stimulation, placebos, neuralgia

List of abbreviations:

RoB 2: Revised Cochrane Risk of Bias Tool

ROBINS-I: Risk of Bias in Non-Randomized Studies - of Interventions

EBRO: Evidence-Based Guideline Development Approach

PES: Peripheral Electrical Stimulation

tDCS: Transcranial Direct Current Stimulation

PNP: Peripheral Neuropathic Pain

CR: Cortical Reorganization

CBO:Dutch Institute for Health Care Improvement

PROSPERO: International Prospective Register of Systematic Reviews

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines

INTRODUCTION

The somatosensory system comprises components of both the peripheral and central nervous system[1]. It allows for the perception of somatosensory input including touch, pressure, temperature, nociception, vibration, and proprioception (movement and position perception of the body part). Additionally, it provides sensory feedback to the motor system for the coordination of motor function[1]. A lesion or disease of the somatosensory system at the level of the peripheral nervous system can lead to peripheral neuropathic pain (PNP)[2, 3]. Pathologies such as radiculopathies, amputation, nerve injuries and diabetes can cause PNP[2]. The prevalence of PNP ranges from 1% to 5% in the general population[4, 5]. Peripheral neuropathic pain has an enormous socioeconomic impact because it is often accompanied by anxiety, depression, sleep disorders, work loss, reduced quality of life and productivity[6]. The exact cost of PNP worldwide is unknown, but the total annual direct cost of the PNP seen after radiculopathy is £268 million in the UK alone, stressing the importance of the problem[7, 8].

Patients with PNP suffer from sensory abnormalities that can be characterized by the coexistence of gain (pain) and/or loss (sensory deficits in the painful area) of somatosensory function in the area corresponding to the innervation territory of the damaged peripheral nerve, plexus, or nerve root[9, 10]. The gain of somatosensory function can be spontaneously present and/or induced by specific stimuli such as mechanical and/or thermal stimulation[9, 10]. For example, painful responses to non-painful stimuli (allodynia) and increased responses to the normally painful stimuli (hyperalgesia) can occur[9, 10]. In contrast to gaining somatosensory function, sensory loss indicates a deficiency in the perception of mechanical, vibratory, noxious and thermal stimuli[9, 10].

As a consequence of sensory gain and/or loss, the somatosensory system including the spinal cord, brainstem, thalamus, andparticularly in cortical areas undergo robust changes[11]. Furthermore, these alterations are mainly monitored in the somatosensory and motor cortexand can be of functional (blood oxygenation, spatial shift, activation) or structural (cortical thickness, dendritic growth, axonal sprouting) nature[11, 12]. This phenomenon is termed cortical reorganization (CR), andimmediatelyoccurs followingperipheral injuries that selectively eliminate afferent stimulation of the nervous system[11]. Cortical reorganization comprises rapid decreases of intracortical inhibition, then expansion of the sensory area of the affected limb and reception of feed-forward inputs from non-lesioned peripheral areas with adjacent cortical representations in the early stage[11, 13]. Over time, the sensory area of the affected limb shrinks and inhibition at the cortical area dissipates[11, 13]. However, CR and the related processes can be adaptive or maladaptive in nature[14]. Adaptive CR provides a basisforrecoverybyoptimizingtheuse of centralresourcesforsensoryprocessing of remnantsensoryreceptorsor motor function[13]. Contrary to that, maladaptive CR contributes to residual sensory abnormalities such as neuropathic pain and phantom sensation[14]. Maladaptive CR results in enhanced hypersensitivity of the pain processing neural network within the somatosensory system[14]. Maladaptive CR alters the shape and size of the limb representation in the somatosensory system and contributes to pain by producing a sensorimotor conflict resulting in incongruent information between the sensory system and the motor output[15, 16]. Moreover, positive associations between CR, specifically within the primary somatosensory cortex, and sensory abnormalities have been shown in patients with PNP such as complex regional pain syndrome, phantom pain, and carpal tunnel syndrome[17-19].

Due to the association between maladaptive cortical reorganization and pain severity, reversal of maladaptive cortical reorganization has been assumed to be a key goal in the treatment of PNP. Based on the suggestion that sensory abnormalities result in maladaptive CR, the use of sensory re-training that intends to reduce sensory abnormalities has been proposed to reverse maladaptive CR in treatment of PNP[20, 21]. Sensory re-training aims to optimize the sensory potential of the remnant tissue by restoring normal cortical processing, particularly in the primary somatosensory cortex which involves sensory processing and can drive motor output in coordination with or independent of the primary motor cortex[20-22]. This is achieved through the application of repetitive sensory stimuli. Sensory re-training can be classified as either passive or active. Passive sensory re-training entails that the participant does not actively focus on the external applied sensory stimuli (e.g., peripheral electrical stimulation, vibration)[23]. Active sensory re-training (e.g., graded motor imagery, two-point discrimination, tactile acuity) is focused on engaging the participant in the process of their CR through attention to the stimuli, anticipation of the feature (e.g., type, shape) of the sensory stimuli, and implementation of the feedback about it[24-27].

Despite seemingly promising outcomes of sensory re-training on maladaptive CR, its effect is not clearly documented in patients with painful PNP in the literature until now. Clearly identifying the sensory re-training influence on maladaptive CR is needed to optimize the treatment effects and cost-effectiveness of rehabilitation programs. Therefore, this systematic review summarized the current evidence in the literature regarding the effects of sensory re-training on maladaptive CR compared to other rehabilitative techniques in patients suffering from PNP.

METHODS

Protocol Registration

The systematic review protocol was prospectively registered within the International Prospective Register of Systematic Reviews (PROSPERO, registration number XXXXX) on date January 5th 2022 and reported consistently with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [28].

Eligibility Criteria

Eligibility criteria were derived from the "PICOS" question, referring to patient (P = patients with possible/probable/definite PNP), intervention (I = sensory re-training as a standalone treatment), comparison (C = other treatment methods than sensory re-training used in rehabilitation), outcome (O = cortical reorganization) and study design (S = (non-)randomized controlled trials). Theclinicaldiagnosis of neuropathicpainwasmadebased on therevised NP diagnostic criteria[29]. Accordingtotherevised NP[29]: *Possible PNP* wasdeterminedifthepatient'shistory, paindistributionarea, andvalidatedscreeningtoolssuggesttheexistence of the PNP. *Probable PNP* wasdeterminedifsensoryabnormalities in thepainfulareahavethesameneuroanatomicallyplausibledistribution. *Definite PNP* determinedifftheobjectivediagnostic test confirmsthelesionordisease of theperipheralsomatosensorynervoussystem (such as neurophysiologicaltests).

Search Strategy

The studies were identified through a search of three medical databases including PubMed, Web of Science, and Embase using a pre-established set of search terms on the 26th of June 2023. The search strategy was derived from the PICOS elements (Patient, Intervention, and

Outcome) by combining free-text key words and Medical Subject Heading (MeSH) terms with Boolean operators (AND/OR/NOT), and modified based on indexing the systems of each database (Appendix 1). The comparison element was not included in the search strategy to avoid missing any relevant article. No filters were used. **The search strategy for each database can be found in Appendix 1.**

The detailed inclusion and exclusion criteria which were designed based on the PICOS elements and used in this study are shown in Table 1.

StudySelection

After searching each database, duplicates were removed with the help of Endnote X9[30] and the remaining references imported into Rayyan[31]. All of the studies were independently screened in a blinded way by the first two authors (KC and JVO) to identify potentially relevant articles based on title and abstract during the first screening phase. Afterwards, full-text articles of all potentially relevant studies were evaluated for eligibility by the same two independent authors during the second screening phase. Conflicts were resolved during a consensus meeting or if necessary, a third author (KDM) was consulted of which the opinion was decisive. Articles that had no available full text were excluded. **Although initially only randomizedcontrolledtrials were aimed to be included in this review, veryfewarticlesremained after the first study selection process, and, therefore, the study selection process was repeated to allowfortheinclusion of non-randomizedcontrolledtrials**.

Assessment of Risk of Bias

The risk of bias was independently assessed by the same two authors (KC and JVO), who were blinded to each other's evaluation, using the revised Cochrane Risk of Bias Tool (RoB 2)[32] for randomized controlled trials and the risk of bias in non-randomizedstudies – of interventions (ROBINS-I)[33] for non-randomized intervention studies. TheRoB 2 consists of fivedomainswhichevaluatetherandomizationprocess, intendedinterventions, missingoutcome data, measurement of theoutcome, andreportedresults. Each domain can be classified as "low risk of bias", "someconcerns" or "high risk of bias". Ifalldomains of thetoolwererated as 'low risk of bias', wejudged an overall 'low risk bias'. Ifoneormoredomainswererated as 'someconcerns' but were not rated as 'high risk of bias' in any domain, wejudged an overall 'someconcernsfor risk of bias'. Ifoneormoredomainswererated 'high risk of bias', wejudged an overall 'high risk of bias'.

The ROBINS-I consists of seven domains: biasduetoconfounding, bias in theselection of participantsintothestudy, bias in classification of interventionsforalloutcomes, biasduetodeviationsfromintendedinterventionsforalloutcomes, biasduetomissing data foralloutcomes, bias in measurement of outcomes, andbias in selection of thereportedresults.

Synthesis of results

Thelevel of evidenceandstrength of conclusionweregraded in accordancewiththeevidence-basedguidelinedevelopment (EBRO) methoddevelopedbytheDutchInstituteforHealthCareImprovement (CBO)[34]. Theselectedstudieswereratedbased on thefollowingcriteria: A2, a double-blindedcontrolled trial withsoundmethodologyor B, a comparativecontrolledtrial not satisfyingtheconditions of A2. Finally, theselevels were used to determine the strength of conclusion. The detailed EBRO criteria can be found in Table 2.

Data Extraction

Data were extracted by one author (KC) and independently confirmed by the second and the last authors (JVO and KDM). The extracted data can be found in Table 3 and consisted of the following items: author and year of publication, study design, sample characteristics of the experimental/control group population (pathology, sample size, sex, age, symptom duration), pain assessment, follow-up, results.

RESULTS

The initial search yielded a total of 4432 articles. After duplicates were removed, 4025 articles remained and were screened based on title and abstract. Eliminating the irrelevant studies resulted in the inclusion of 34 articles for further full-text assessment. Of these, four met the eligibility criteria and were included in the qualitative analysis. Reasons for exclusion were as follows: wrong population (n = 4), wrong study outcome (n = 12), wrong study design (n = 9), wrong exposure (n = 15), and/or no full text available (n = 5). A flowchart of the study selection is shown in Figure 1.

Study Characteristics

Of the four included studies, two studies were registered with the same clinical trial number[24, 25]. Two studies were performed in a rehabilitation hospital[24, 25], the other studies did not report the study setting[26, 27]. Three studies[24-26] were randomized clinical trials, and one study was a non-randomized clinical trial [27].

All of the included studies assessed cortical excitability and cortical representation as outcome measure of CR[24-27]. Cortical excitability was evaluated using intracortical inhibition and facilitation in three studies[24-26], and cortical activation in one study[26]. In addition to that, two studies evaluated map volume, a measure of the total excitability of the cortical representation[24, 27]. Cortical representation was evaluated using the number of discrete map peaks in one study[27], center of gravity in two studies[24, 27], and thumb and littlefinger representation distance in one study [26].

Participants Characteristics

The sample sizes ranged from 16[27] to 98[25] participants with a total of 247 participants. Of these, 94 (38.05%) were female and 153 (61.95%) were male. The mean age of the participants ranged between 30±2.0 years[27] and 54.71±14.13 years[26]. All participants had chronic pain ranging between 3 months and 4.2±0.7 years[24-27]. Although one study did not report pain duration, the time after disease onset was reported to be 58.24±43.88 months (range: 4–172 months) which can be considered as chronic[27].

One study reported dropouts that were included for all analyses with a total of 14 participants[24]. One study reported dropouts that had to be excluded from all analyses with 2 participants[27]. Two studies reported missing data that had to be excluded from all analyses with a total of 6 participants[26, 27]. One study reported missing data that had to be excluded for analyses of the intracortical inhibition (5 participants) and analysis of the intracortical facilitation (6 participants)[25].

Intervention characteristics

Across the studies experimental interventions included mirror therapy in two studies[24, 25], peripheral electrical stimulation in one study[27], and graded motor imagery in one study[26]. Control interventions included anodal transcranial direct current stimulation in three studies[24, 25, 27], sham therapy in three studies[24, 25, 27] and a wait-list control group who received no control intervention was included in one study[26]. Considering sham therapy, all three studies used a combination of the two different types of sham therapy[24, 25, 27]. Thisincludedsham tDCSover the affected hemisphere with 30-second stimulation in threestudies[24, 25, 27], which was substituted by imagining a mirrored reflection using a covered mirror in two studies [24, 25] or sham PES over the painful area with no stimulus intensity in one study [27].

Different treatment frequencies were applied in the studies, ranging from only one session[27] to daily sessions for six weeks[26]. The session duration varied from 40 minutes[24, 25] to at least 10 minutes every waking hour[26]. Two studies applied 10 home exercise sessions over a two-week period after treatment[24, 25].

Outcome characteristics

The cortical reorganization was evaluated using transcranial magnetic stimulation (TMS) in four studies[24-27] and functional magneticresonance imaging (fMRI) in one study[26]. The excitability and organization of corticospinal inputs to the studied muscles at the cortex were examined using TMS. The representation the first dorsal interosseous muscle from the affected and unaffected side at the cortex was mapped in three studies[24-26] and the representation at the cortex of the paraspinal muscles contralateral to the side of the worst pain was mapped in one study[27]. fMRI scanning was performed during a hand grip motor task and somatosensory stimulation on the distal phalanx of the first and fifth fingers on both hands in one study[26].

The total evaluation time of the cortical reorganization was only reported in one study (around 20 minutes)[26].The duration of follow-up of cortical reorganization varied among the studies including short- (immediately before and after application of the intervention)[27] or long-term (baseline, and 4, 6 or 12 weeks from the baseline)[24-26] follow-up assessments.

Risk of Bias and Levels of Evidence

The overall risk of bias of the randomized controlled trials was low in one study[25], some concerns were present in one study[24], and risk of bias was high in one study[26]. The latter being due to the selection of the reported results, since differences between experimental mirror therapy and sham therapy were reported but were not reported between mirror therapy and tDCS[24]. The high risk of bias was due to results not being displayed separately for each follow-up measurement[26]. The overall risk of bias of the non-randomized controlled trial was moderate in one study [27] since awareness of the outcome assessors was not known, proportions for missing participants differ slightly across experimental groups, and the analysis is unlikely to have removed the risk of bias arising from the missing data. The risk of bias assessment of the randomized controlled trials and non-randomized controlled trials is reported in Tables 4 and 5, respectively.

Levels of evidence for three studies which use randomization of the study subject was assigned an A2 score[24-26], and one study without randomization of the study subjects was rated a B score[27]. The methodological quality of per outcome of all included articles are presented in Table 6.

Results of Cortical Reorganization from individual studies

Cortical Excitability

Intracortical Inhibition (Short IntervalIntracortical Inhibition) and Facilitation

Three studies reported the long-term effects of sensory re-training on *intracortical inhibition and facilitation*[24-26]. Therefore two studies compared mirror therapy with sham therapy (sham mirror therapy with sham tDCS), or tDCS, and one study compared graded motor imagery with wait-list yielded limited results.

In regards of long-termeffects both Gunduz et al.[24] and Teixeria et al.[25] found no significant differences between mirror therapy and sham therapy, or tDCS on *intracortical inhibition and facilitation* at the **primary motor cortex** of the *affected hemisphere* (contralateral to the affected side) after four weeks of intervention. The last study performed by Strauss et al.[26] found a significantly higher increase of *intracortical inhibition* at the **primary somatosensory cortex** of the *affected hemisphere* after graded motor imagery compared to wait-list after 12 weeks of intervention, but no significant differences regarding *intracortical facilitation*.

No significant differences were found for the **primary motor cortex** of the *non-affected hemisphere* (ipsilateral to the affected side)[24, 25].

Cortical Activation

One study documented the long-term effect of sensory re-training on *cortical activation*[26].

In regards of long-termeffects Strauss et al.[26] reported a significantly higher decrease of *cortical activation* at the **primary somatosensory cortex** of the *affected hemisphere* during a motor task after graded motor imagery compared to wait-list after 12 weeks of intervention, but no significant differences were found during a somatosensory task.

Map Volume

Two studies reported the effect of sensory re-training on *map volume*[24, 27]. One of them investigated short-term effects[27], while the other examined long-term effects[24].

In regards of short-termeffects Schabrun et al.[27] found a significantly higher decrease in *map volume* at the **primary motor cortex** of the *affected hemisphere* after PES compared to sham therapy and tDCS immediately after intervention.

In regards of long-termeffectsGunduz et al.[24] found no significant differences between mirror therapy and sham therapy related to changes in *map volume* at the **primary motor cortex** of the *affected and non-affected* hemisphere after four weeks of intervention.

Cortical Representation

Discrete Map Peaks

One study reported the short-term effect of sensory re-training on *discrete map peaks*[27].

In regards of short-termeffects Schabrun et al.[27] found no significantly higher increase of the proportion of the *individual maps containing two peaks* in the **primary motor cortex** of the *affected hemisphere* after PES compared to tDCS, and sham therapy (sham PES with sham tDCS) immediately after intervention. No significant differences between PES with tDCS and sham therapy concerning changes in the *number of the single map peaks* at the **primary motor cortex** of the *affected hemisphere* were found immediately after intervention[27].

Center of Gravity

Two studies reported the effect of sensory re-training on *center of gravity*[24, 27]. One study documented short-term effects[27], while the other study reported long-term effects[24].

In regards of short-termeffects Schabrun et al.[27] found no significant differences between PES with tDCS and sham therapy (sham PES with sham tDCS) on the *center of gravity* at the **primary motor cortex** of the *affected hemisphere* immediately after intervention.

In regards of long-termeffects Gunduz et al.[24] found no significant differences between *center of gravity (x) and (y)* at the **primary motor cortex** of the *affected hemisphere* after mirror therapy compared to sham therapy (sham mirror therapy with sham tDCS) after four weeks of intervention, but they did not find any significant differences in the *non-affected hemisphere*[24].

Cortical Map Distances

One study reported long-term effect of sensory re-training on *hand representation*[26].

In regards of long-termeffects Strauss et al.[26] reported no significant differences between graded motor imagery and wait-list concerning the first-fifth finger of the *hand representation distance* at the **primary somatosensory cortex** of the *affected hemisphere* after 12 weeks of intervention.

Adverse events

Only one study reported adverse events (sleepiness, tingling, trouble to concentrate, headache, scalp pain, skin redness, acute mood change) and found these to be similarly distributed among the intervention and control groups, receiving mirror therapy, covered mirror therapy, and tDCS respectively [24]. Three studies did not report the presence/absence of adverse effects[25-27].

DISCUSSION

To the best of our knowledge, this is the first systematic review aimed to investigate sensory re-training effects on CR compared to other rehabilitative techniques. This review indicates no differences between mirror therapy and sham therapy, and tDCS for the changes in

cortical excitability in the *affected hemisphere*withlimitedevidence. Higher decreases of *cortical excitability* in the *affected hemisphere* are revealed after PES compared to tDCS, and sham therapy in the short term, and after graded motor imagery compared to wait-list in the long termwithlimitedevidence. Regarding changes in the *cortical representation* in the *affected hemisphere*, there are no differences between PES and tDCS, PES and sham therapy, mirror therapy and sham therapy, and graded motor imagery and wait-listwithlimitedevidence. No differences exist in any parameters in the *non-affected hemisphere*.

Mirror therapy

This review showed limited evidence for no differences between mirror therapy and sham therapy in *intracortical inhibition and facilitation, map volume and center of gravity* of the **primary motor cortex** of the *affected hemisphere* in the long term. No differences were revealed between mirror therapy and tDCS in *intracortical inhibition and facilitation* of the **primary motor cortex** of the *affected hemisphere* in the long term.

Mirrortherapyinvolvestheexecution of movements of theunaffectedlimborbothunaffected/affectedlimbwhilethepatient has towatchtheunaffectedlimbreflection in a mirror[35]. Bilateralmovement has beenshowntoinducemoreactivation of the**primary motor cortex**thanunilateralmovementduringmirror therapy[36]. However, bilateral movements may be impossible during mirror therapy in some PNP patients such as amputeesbut not complex regional pain syndrome. Therefore, theresults of theincludedstudies, performedbyGunduz et al.[24] and Teixeria et al.[25] in patients with lower limb amputees cannot be generalized to all PNP patients[24, 25]. One of themechanismsunderlyingthemirrortherapyeffect on thecortex is

themirror neuron system that modulates **primary motor cortex** activity[20]. It has been well known that usage of regular lower limb prosthesis may have increased the mirror neuron system activityduringphantomankle movement[37]. Regularusage of theprosthesisprovidesnearly a physiologicalamount of thecutaneousandproprioceptivefeedbackfromtheperipherytothecontralateral**somatosensoryco rtex** in thesameregion as thephantom limb[38]. Additionally, prosthesesmodify**somatosensoryand motor cortex**representation of theaffectedlimbandthushelps in maintaining the *cortical representation*. Particularly, upper extremity amputees who frequently use myoelectricprosthesisdemonstratedless CR thanupper extremity amputees who used either a cosmeticornoprosthesisorwore myoelectric prostheses for minimal time[39]. Hence, differences in the prosthesis use duration and the type of prosthesis between the groups may haveinfluenced the results. Gunduz et al.[24] and Teixeria et al[25]did not reporttheprosthesisutilizationdurationortype.

tDCS comprised of non-invasive direct stimulation of the brain by delivering weak direct currents over the scalp, and can be applied as anodal or cathodal tDCS[51]. In contrast to cathodal tDCS, which is expected to decrease *cortical excitability*, anodal tDCS is expected to increase *cortical excitability*[51, 52]. Teixeria et al.[25] used direct application of currents to the brain via anodal tDCS over the **primary motor cortex** to the *affected hemisphere*[41, 48]. Teixeria et al.[25] did not compare changes between *intracortical inhibition and facilitation*, preventing us from deciding if *cortical excitability* decreases or increases. The result of the study performed by Teixeria et al.[25] may be influenced by age.It has been known that changes in *intracortical inhibition and facilitation* are lower when subjects are older. However, Teixeria et al.[25] did not provide age distribution separately for the groups.

In the literature, several studies have revealed shifted *activation balance* within the **primary motor cortex** towards the *affected hemisphere*, a *higher activation* in **multiple brain regions** in the *affected and/or non-affected hemisphere*, and stronger *activation* in the **supplementary motor area** after mirror therapy compared to control treatments[40-42]. However, thesestudieswereperformed in centralneuropathicpainpatientsandtheresults can not be generalizedtothepatientswith PNP since centralandperipheralneuropathicpainhavedifferent CR mechanisms. Substantialandperhapsirreversibleneuronalchangeshaveoccurred in centralneuropathicpain in responsetodirectinjury of thecentralnervoussystem, whereasanatomicallesiontothecentralnervoussystemdoes not occur in PNP[43, 44]. Thesedifferencesmake it alsodifficulttodirectlycomparethetreatments in thisreviewwiththe literature[43].

Graded Motor Imagery

Limited evidence points out that graded motor imagery leads to significantly higher increase in *intracortical inhibition and decrease* in *cortical activation* during motor tasks at the **primary somatosensory cortex** of the *affected hemisphere*, compared to wait-list, in the long-term. The result of the only included study, performed by Strauss et al.[26], in this review may have been influenced by pain medication usage[26]. It has been known that pain medication usage may affect CR due to the correlation between CR and pain severity in patients with PNP. However, Strauss et al.[26] did not report anything about the pain medication utilization[26].

PES

This review indicates a higher decrease in *map volume* but no significant differences concerning *cortical representation* at the **primary motor cortex** of the *affected hemisphere*

after PES, compared to tDCS and sham treatment in the short term with limited evidence. The

only included study performed bySchabrunn et al.[27] used TMS to assess *map volume* for total *cortical excitability*, and *center of gravity* for *cortical representation*[27]. TMS has been shown to be unreliable for *map volume*, but highly reliable for *center of gravity* over a short time interval (0.5-7days interval)[45]. Additionally, stimulus parameters and used electrode types are significant factors inducing *cortical excitability* with PES[27, 46, 47]. It has been known that stimulus intensity at the level of sensory stimulation depresses *corticomotor excitability* of the stimulated muscle, whereas stimulus intensity above the motor threshold increases *corticospinal excitability*[46, 47]. In their study Schabrunn et al.[27] used a strong sensory tingling stimulus intensity with surface electromyography to the most painful side of the paraspinal muscles on the low back for one session to identify *cortical maps*[27]. The results of Schrabrunn et al.[27] were consistent with those of Elgueta-Cancino et al.[48] who reported that one session of PES to the back muscle at the level of functional muscle contraction does not modulate excitability of corticospinal inputs to the stimulated muscle. This result may stem from the treatment frequency. Besides, surface electromyography has been shown not always to completely reflect the targeted muscle during rest and may also partly reflect changes in corticospinal excitability of non-target muscles[49]. Gallina et al.[49] suggested that high density surface electromyography and recording during contraction may be more reliable to measure corticospinal excitability.

Strengths, limitations, and recommendations

This review was pre-registered in the PROSPERO which is a publicly available international database. The pre-registration provides an opportunity to specify this review before data collection and refrain from unplanned duplication and publication bias. The use of the

PRISMA guidelines is helpful to ensure the quality of the reporting review through transparent, complete, and accurate summarization of published literature. Inclusion of the blinded reviewers ensures that all relevant articles are included and improves the accuracy of the review with precision of the study selection, strength of the evidence and avoidance of bias.

This systematic review also has some limitations. Only English-published studies were included, and nonpublished randomized controlled trials were not considered in this review. Only a small number of studies were conducted on this topic and provided the current evidence in this review. The patients included in the studies for this review had possible or probable neuropathic pain, and none of them had definite neuropathic pain since objective diagnostic test were not used to confirm the lesion or disease of the peripheralsomatosensory nervous system. Therefore, the results of this review cannot be generalized to all PNP patients. There was a large heterogeneity among the included studies, including follow-up time points and the parameters of tDCS (i.e. intensity and duration) and TMS (i.e. intensity, frequency, and the number of pulses). The risk of bias within the studies was also variable. Therefore, more low risk of bias studies are needed with representative samples of the participants, with an even longer follow-up period, from the data presented in this study. Diagnosis of the participants varying from amputees to complex regional pain syndrome and chronic low back pain in this review since neuropathic pain is not a single disease, but a syndrome caused by a range of different diseases etiologies. However,similar sensory symptoms/signs profiles are present in different disease etiologies and the consequences of the injury to the peripheral somatosensory system include a series of neurobiological events resulting in maladaptive CR, which is a process assumed to be involved in PNP. However, because of addressing patients based on sensory symptom/sign cluster rather than etiology

has been proposed to improve response to the treatment[50], this review gains importance by highlighting the most recent information on the management of maladaptive CR in PNP, focusing on the sensory re-training.

Futurestudiesshouldalsotakeintoaccountprosthesisusageduration, painmedicationutilization, stimulusintensityandelectrodetypeswith TMS on CR. Mirrortherapywith unilateral or bilateral movementsshould be separatelycomparedwithcontroltreatments in various PNP conditions. It mayalso be worthwhiletoexamine the outcomes of the CR in more detail, including neuralnetworks/connectivitybetweenareasorstructuralchanges (e.g., volume/density of thebrainregions). Investigation of the durability of the treatment gains would be helpful in future studies since CR continues to change over time. It would also be interesting to study the effects of different types of sensory retraining (proprioception, tactile acuity training, etc.) on CR in other PNP conditions (peripheral nerve injury, diabetes, etc). This because, although patients with PNP have abundant overlapping somatosensory signs, possible different underlying pathophysiological mechanisms may exist in these conditions. Future studies should also investigate sensory re-training influence on pain intensity/severity, **balance, gait, fall risk, and quality of life** in PNP since there is a well-known positive association between maladaptive cortical reorganization and in these variables in PNP.**Reduction in painintensity/severity, improvement in balance control duringgait, andreduced fall risk are the main factors that have the potential to greatly improve quality of life across a variety of diagnoses that develop PNP, and, therefore, needto be takenintoaccount in thefuturestudies.**

CONCLUSION

Thisreviewindicatesthatgraded motor imagery and PES leadsto higher decrease of cortical excitability of the affected hemisphere compared to wait-list, tDCS and sham treatmentwithlimitedevidence, respectively. Sensory retraining and other rehabilitative techniques have similar cortical re-organizational patterns in the non-affected hemisphere.Further studies are warranted to confirm these results due to the limited number of the present studies.

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Table 1. Inclusion and exclusion criteria

Criteria	Description	
	Inclusion	Exclusion
Patient	- humans - any ages between 18 and 65 years - to be conscious - diagnosed with a PNP ***a. possible neuropathic pain*** ■ patient's history suggests that pain could be related to a neurological lesion or disease ■ the pain distribution should be anatomically consistent with the suspected location of the lesion or disease in the peripheral somatosensory nervous system	- animal studies - elderly participants older than 65 years - children and adolescents <18 years of age - unconscious participant - healthy participant - cognitive disorders - central neurological conditions (e.g. amyotrophic lateral sclerosis, spinal cord disease, multiple sclerosis, stroke, Alzheimer, cortical or subcortical brain injury) - congenital amputation - neoplasm - myelopathy - Guillain-Barre syndrome

	(such as postamputation pain in the missing body part and/or in the residual limb) ■ the validated screening tools (such as LANSS, the neuropathic pain questionnaire, the DouleurNeuropathiqueen questions, the painDETECT and ID-Pain, Groningen Questionnaire after Arm Amputation) ***b. probable neuropathic pain*** ■ sensory abnormalities in the painful area in the same neuroanatomically plausible distribution ■ ***c. definite neuropathic pain*** theobjective d iagnostic test	- Charcot-Marie-tooth disease - pregnancy

	confirmsthelesionordisease of theperipheralsomatosensorynervoussystem (such as neurophysiologicaltests	
Intervention(s)	at least one of the following sensory re-training modalities: - proprioceptiontraining (vibration, jointposition sense orkinesthesia) - pointtopointtraining - tactile/tactileacuitytraining - tactileobjectrecognition (e.g. twopointdiscrimination) training - electricalstimulationdiscriminationtraining - temperaturediscriminationtraining - graphestesiatraining - localizationtraining - motor imaginarytraining	- combination of thesensorytrainingwithanyothertreatment as theeffects of sensorytrainingcannot be isolatedfromtheeffects of theothertreatment(s) - massage - brainstimulationtechniques (transcranialmagneticstimulation, EEG) - strengteningexercises (theraband)

	- visualimagerytraining - auditoryimagerytraining - touchimagerytraining - mirrortherapy - spatialorganizationtraining - virtualreality	
Comparison(s)	- placebo/sham treatment - no-intervention/ waiting list - other treatment methods used in rehabilitation except sensory re-training: - exercise - musculoskeletal manipulations - acupressure - traction - manual therapy - osteopathy - physical therapy	

	- physiotherapy - invasive therapy/techniques (drug injection) - non-invasive techniques (transcranial direct current stimulation, transcranial magnetic stimulation) - craniosacral therapy - ultrasound therapy - ischemic compression - music therapy - dance therapy - aqua therapy - hippotherapy - relaxation techniques - kinesiotherapy - psychologically based interventions (acceptance commitment therapy,	

	cognitive-behavioral therapies, mindfulness-based therapies)	
Outcom	cortical reorganization	no description of cortical reorganization as an outcome
Study design and report	- randomized controlled trial - non-randomized controlled trial - reported only in English	- uncontrolled studies - non-experimental studies - reported in other languages than English

PNP: Peripheralneuropathicpain, EEG:Electroencephalogram.

Table 2. Evidence-BasedGuideline Development (EBRO) Method

Level of evidence

A1	Systematicreviewsand meta-analysesbased on minimally 2 independent A2 studies
A2	Randomizedcontroltrials (RCTs): double-blinded; withsoundmethodologyandsufficientsample size
B	Comparativestudies, but lackingthequalitycriteria of A2 (includingcohortstudiesandcase-controlstudies)
C	Noncomparativestudies
D	Expertopinion

Table 3: Evidence Table of Included Studies

Author and Year of Publication and Country	Study Design	Pathology; Sample Size (n); Age (in years Mean ± SD or Median ± IQR); Gender (F/M in %); Time Since Disease Onset (in months); Pain Intensity (Mean ± SD or Median ± IQR)	Intervention Duration; Frequency; Follow Up or Home Exercise if Available	Investigation Technique (Modality and Characteristics)	Cortical Reorganization Assessment; Investigated Hemisphere; Investigated Brain Region; Evaluation Time	Results
Gunduz et al (2021) USA	randomized, sham-controlled, 2 × 2 factorialclinical trial	Unilateral Traumatic Lower Limb Amputation **tDCS and Mirror Therapy Group** n = 29 48.24 + 16.28 years F/M = 24.14% / 75.76% time since disease onset (amputation) = 88.41+12.68 months	**tDCS and Mirror Therapy Group** Treatments a. tDCS b. Mirror Therapy *tDCS* - anodal electrode = over the primary motor cortex contralateral to the amputation side	TMS Single PulseTMS - coil model = Magstim - coil type = figure-of-eight coil - muscle = first dorsal interosseous muscle Double Pulse TMS - conditioning stimulus	cortical reorganization assessment - corticalexcitability •shortintervalintracorticalinhibition • intracortical facilitation - total excitability of the cortical representation •mapvolume - cortical mapping •center of gravity	**Short Interval Intracortical Inhibition Percentage Changes** *affected hemisphere* no statistically significant increase with: - Mirror therapy compared to sham therapy (B = 0.2, p = 0.57)

		pain intensity (VAS) = 6.18 + 1.88 **Mirror Therapy Group** n = 28 46 + 12.73 years F/M = 39.29% - 60.71% time since disease onset (amputation) = 90.39 ± 13.17 months pain intensity (VAS) = 6.03 ± 1.75 **tDCS Group** n = 28 39.96 ± 15.96 years F/M = 35.71% - 64.29% time since disease onset (amputation) = 56 ± 9.97	- cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = 20 minutes - frequency = daily session for 10 days *Mirror Therapy* - light tactile stimulation - active range of motion - functional task while watching its mirrored reflection, simultaneously with the tDCS - duration = 20 minutes - frequency = daily session for 10 days -home exercise = 10 sessions at home over 2	intensity = 80% of the resting motor thresholds - test stimulus intensity = 120% of the resting motor thresholds - interstimulus interval = 10 recording of 2 and 10 milliseconds	investigated hemisphere -affected hemisphere -non-affected hemisphere investigated brain region - primary motor cortex evaluation time - baseline - 4 weeks after intervention	*non-affected hemisphere* no statistically significant changes with: - Mirror therapy compared to sham therapy (p value not reported) **Intracortical Facilitation Percentage Changes** *affected hemisphere* no statistically significant increase with: - Mirror therapy compared to sham therapy (B = 1.28, p = 0.22) *non-affected hemisphere* no statistically significant changes with:

		months pain intensity (VAS) = 6.28 + 1.67 **Sham Treatment Group** n = 27 42.96 ± 12.28 years F/M = 37.04% - 62.96 time since disease onset (amputation) = 63.88 ± 9.55 months pain intensity (VAS) = 5.89 ± 1.57	weeks period **Mirror Therapy Group** Treatments a. Mirror Therapy b. Sham tDCS <u>*Mirror Therapy*</u> - light tactile stimulation - active range of motion - functional task while watching its mirrored reflection, simultaneously with the tDCS- - duration = 20 minutes - frequency = daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period			<u>- Mirror therapy compared to sham therapy</u> (p value not reported) **Map Volume Changes** <u>*affected hemisphere*</u> no statistically significant decrease with: <u>- Mirror therapy compared to sham therapy</u> (B = -0.31, p = 0.72) <u>*non-affected hemisphere*</u> no statistically significant changes with: <u>- Mirror therapy compared to sham therapy</u> (p value not reported) **Center of Gravity**

			Sham tDCS - anodal electrode = over the primary motor cortex contralateral to the amputation side - cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = current is applied at first 30 seconds of the 20 min - frequency = daily session for 10 days **tDCS Group** Treatments a. Transcranial Direct Current Stimulation b. Covered Mirror			**Changes (x angle)** *affected hemisphere* no statistically significant increase with: - Mirror therapy compared to sham therapy (B = 0.03, p = 0.95) *non-affected hemisphere* no statistically significant changes with: - Mirror therapy compared to sham therapy (p value not reported) **Center of Gravity Changes (y angle)** *affected hemisphere* statistically significant more lateral

			Therapy *tDCS* - anodal electrode = over the primary motor cortex contralateral to the amputation side - cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = 20 minutes - frequency = daily session for 10 days *Covered Mirror Therapy* - functional task with the covered mirror by imagining movement - duration = 20 minutes - frequency = daily session			center of gravity with: - Mirror therapy compared to sham therapy (B = 0.03, p = 0.92) *non-affected hemisphere* no statistically significant changes with: - Mirror therapy compared to sham therapy (p value not reported)

			for 10 days - home exercise = 10 sessions at home over 2 weeks period **Sham Treatment Group** Treatments a. Sham tDCS b. Covered Mirror Therapy *Sham tDCS* - anodal electrode = over the primary motor cortex contralateral to the amputation side - cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = current is			

			applied at first 30 seconds of the 20 min - frequency = daily session for 10 days *Covered Mirror Therapy* - functional task with the covered mirror by imagining movement - duration = 20 minutes - frequency = daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period			
Schabrun et al (2014)[1] not reported	placebocontrol ledcrossoverst udy	non-specific chronic low back pain without neurological involvement n = 16	**tDCS and Peripheral Electrical Stimulation Group** Treatments	TMS Single Pulse TMS - coil model = Magstim 200	cortical reorganization assessment - total excitability of the cortical representation •map volume	**Map Volume** *affected hemisphere* statistically significant decreases with:

[1]Since analysis were made using ANOVA, the result section included to p value, in orderly with their above written treatments.

		30 ± 2.0 years F/M = 43.75% - 56.25% time since disease onset = not reported pain intensity (NRS) = 5.3 ± 0.4	a. tDCS b. Peripheral Electrical Stimulation *tDCS* - anodal electrode = motor cortical representation of the back muscles contralateral to the side of worst pain - cathodal electrode = contralateral supraorbital region. - current density= (0-1 mA) and down (1-0 mA) over 10 s at the beginning and end of the 30-min stimulation period - duration = 30 minutes - frequency = one session	- coil type = figure-of-eight coil - muscle = paraspinal muscles	- cortical representation •number of discretepeaks •center of gravity investigated hemisphere - affected hemisphere investigated brain region - primary motor cortex evaluation time - baseline - immediately after post-intervention	**- Peripheral electrical stimulation** compared to tDCS **(p = 0.024*)** (p = 0.73) **- Peripheral electrical stimulation** compared to sham treatments **(p = 0.024*)** (p = 0.59) **Number of Discrete Peaks** ***Proportion of Individual Maps Containing Two Peaks*** *affected hemisphere* no statistically significant differences with: - Peripheral electrical stimulation compared to tDCS

			Peripheral Electrical Stimulation - biphasic waveform - pulse duration = 0.1 ms -stimulation intensity = 2x3 perceptual threshold - duration = 30 minutes - frequency = one session **tDCS Group** Treatments a. tDCS b. Sham Peripheral Electrical Stimulation *tDCS* - anodal electrode= motor cortical			(p value not reported for both of the groups) no statistically significant differences with: - Peripheral electrical stimulation compared to sham treatment (p value not reported for both of the groups) ***One Single Peak*** *affected hemisphere* no statistically significant differences with: - Peripheral electrical stimulation compared to tDCS (0.0 ± 0.00) (p = 0.42) (p = 0.23) - Peripheral electrical

			representation of the back muscles contralateral to the side of worst pain - cathodal electrode = contralateral supraorbital region - current density = (0-1 mA) and down (1-0 mA) over 10 s at the beginning and end of the 30-min stimulation period - duration = 30 minutes - frequency = one session *Sham Peripheral Electrical Stimulation* - biphasic waveform - pulse duration:0.1 ms - stimulation intensity: 0			stimulation compared to sham treatment (0.2 ± 0.2) (p = 0.42) (p = 0.69) **Center of Gravity (x angle)** *affected hemisphere* no statistically significant differences with: - Peripheral electrical stimulation compared to tDCS (p value not reported for both of the groups) - Peripheral electrical stimulation compared to sham treatment (p value not reported for both of the groups)

			mA perceptual threshold - duration = 30 minutes - frequency = one session **Peripheral Electrical Stimulation Group** Treatments a.Peripheral Electrical Stimulation b. Sham tDCS *Peripheral Electrical Stimulation* - biphasic waveform - pulse duration = 0.1 ms -stimulation intensity = 2x3 perceptual threshold - duration = 30 minutes - frequency = one session			**Center of Gravity (y angle)** *affected hemisphere* no statistically significant differences with: - Peripheral electrical stimulation compared to tDCS (p value not reported for both of the groups) - Peripheral electrical stimulation compared to sham treatment (p value not reported for both of the groups)

			Sham tDCS - anodal electrode = motor cortical representation of the back muscles contralateral to the side of worst pain - cathodal electrode = contralateral supraorbital region. - current density = (0-1 mA) and down (1-0 mA) over 5 second stimulation period - duration = 15 s of the 30 minutes - frequency = one session **Sham Treatment Group** Treatments:			

			a. Sham tDCS b. Sham Peripheral Electrical Stimulation <u>*Sham tDCS*</u> - anodal electrode = motor cortical representation of the back muscles contralateral to the side of worst pain - cathodal electrode = contralateral supraorbital region. - current density = (0-1 mA) and down (1-0 mA) over 5 second stimulation period - duration = 15 s of the 30 minutes			

			- frequency= one session <u>*Sham Peripheral Electrical Stimulation*</u> - biphasic waveform - pulse duration=0.1 ms - stimulation intensity: 0 mA perceptual threshold - duration = 30 minutes - frequency= one session			
Strauss et al (2021)[2] Northern Germany	crossover study design	Upper Limb CRPS n = 21 54.71 ± 14.13 years F/M = 80.95% / 19.05% time since disease onset = 58.24 ± 43.88 months pain intensity (VAS) =	**Graded Motor Imagery Group** Treatments a. Right / Left Hand Laterality Training b. Imagined Movements c. Mirror Therapy	fMRI - stimulus application = somatosensory stimulation application on distal phalanx of the firstandfifthfinger on bothhands	cortical reorganization assessment - cortical excitability •shortintervalintracortical inhibition •intracorticalfacilitation •cortical activation - corticalrepresentation	**Short Interval Intracortical Inhibition** <u>*affected hemisphere*</u> statistically significant increase with: <u>**- Graded motor imagery**</u> <u>compared to wait – list</u>

[2]Only this study included in this review did not consider drop-outs for features of demographics of this study including sample size, age, time since onset and pain intensity.

		4.3 ± 2.6	*Right / Left Hand Laterality Training* - duration = at least 10 minutes for every hour when awake - frequency = every day for first 2 weeks *Imagined Movements* - duration = at least 10 minutes for every hour when awake - frequency= every day between 2 nd and 4 th week *Mirror Therapy* - duration = at least 10 minutes for every hour	- scanner= 3 Tesla magneticresonansimaging - software = SPM 12 - echo time = 40.8 milliseconds - repetition time = 1000 milliseconds - stimulus application = 33% of maximal force of the both hands grip motor task - scanner= 3 Tesla magneticresonansimaging - software = SPM 12 - echo time = 23 milliseconds - repetition time = 2000	•thumb–little finger distance of the hand representation investigated hemisphere - affectedhemisphere - non-affectedhemisphere investigated brain region - primarysomatosensorycortex evaluation time - baseline - 6 weeks after intervention - 12 weeks after intervention	**(31.22%)** (F (1,20) = 4.18; p = 0.054) **(t (20) = -3.69, p = 0.001)** **Intracortical Facilitation** *affected hemisphere* no statistically significant differences with: - Graded motor imagery compared to wait – list F (1,20) = 3.81, p = 0.065) (t (20) =1.73, p value reported as a not significant) **Primary Somatosensory Cortex Activation During Motor Task** *affected hemisphere*

			when awake -frequency = every day between 4 th and 6 th weeks ***Wait - List Group*** - continue routine pharmacologic treatment but no additional treatments - duration = 6 weeks	milliseconds TMS Single Pulse TMS - coil model = MagVenture - coil type = figure-of-eight coil - muscle = firstdorsalinterosseous muscle		statistically significant decreases with: - **Graded motor imagery** compared to wait – list **(t (19) = 2.82,p = 0.011***)) (t (19) = -1.97, p value reported as a not significant)) **Primary Somatosensory Cortex Activation During Somatosensory Task** <u>*affected hemisphere*</u> no statistically significant differences between: - Graded motor imagery compared to wait – list (t (29) = 1.70, p value reported as a not significant)

						(t (18) = 0.77, p value reported as a not significant)) **Distance of the First and Fifth Finger of the Hand Representation in Primary Somatosensory Cortex** *affected hemisphere* no statistically significant differences between: - Graded motor imagery compared to wait – list (p value not reported for both of the groups)

Teixeria et al (2021)[3] USA	randomized, blinded, sham-controlled, 2 × 2 factorialclinical trial	Traumatic Lower Limb Amputation n = 98 43.1 ± 14.3 years F/M = 32.7% - 67.3% time since disease onset (amputation) = 22.5 ± 75 months pain intensity (VAS) = 6.2 ± 1.7	**tDCS and Mirror Therapy Group** Treatments a. tDCS b. Mirror Therapy *tDCS* - anodal electrode = over the primary motor cortex contralateral to the amputation side - cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = 20 minutes	TMS Single pulse TMS -coil model = Bistim2 -coil type = figure-of-eight coil -muscle = first dorsal interosseous muscle Double pulse TMS - conditioning stimulus intensity = 80% of the resting motor thresholds - test stimulus intensity = 120% of the resting	cortical reorganization assessment - corticalexcitability •intracorticalinhibition •intracorticalfacilitation investigated hemisphere - affected hemisphere - non-affected hemisphere investigated brain region - primary motor cortex evaluation time - baseline - 4 weeks after intervention	**Intracortical Inhibition Percentage Changes** *affected hemisphere* no statistically significant differences between: - Mirror therapy comparedto tDCS (B = -9.40, p = 0.563) (B = 15.22, p = 0.342) *non-affected hemisphere* no statistically significant differences between: - Mirror Therapy comparedto tDCS

[3]This study share same Clinical Trial Number with the study performed by Gunduz et al (2021). Chances in intracortical inhibition and intracortical facilitation proportion were calculated for all groups, not seperately, keeping in mind that thelongitudinalchangesofintracorticalexcitabilitywith-insubjects(post-predifference)werenotstatistically significantlydifferent in this study. However, multivariatemodelsforthechangeinintracortical inhibition and intracortical facilitation forbothhemispheres were calculated and independent variables of treatment groups (mirror therapy and tDCS) were forced into the model to control for the effect of the interventions

			- frequency= daily session for 10 days *Mirror Therapy* - light tactile stimulation - active range of motion - functional task while watching its mirrored reflection, simultaneously with the tDCS - duration = 20 minutes - frequency= daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period **Mirror Therapy Group** Treatments a. Mirror Therapy	motor thresholds - interstimulus interval = 10 recording of 2 and 10 milliseconds		(B = -3.89, p = 0.781) (B = -28.19, p = 0.046) **Intracortical Facilitation Percentage Changes** *affected hemisphere* no statistically significant differences between: - Mirror therapy comparedto tDCS (B = -35.12, p = 0.379) (B = 1.54, p = 0.968) *non-affected hemisphere* no statistically significant differences between: - Mirror therapy comparedto tDCS (B = 45.85, p = 0.33) (B = -88.65, p = 0.238)

			b. Sham tDCS <u>*Mirror Therapy*</u> - light tactile stimulation - active range of motion - functional task while watching its mirrored reflection, simultaneously with the tDCS - duration = 20 minutes - frequency= daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period <u>*Sham tDCS*</u> - anodal electrode = over the primary motor cortex contralateral to the amputation side			

			- cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = current is applied at first 30 seconds of the 20 minutes - frequency = daily session for 10 days **tDCS Group** Treatments a. tDCS b. Covered Mirror Therapy *tDCS* - anodal electrode = over the primary motor cortex contralateral to the amputation side			

			- cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = 20 minutes - frequency = daily session for 10 days <u>*Covered Mirror Therapy*</u> - functional task with the covered mirror by imagining movement - duration = 20 minutes - frequency = daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period **Sham Treatment Group**			

			Treatments: a. Sham tDCS b. Covered Mirror Therapy <u>*Sham tDCS*</u> - anodal electrode = over the primary motor cortex contralateral to the amputation side - cathodal electrode = over the contralateral supraorbital area - current density = 2 mA - duration = current is applied at first 30 seconds of the 20 minutes - frequency= daily session for 10 days <u>*Covered Mirror Therapy*</u> - functional task with the			

			covered mirror by imagining movement - duration = 20 minutes - frequency = daily session for 10 days - home exercise = 10 sessions at home over 2 weeks period			

n: Sample Size. F: Female. SD: Standart Deviation. VAS: Visual Analog Scale. NRS: Numerical Rating Scale. IQR: Interquartile Range. tDCS: Transcranial Direct Current Stimulation. mA: Milliampere. BE: Coefficient. *$p<0.05$.

Table 4. Risk of bias assessment in randomized controlled trials using the Cochrane RoB 2 tool

Author andyear	randomization	intended intervention	missing data	outcomemeasurement	reportedresult	overallresult	Level of evidence
Gunduz et al. (2021)	low	someconcerns	low	low	someconcerns	someconcerns	A2
Teixeira et al. (2021)	low	low	low	low	low	low	A2
Strauss et al. (2021)	low	someconcerns	low	low	high	high	A2

Table 5. Risk of bias assessment in non-randomized studies of interventions using the ROBINS-I tool

Author andyear	confounding	selection of participants	classification of intervention	deviationsfromintendedintervention	missing data	outcome measurement	reportedresults	overallresult	Level of evidence
Schabrun et al. (2014)	low	low	low	low	moderate	moderate	low	moderate	B

Table 6. Methodological qualities for per outcome of all included articles

Outcomes		**Studies**	**Sensorytraining**	**Control group**	**Primary motor cortex** **Affectedhemisphere**	**Primary motor cortex** **Non-affectedhemisphere**	**Primarysomatosensorycortex** **Affected hemisphere**	**Level of evidence**	**Risk of Bias**
	Intracortical inhibition and facilitation	Gunduz et al. (2021)	Mirror therapy[24, 25]	Sham therapy[24]	• response rate =	• response rate =		A2	Some
		Teixeira et al. (2021)		tDCS[25]	• response rate =	• response rate =		A2	Low
		Strauss	Graded motor	Wait-			• inhibition ↑	A2	High

		et al. (2021)	imagery[26]	list[26]			• facilitation =		
Cortical excitability	Cortical activation	Strauss et al. (2021)	Graded motor imagery[26]	Wait-list[26]			• during motor task ↓ • during somatosensory task =	A2	High
	Map volume	Schabrun et al. (2014)	PES[27]	tDCS[27]	• response (short term) ↓			B	Moderate
				Sham therapy[27]	• response (short term) ↓				
		Gunduz et al. (2021)	Mirror therapy[24]	Sham therapy[24]	• response rate =	• response rate =		A2	Some
	Discrete map peaks	Schabrun et al. (2014)	PES[27]	tDCS[27]	• number of discrete peaks =	• number of discrete peaks =		B	Moderate
				Sham therapy[27]	• number of discrete peaks =	• number of discrete peaks =			
Cortical representation	Center of gravity	Schabrun et al. (2014)	PES[27]	tDCS[27]	• x & y angle (short term) =			B	Moderate
		Gunduz et al. (2021)	Mirror therapy[24]	Sham therapy[24]	• x & y angle =	• x & y angle =		A2	Some
	Distances between	Strauss et al.	Graded motor	Wait-			• distance of the thumb and little finger =	A2	High

	representations	(2021)	imagery[26]	list[26]					

PES: Peripheral electrical stimulation, tDCS: Transcranial direct current stimulation, =: Insignificant differences, ↑: Significant increase, ↓: Significant decrease.

FIGURE LEGENDS

Fig 1. The flowchart of the study selection

Appendix 1

Pubmed:

((("Pain"[Mesh] AND ("Complex Regional Pain Syndromes"[Mesh] OR "Causalgia"[Mesh] OR"Neuralgia"[Mesh] OR "Reflex Sympathetic Dystrophy"[Mesh] OR "Phantom Limb"[Mesh] OR "Amputees"[Mesh] OR "Amputation"[Mesh] OR "Amputation Stumps"[Mesh] OR "Amputation, Traumatic"[Mesh] OR "Peripheral Nerve Injuries"[Mesh] OR "Peripheral Nervous System Diseases"[Mesh] OR "Brachial Plexus Neuropathies"[Mesh] OR "Denervation"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Diabetes Complications"[Mesh] OR "Carpal Tunnel Syndrome"[Mesh] OR "Cubital Tunnel Syndrome"[Mesh] OR "Thoracic Outlet Syndrome"[Mesh] OR "Back Pain"[Mesh] OR "Low Back Pain"[Mesh] OR "Sciatica"[Mesh] OR "Neck Pain"[Mesh] OR "Upper Extremity"[Mesh] OR "Lower Extremity"[Mesh] OR "Extremities"[Mesh] OR "Foot"[Mesh] OR "Hand"[Mesh] OR "Shoulder"[Mesh] OR "Shoulder Pain"[Mesh] OR "Elbow"[Mesh] OR neuropath* OR radiculopat* OR discogenic OR diabet* OR radiat* OR forearm OR arm OR leg OR (nerve AND (reinnervation OR injury OR regeneration OR syndrome OR compression OR paralysis OR entrapment OR graft OR trans*)) OR neurolysis OR mechanical interface OR sensory loss OR deafferentation OR Complex regional pain syndrome OR reflex sympathetic dystrophy OR sudeck atrophy OR algodystrophy OR post-traumatic dystrophy OR (syndrome AND (shoulder hand OR pronator OR Kiloh-Nevin OR radial tunnel OR Struthers OR Wartenberg OR personage turner OR double crush OR thorax outlet)) OR brachial plexopathy OR brachial plexitis OR neuralgic amyotrophy OR neuritis)) NOT (congenital amputation OR "Spinal Cord Injuries"[Mesh] OR "Stroke"[Mesh] OR "Multiple Sclerosis"[Mesh])) AND ("Feedback, Sensory"[Mesh] OR "Kinesthesi*"[Mesh] OR "Stereognosis"[Mesh] OR "Touch"[Mesh] OR

"Touch Perception"[Mesh] OR "Vibration"[Mesh] OR "Vision, Ocular"[Mesh] OR "Electric Stimulation"[Mesh] OR "Hearing"[MeSH Terms] OR sensory OR tactile acuity OR discrimination OR two point OR tactile OR pressure OR graphesthesia OR point to point OR joint position sense OR vestibular OR propriocep* OR vibrat* OR localization OR mirror OR lateralization OR oculomotor OR visualization OR verbalization OR audio-visual OR auditory OR imag* OR electr*) AND (cortex OR cortices OR cortical) AND (reorganisation OR reorganization OR organization OR plasticity OR changes OR alteration OR adaptation OR modification OR remodeling OR remap* OR reshaping OR rearrangement OR homunculus)))

WoS:

(((("Pain" AND ("Complex Regional Pain Syndromes" OR "Causalgia" OR"Neuralgia" OR "Reflex Sympathetic Dystrophy" OR "Phantom Limb" OR "Amputees" OR "Amputation" OR "Amputation Stumps" OR "Amputation, Traumatic" OR "Peripheral Nerve Injuries" OR "Peripheral Nervous System Diseases" OR "Brachial Plexus Neuropathies" OR "Denervation" OR "Diabetes Mellitus" OR "Diabetes Complications" OR "Carpal Tunnel Syndrome" OR "Cubital Tunnel Syndrome" OR "Thoracic Outlet Syndrome" OR "Back Pain" OR "Low Back Pain" OR "Sciatica" OR "Neck Pain" OR "Upper Extremity" OR "Lower Extremity" OR "Extremities" OR "Foot" OR "Hand" OR "Shoulder" OR "Shoulder Pain" OR "Elbow" OR (neuropath* OR radiculopat* OR discogenic OR diabet* OR radiat* OR forearm OR arm OR leg) OR (nerve AND (reinnervation OR injury OR regeneration OR syndrome OR compression OR paralysis OR entrapment OR graft OR trans*)) OR neurolysis OR mechanical interface OR sensory loss OR deafferentation OR Complex regional pain syndrome OR reflex sympathetic dystrophy OR sudeck atrophy OR

algodystrophy OR post-traumatic dystrophy OR (syndrome AND (shoulder hand OR pronator OR Kiloh-Nevin OR radial tunnel OR Struthers OR Wartenberg OR personage turner OR double crush OR thorax outlet)) OR brachial plexopathy OR brachial plexitis OR neuralgic amyotrophy OR neuritis)) NOT (congenital amputation OR "Spinal Cord Injuries" OR "Stroke" OR "Multiple Sclerosis")) AND ("Feedback, Sensory" OR "Kinesthesi*" OR "Stereognosis" OR "Touch" OR "Touch Perception" OR "Vibration" OR "Vision, Ocular" OR "Electric Stimulation" OR "Hearing" OR sensory OR tactile acuity OR discrimination OR two point OR tactile OR pressure OR graphesthesia OR point to point OR joint position sense OR vestibular OR propriocep* OR vibrat* OR localization OR mirror OR lateralization OR oculomotor OR visualization OR verbalization OR audio-visual OR auditory OR imag* OR electr*) AND (cortex OR cortices OR cortical) AND (reorganisation OR reorganization OR organization OR plasticity OR changes OR alteration OR adaptation OR modification OR remodeling OR remap* OR reshaping OR rearrangement OR homunculus)))

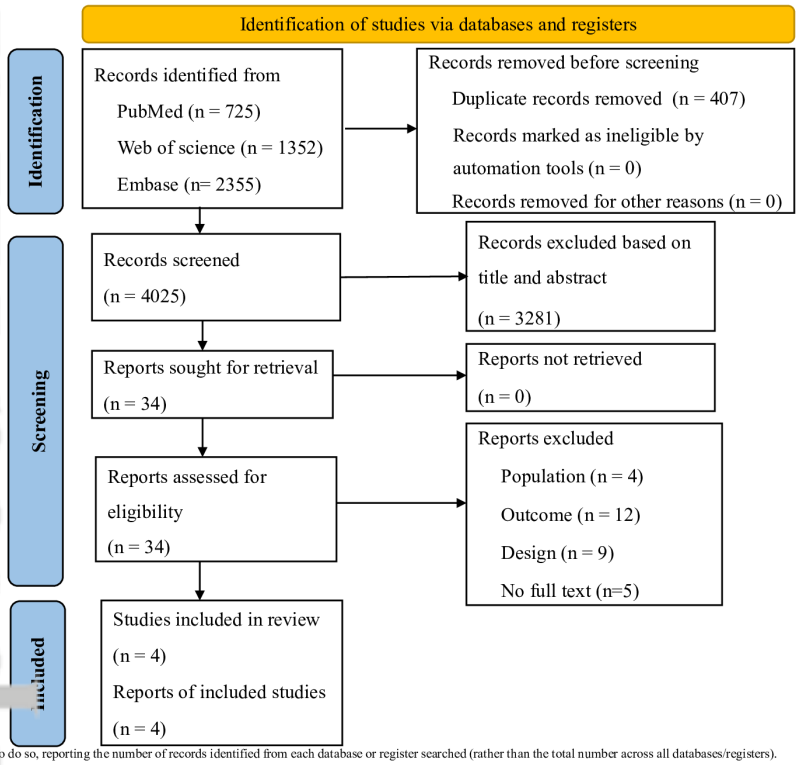
Embase:

('pain'/exp OR 'pain') AND ('complex regional pain syndromes'/exp OR 'complex regional painsyndromes' OR 'causalgia'/exp OR 'causalgia' OR 'neuralgia'/exp OR 'neuralgia' OR 'phantomlimb'/exp OR 'phantom limb' OR 'amputees'/exp OR 'amputees' OR 'amputation'/exp OR'amputation' OR 'amputation stumps'/exp OR 'amputation stumps' OR 'amputation,traumatic'/exp OR 'amputation, traumatic' OR 'peripheral nerve injuries'/exp OR 'peripheralnerve injuries' OR 'peripheral nervous system diseases'/exp OR 'peripheral nervous systemdiseases' OR 'brachial plexus neuropathies'/exp OR 'brachial plexus neuropathies' OR'denervation'/exp OR 'denervation' OR 'diabetes mellitus'/exp OR

'diabetes mellitus' OR'diabetes complications'/exp OR 'diabetes complications' OR 'carpal tunnel syndrome'/exp OR'carpal tunnel syndrome' OR 'cubital tunnel syndrome'/exp OR 'cubital tunnel syndrome' OR'thoracic outlet syndrome'/exp OR 'thoracic outlet syndrome' OR 'back pain'/exp OR 'back pain'OR 'low back pain'/exp OR 'low back pain' OR 'sciatica'/exp OR 'sciatica' OR 'neck pain'/exp OR'neck pain' OR 'upper extremity'/exp OR 'upper extremity' OR 'lower extremity'/exp OR 'lowerextremity'OR'extremities'/expOR'extremities'OR'foot'/expOR'foot'OR'hand'/expOR'hand'OR 'shoulder'/exp OR 'shoulder' OR 'shoulder pain'/exp OR 'shoulder pain' OR 'elbow'/exp OR'elbow' OR neuropath* OR radiculopat* OR discogenic OR diabet* OR radiat* OR 'forearm'/expOR forearm OR 'arm'/exp OR arm OR 'leg'/exp OR leg OR (('nerve'/exp OR nerve) AND('reinnervation'/exp OR reinnervation OR 'injury'/exp OR injury OR 'regeneration'/exp ORregeneration OR 'syndrome'/exp OR syndrome OR 'compression'/exp OR compression OR'paralysis'/exp OR paralysis OR 'entrapment'/exp OR entrapment OR 'graft'/exp OR graft ORtrans*)) OR 'neurolysis'/exp OR neurolysis OR 'mechanical interface' OR (mechanical AND('interface'/exp OR interface)) OR 'sensory loss'/exp OR 'sensory loss' OR (('sensory'/exp ORsensory) AND ('loss'/exp OR loss)) OR 'deafferentation'/exp OR deafferentation OR 'complexregional pain syndrome'/exp OR 'complex regional pain syndrome' OR (('complex'/exp ORcomplex) AND regional AND ('pain'/exp OR pain) AND ('syndrome'/exp OR syndrome)) OR'reflex sympathetic dystrophy'/exp OR 'reflex sympathetic dystrophy' OR (('reflex'/exp ORreflex)AND('sympathetic'/expORsympathetic)AND('dystrophy'/expORdystrophy)) OR 'sudeck atrophy'/exp OR 'sudeck atrophy' OR (sudeck AND ('atrophy'/exp OR atrophy)) OR'algodystrophy'/exp OR algodystrophy OR 'post-traumatic dystrophy'/exp OR 'post-traumaticdystrophy' OR ('post traumatic' AND ('dystrophy'/exp OR dystrophy)) OR

(('syndrome'/exp ORsyndrome) AND ('shoulder hand' OR (('shoulder'/exp OR shoulder) AND ('hand'/exp OR hand))OR pronator OR 'kiloh nevin' OR 'radial tunnel' OR (radial AND ('tunnel'/exp OR tunnel)) ORstruthers OR wartenberg OR 'personage turner' OR (personage AND turner) OR 'double crush'OR (double AND crush) OR 'thorax outlet' OR (('thorax'/exp OR thorax) AND outlet))) OR'brachial plexopathy'/exp OR 'brachial plexopathy' OR (brachial AND ('plexopathy'/exp ORplexopathy)) OR 'brachial plexitis'/exp OR 'brachial plexitis' OR (brachial AND plexitis) OR'neuralgic amyotrophy'/exp OR 'neuralgic amyotrophy' OR (neuralgic AND ('amyotrophy'/expOR amyotrophy)) OR 'neuritis'/exp OR neuritis) NOT ('congenital amputation'/exp OR'congenital amputation' OR (('congenital'/exp OR congenital) AND ('amputation'/exp ORamputation)) OR 'spinal cord injuries'/exp OR 'spinal cord injuries' OR 'stroke'/exp OR 'stroke'OR 'multiple sclerosis'/exp OR 'multiple sclerosis' OR 'spinal cord'/exp OR 'spinal cord' OR'hereditary motor sensory neuropathy' OR 'charcot marie tooth disease' OR 'guillain barresyndrome'/exp OR 'guillain barre syndrome' OR 'rat'/exp OR rat OR rodent* OR 'mouse'/exp OR'mouse' OR 'mice'/exp OR 'mice' OR rabbit* OR animal*) AND ('feedback, sensory'/exp OR'feedback, sensory' OR kinesthesi*' OR 'stereognosis'/exp OR 'stereognosis' OR 'touch'/exp OR'touch' OR 'touch perception'/exp OR 'touch perception' OR 'vibration'/exp OR 'vibration' OR'vision, ocular'/exp OR 'vision, ocular' OR 'electric stimulation'/exp OR 'electric stimulation' OR'hearing'/expOR'hearing'OR'sensory'/expORsensoryOR'tactileacuity'/expOR'tactileacuit y'OR (tactile AND ('acuity'/exp OR acuity)) OR (('discrimination'/exp OR discrimination) AND ('twopoint' OR (two AND point) OR tactile OR electro*)) 'pressure'/exp OR pressure OR'graphesthesia'/exp OR graphesthesia OR 'point to point' OR (to AND point) OR 'joint positionsense'/exp OR 'joint position sense' OR (('joint'/exp OR joint) AND ('position'/exp OR position)AND ('sense'/exp OR sense)) OR vestibular OR propriocep* OR vibrat* OR

'localization'/exp ORlocalization OR 'mirror'/exp OR mirror OR 'lateralization'/exp OR lateralization OR oculomotorOR 'visualization'/exp OR visualization OR 'verbalization'/exp OR verbalization OR 'audio visual'OR auditory OR imag*) AND ('cortex'/exp OR cortex OR cortices OR cortical) AND(reorganisation OR 'reorganization'/exp OR reorganization OR 'organization'/exp ORorganization OR 'plasticity'/exp OR plasticity OR changes OR alteration OR 'adaptation'/exp ORadaptation OR 'modification'/exp OR modification OR remodeling OR remap* OR reshaping OR'rearrangement'/expOR rearrangement OR'homunculus'/expORhomunculus)



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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

For more information, visit: http://www.prisma-statement.org/

Figure 1 .tiff