

This item is the archived peer-reviewed author-version of:

Influence of sensory re-training on cortical reorganization in peripheral neuropathy : a systematic review

Reference:

Canlı Kübra, Van Oijen Joris, van Oosterwijck Jessica, Meeus Mira, Van Oosterwijck Sophie, De Meulemeester Kayleigh, Canli Kuebra.- Influence of sensory re-training on cortical reorganization in peripheral neuropathy : a systematic review
PM&R : the journal of injury, function, and rehabilitation / American Academy of Physical Medicine and Rehabilitation - ISSN 1934-1563 - (2023), p. 1-20
Full text (Publisher's DOI): <https://doi.org/10.1002/PMRJ.13126>
To cite this reference: <https://hdl.handle.net/10067/2043860151162165141>

Canlı Kübra (Orcid ID: 0000-0002-9929-842X)
VanOosterwijck Jessica (Orcid ID: 0000-0002-8946-4383)
Meeus Mira (Orcid ID: 0000-0002-2022-5114)
De Meulemeester Kayleigh E. (Orcid ID: 0000-0003-0877-5022)

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

Running Title: Cortical Reorganization After Sensory Re-training

Kübra Canlı MSc¹, Joris Van Oijen MSc², Jessica Van Oosterwijck PhD^{2,3}, Mira Meeus PhD^{2,3,4},
Sophie Van Oosterwijck MSc^{2,3,5}, Kayleigh De Meulemeester PhD^{2,3}

¹Faculty of Physical Therapy and Rehabilitation, Hacettepe University, Ankara, Türkiye.

² Department of Rehabilitation Sciences, Spine, Pain and Head Research Unit Ghent, Ghent University, Belgium.

³Pain in Motion international research group, www.paininmotion.be, Belgium.

⁴Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Antwerpen, Belgium.

⁵Research Foundation - Flanders (FWO), Brussels, Belgium.

Corresponding Author: Kübra Canlı, Department of Physiotherapy and Rehabilitation, Hacettepe University, Ankara, Türkiye, 0498 07 23 24, kbrac91@gmail.com

Funding Source: There was no funding provided for this review from any source.

Conflict of Interest: The authors have no relevant financial or non-financial conflict of interest.

Financial Disclosure: The other authors have nothing to disclose.

PROSPERO Registration Number: CRD42022296602

Word count:

ABSTRACT

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1002/pmrj.13126](https://doi.org/10.1002/pmrj.13126)

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

Accepted Article

INTRODUCTION

The somatosensory system comprises components of both the peripheral and central nervous system¹. 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 function¹. 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 PNP². 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 productivity⁶. 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, and particularly in cortical areas undergo robust changes¹¹. Furthermore, these alterations are mainly monitored in the somatosensory and motor cortex and 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), and immediately occurs following peripheral injuries that selectively eliminate afferent stimulation of the nervous system¹¹. 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 nature¹⁴. Adaptive CR provides a basis for recovery by optimizing the use of central resources for sensory processing of remnant sensory receptors or motor function¹³. Contrary to that, maladaptive CR contributes to residual sensory abnormalities such as neuropathic pain and phantom sensation¹⁴. Maladaptive CR results in enhanced hypersensitivity of the pain processing neural network within the somatosensory system¹⁴. 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 syndrome¹⁷⁻¹⁹.

Accepted Article

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 cortex²⁰⁻²². 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 it²⁴⁻²⁷.

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). The clinical diagnosis of neuropathic pain was made based on the revised NP diagnostic criteria²⁹. According to the revised NP²⁹: *Possible PNP* was determined if the patient's history, pain distribution area, and validated screening tools suggest the existence of the PNP. *Probable PNP* was determined if sensory abnormalities in the painful area have the same neuroanatomically plausible distribution. *Definite PNP* determined if the objective diagnostic test confirms the lesion or disease of the peripheral somatosensory nervous system (such as neurophysiological tests).

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.

Study Selection

After searching each database, duplicates were removed with the help of Endnote X9³⁰ and the remaining references imported into Rayyan³¹. 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 randomized controlled trials were aimed to be included in this review, very few articles remained after the first study selection process, and, therefore, the study selection process was repeated to allow for the inclusion of non-randomized controlled trials.**

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-randomized studies – of interventions (ROBINS-I)³³ for non-randomized intervention studies. The RoB 2 consists of five domains which evaluate the randomization process, intended interventions, missing outcome data, measurement of the outcome, and reported results. Each domain can be classified as “low risk of bias”, “some concerns” or “high risk of bias”. If all domains of the tool were rated as ‘low risk of bias’, we judged an overall ‘low risk bias’. If one or more domains were rated as ‘some concerns’ but were not rated as ‘high risk of bias’ in any domain, we judged an overall ‘some concerns for risk of bias’. If one or more domains were rated ‘high risk of bias’, we judged an overall ‘high risk of bias’.

The ROBINS-I consists of seven domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions for all outcomes, bias due to deviations from intended interventions for all outcomes, bias due to missing data for all outcomes, bias in measurement of outcomes, and bias in selection of the reported results.

Synthesis of results

The level of evidence and strength of conclusion were graded in accordance with the evidence-based guideline development (EBRO)

method developed by the Dutch Institute for Health Care Improvement (CBO)³⁴.

These selected studies were rated based on the following criteria: A2, a double-blinded controlled trial with sound methodology or B, a comparative controlled trial not satisfying the conditions of A2. Finally, these levels 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 number²⁴,²⁵. Two studies were performed in a rehabilitation hospital²⁴,²⁵, the other studies did not report the study setting²⁶,²⁷. Three studies²⁴⁻²⁶ were randomized clinical trials, and one study was a non-randomized clinical trial²⁷.

All of the included studies assessed cortical excitability and cortical representation as outcome measure of CR²⁴⁻²⁷. Cortical excitability was evaluated using intracortical inhibition and facilitation in three studies²⁴⁻²⁶, and cortical activation in one study²⁶. 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 study²⁷, center of gravity in two studies^{24, 27}, and thumb and littlefinger representation distance in one study²⁶.

Participants Characteristics

The sample sizes ranged from 16²⁷ to 98²⁵ 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 years²⁷ and 54.71±14.13 years²⁶. All participants had chronic pain ranging between 3 months and 4.2±0.7 years²⁴⁻²⁷. 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 chronic²⁷.

One study reported dropouts that were included for all analyses with a total of 14 participants²⁴. One study reported dropouts that had to be excluded from all analyses with 2 participants²⁷. 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 study²⁷, and graded motor imagery in one study²⁶. 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 study²⁶. Considering sham therapy, all three studies used a combination of the two different types of sham therapy^{24, 25, 27}. This included sham tDCS over the affected hemisphere with 30-second stimulation in three studies^{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 study²⁷.

Different treatment frequencies were applied in the studies, ranging from only one session²⁷ to daily sessions for six weeks²⁶. The session duration varied from 40 minutes^{24, 25} to at least 10 minutes every waking hour²⁶. 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 studies²⁴⁻²⁷ and functional magnetic resonance imaging (fMRI) in one study²⁶. The excitability and organization of corticospinal inputs to the studied muscles at the cortex were examined using TMS. The representation of the first dorsal interosseous muscle from the affected and unaffected side at the cortex was mapped in three studies²⁴⁻²⁶ and the representation at the cortex of the paraspinal muscles contralateral to the side of the worst pain was mapped in one study²⁷. 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 study²⁶.

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 study²⁵, some concerns were present in one study²⁴, and risk of bias was high in one study²⁶. 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 tDCS²⁴. The high risk of bias was due to results not being displayed separately for each follow-up measurement²⁶. The overall risk of bias of the non-randomized controlled trial was moderate in one study²⁷ 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 score²⁴⁻²⁶, and one study without randomization of the study subjects was rated a B score²⁷. 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 Interval Intracortical 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-term effects both Gunduz et al.²⁴ and Teixeira 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-term effects 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 effects²⁷, while the other examined long-term effects²⁴.

In regards of short-term effects 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-term effects Gunduz 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-term effects 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 intervention²⁷.

Center of Gravity

Two studies reported the effect of sensory re-training on *center of gravity*^{24, 27}. One study documented short-term effects²⁷, while the other study reported long-term effects²⁴.

In regards of short-term effects 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-term effects 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-term effects 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 effects²⁵⁻²⁷.

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* with limited evidence. 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 term with limited evidence. 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-list with limited evidence. 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.

Mirror therapy involves the execution of movements of the unaffected limb or both unaffected/affected limb while the patient has to watch the unaffected limb reflection in a mirror³⁵. Bilateral movement has been shown to induce more reactivation of the **primary motor cortex** than unilateral movement during mirror therapy³⁶. However, bilateral movements may be impossible during mirror therapy in some PNP patients such as amputees but not complex regional pain syndrome. Therefore, the results of the included studies, performed by Gunduz et al.²⁴ and Teixeira et al.²⁵ in patients with lower limb amputees cannot be generalized to all PNP patients^{24, 25}. One of the mechanisms underlying the mirror therapy effect on the cortex is

the mirror neuron system that modulates **primary motor cortex** activity²⁰. It has been well known that usage of regular lower limb prosthesis may have increased the mirror neuron system activity during phantom ankle movement³⁷. Regular usage of the prosthesis provides nearly a physiological amount of the cutaneous and proprioceptive feedback from the periphery to the contralateral **somatosensory cortex** in the same region as the phantom limb³⁸. Additionally, prostheses modify **somatosensory and motor cortex** representation of the affected limb and thus help in maintaining the *cortical representation*. Particularly, upper extremity amputees who frequently use myoelectric prosthesis demonstrated less CR than upper extremity amputees who used either a cosmetic or no prosthesis or wore myoelectric prostheses for minimal time³⁹. Hence, differences in the prosthesis use duration and the type of prosthesis between the groups may have influenced the results. Gunduz et al.²⁴ and Teixeira et al.²⁵ did not report the prosthesis utilization duration or type.

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 tDCS⁵¹. In contrast to cathodal tDCS, which is expected to decrease *cortical excitability*, anodal tDCS is expected to increase *cortical excitability*^{51, 52}. Teixeira 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}. Teixeira 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 Teixeira 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, Teixeira 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 treatments⁴⁰⁻⁴². However, these studies were performed in central neuropathic pain patients and the results can not be generalized to the patients with PNP since central and peripheral neuropathic pain have different CR mechanisms. Substantial and perhaps irreversible neuronal changes have occurred in central neuropathic pain in response to direct injury of the central nervous system, whereas an anatomical lesion to the central nervous system does not occur in PNP^{43, 44}. These differences make it also difficult to directly compare the treatments in this review with the literature⁴³.

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 usage²⁶. 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 utilization²⁶.

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 by Schabrunn 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 Schabrunn 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 muscles⁴⁹. 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 treatment⁵⁰, this review gains importance by highlighting the most recent information on the management of maladaptive CR in PNP, focusing on the sensory re-training.

Future studies should also take into account prosthesis usage duration, pain medication utilization, stimulus intensity and electrode types with TMS on CR. Mirror therapy with unilateral or bilateral movements should be separately compared with control treatments in various PNP conditions. It may also be worthwhile to examine the outcomes of the CR in more detail, including neural networks/connectivity between areas or structural changes (e.g., volume/density of the brain regions). 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 pain intensity/severity, improvement in balance control during gait, and reduced 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, need to be taken into account in the future studies.**

CONCLUSION

This review indicates that graded motor imagery and PES lead to higher decrease of cortical excitability of the affected hemisphere compared to wait-list, tDCS and sham treatment with limited evidence, 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.

REFERENCES

1. Arezzo JC, Schaumburg HH and Spencer PS. Structure and function of the somatosensory system: a neurotoxicological perspective. *Environ Health Perspect* 1982; 44: 23-30. 1982/04/01. DOI: 10.1289/ehp.824423.
2. Costigan M, Scholz J and Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci* 2009; 32: 1-32. 2009/04/30. DOI: 10.1146/annurev.neuro.051508.135531.
3. Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. *Pain* 2011; 152: 2204-2205. 2011/07/19. DOI: 10.1016/j.pain.2011.06.017.
4. Bouhassira D, Lantéri-Minet M, Attal N, et al. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008; 136: 380-387. 2007/09/25. DOI: 10.1016/j.pain.2007.08.013.
5. Dieleman JP, Kerklaan J, Huygen F, et al. Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain* 2008; 137: 681-688. 2008/04/29. DOI: 10.1016/j.pain.2008.03.002.
6. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics* 2009; 27: 95-112. 2009/03/04. DOI: 10.2165/00019053-200927020-00002.
7. van Tulder MW, Koes BW and Bouter LM. A cost-of-illness study of back pain in The Netherlands. *Pain* 1995; 62: 233-240. 1995/08/01. DOI: 10.1016/0304-3959(94)00272-g.
8. Foster NE, Konstantinou K, Lewis M, et al. The clinical and cost-effectiveness of stratified care for patients with sciatica: the SCOPiC randomised controlled trial protocol (ISRCTN75449581). *BMC Musculoskelet Disord* 2017; 18: 172. 2017/04/27. DOI: 10.1186/s12891-017-1513-5.

9. Kerstman E, Ahn S, Battu S, et al. Neuropathic pain. *Handb Clin Neurol* 2013; 110: 175-187. 2013/01/15. DOI: 10.1016/b978-0-444-52901-5.00015-0.
10. Baron R, Binder A and Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9: 807-819. 2010/07/24. DOI: 10.1016/s1474-4422(10)70143-5.
11. Sammons RP and Keck T. Adult plasticity and cortical reorganization after peripheral lesions. *Curr Opin Neurobiol* 2015; 35: 136-141. 2015/08/28. DOI: 10.1016/j.conb.2015.08.004.
12. Kim W, Kim SK and Nabekura J. Functional and structural plasticity in the primary somatosensory cortex associated with chronic pain. *J Neurochem* 2017; 141: 499-506. 2017/03/10. DOI: 10.1111/jnc.14012.
13. Osborne NR, Anastakis DJ and Davis KD. Peripheral nerve injuries, pain, and neuroplasticity. *J Hand Ther* 2018; 31: 184-194. 2018/05/01. DOI: 10.1016/j.jht.2018.01.011.
14. Mohan A and Vanneste S. Adaptive and maladaptive neural compensatory consequences of sensory deprivation-From a phantom percept perspective. *Prog Neurobiol* 2017; 153: 1-17. 2017/04/15. DOI: 10.1016/j.pneurobio.2017.03.010.
15. Harris AJ. Cortical origin of pathological pain. *Lancet* 1999; 354: 1464-1466. 1999/10/30. DOI: 10.1016/s0140-6736(99)05003-5.
16. Vartiainen N, Kirveskari E, Kallio-Laine K, et al. Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain. *J Pain* 2009; 10: 854-859. 2009/07/30. DOI: 10.1016/j.jpain.2009.02.006.
17. Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995; 375: 482-484. 1995/06/08. DOI: 10.1038/375482a0.

18. Pleger B, Ragert P, Schwenkreis P, et al. Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. *Neuroimage* 2006; 32: 503-510. 2006/06/07. DOI: 10.1016/j.neuroimage.2006.03.045.
19. Tecchio F, Padua L, Aprile I, et al. Carpal tunnel syndrome modifies sensory hand cortical somatotopy: a MEG study. *Hum Brain Mapp* 2002; 17: 28-36. 2002/08/31. DOI: 10.1002/hbm.10049.
20. Deconinck FJ, Smorenburg AR, Benham A, et al. Reflections on mirror therapy: a systematic review of the effect of mirror visual feedback on the brain. *Neurorehabil Neural Repair* 2015; 29: 349-361. 2014/08/28. DOI: 10.1177/1545968314546134.
21. Flor H, Denke C, Schaefer M, et al. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. *Lancet* 2001; 357: 1763-1764. 2001/06/14. DOI: 10.1016/s0140-6736(00)04890-x.
22. Flor H and Birbaumer N. Phantom limb pain: cortical plasticity and novel therapeutic approaches. *Curr Opin Anaesthesiol* 2000; 13: 561-564. 2006/10/04. DOI: 10.1097/00001503-200010000-00013.
23. Schabrun SM and Hillier S. Evidence for the retraining of sensation after stroke: a systematic review. *Clin Rehabil* 2009; 23: 27-39. 2008/12/31. DOI: 10.1177/0269215508098897.
24. Gunduz ME, Pacheco-Barrios K, Bonin Pinto C, et al. Effects of Combined and Alone Transcranial Motor Cortex Stimulation and Mirror Therapy in Phantom Limb Pain: A Randomized Factorial Trial. *Neurorehabil Neural Repair* 2021; 35: 704-716. 2021/06/02. DOI: 10.1177/15459683211017509.
25. Teixeira PEP, Pacheco-Barrios K, Gunduz ME, et al. Understanding intracortical excitability in phantom limb pain: A multivariate analysis from a multicenter randomized clinical trial. *Neurophysiol Clin* 2021; 51: 161-173. 2021/03/03. DOI: 10.1016/j.neucli.2020.12.006.

26. Strauss S, Barby S, Härtner J, et al. Graded motor imagery modifies movement pain, cortical excitability and sensorimotor function in complex regional pain syndrome. *Brain Commun* 2021; 3: fcab216. 2021/10/19. DOI: 10.1093/braincomms/fcab216.
27. Schabrun SM, Jones E, Elgueta Cancino EL, et al. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul* 2014; 7: 451-459.
28. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med* 2021; 18: e1003583. 2021/03/30. DOI: 10.1371/journal.pmed.1003583.
29. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 2016; 157: 1599-1606. 2016/04/27. DOI: 10.1097/j.pain.0000000000000492.
30. Team TE. EndNote, EndNote. X9 ed. Philadelphia, PA: Clarivate Analytics, 2013.
31. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; 5: 210. 2016/12/07. DOI: 10.1186/s13643-016-0384-4.
32. Collaboration C. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials, (accessed December 6 2019).
33. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj* 2016; 355: i4919. 2016/10/14. DOI: 10.1136/bmj.i4919.
34. Meeus M GN. *Health literacy: from reference to review*. Leuven, Belgium: ACCO Uitgeverij, 2016.
35. Stevens JA and Stoykov ME. Using motor imagery in the rehabilitation of hemiparesis. *Arch Phys Med Rehabil* 2003; 84: 1090-1092. 2003/07/26. DOI: 10.1016/s0003-9993(03)00042-x.

36. Tai RY, Zhu JD, Cheng CH, et al. Cortical neural activity evoked by bilateral and unilateral mirror therapy after stroke. *Clin Neurophysiol* 2020; 131: 2333-2340. 2020/08/23. DOI: 10.1016/j.clinph.2020.06.030.
37. Seidel S, Kasprian G, Furtner J, et al. Mirror therapy in lower limb amputees--a look beyond primary motor cortex reorganization. *Rofo* 2011; 183: 1051-1057. 2011/10/01. DOI: 10.1055/s-0031-1281768.
38. Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, et al. Mechanisms underlying embodiment, disembodiment and loss of embodiment. *Neurosci Biobehav Rev* 2008; 32: 143-160. 2007/08/21. DOI: 10.1016/j.neubiorev.2007.07.001.
39. Lotze M, Grodd W, Birbaumer N, et al. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nat Neurosci* 1999; 2: 501-502. 1999/08/17. DOI: 10.1038/9145.
40. Cui W, Huang L, Tian Y, et al. Effect and mechanism of mirror therapy on lower limb rehabilitation after ischemic stroke: A fMRI study. *NeuroRehabilitation* 2022; 51: 65-77. 2022/03/22. DOI: 10.3233/nre-210307.
41. Michielsen ME, Selles RW, van der Geest JN, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabil Neural Repair* 2011; 25: 223-233. 2010/11/06. DOI: 10.1177/1545968310385127.
42. Bae SH JW KK. Effects of mirror therapy on subacute stroke patients' brain waves and upper extremity functions. *J Phys Ther Sci* 2012; 24: 1119-1122.
43. Watson JC and Sandroni P. Central Neuropathic Pain Syndromes. *Mayo Clin Proc* 2016; 91: 372-385. 2016/03/06. DOI: 10.1016/j.mayocp.2016.01.017.

44. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; 152: S2-s15. 2010/10/22. DOI: 10.1016/j.pain.2010.09.030.
45. Héту S, Gagné M, Reilly KT, et al. Short-term reliability of transcranial magnetic stimulation motor maps in upper limb amputees. *J Clin Neurosci* 2011; 18: 728-730. 2011/03/12. DOI: 10.1016/j.jocn.2010.09.011.
46. Chipchase LS, Schabrun SM and Hodges PW. Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study. *Arch Phys Med Rehabil* 2011; 92: 1423-1430. 2011/05/31. DOI: 10.1016/j.apmr.2011.01.011.
47. Chipchase LS, Schabrun SM and Hodges PW. Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. *Clin Neurophysiol* 2011; 122: 456-463. 2010/08/27. DOI: 10.1016/j.clinph.2010.07.025.
48. Elgueta-Cancino E, Massé-Alarie H, Schabrun SM, et al. Electrical Stimulation of Back Muscles Does Not Prime the Corticospinal Pathway. *Neuromodulation* 2019; 22: 555-563. 2019/06/25. DOI: 10.1111/ner.12978.
49. Gallina A, Peters S, Neva JL, et al. Selectivity of conventional electrodes for recording motor evoked potentials: An investigation with high-density surface electromyography. *Muscle Nerve* 2017; 55: 828-834. 2016/09/21. DOI: 10.1002/mus.25412.
50. Freeman R, Baron R, Bouhassira D, et al. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. *Pain* 2014; 155: 367-376. 2014/01/30. DOI: 10.1016/j.pain.2013.10.023.

Table 1. Inclusion and exclusion criteria

Criteria	Description	
	Inclusion	Exclusion
Patient	<ul style="list-style-type: none"> - humans - any ages between 18 and 65 years - to be conscious - diagnosed with a PNP <p><i>a. possible neuropathic pain</i></p> <ul style="list-style-type: none"> ■ 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 	<ul style="list-style-type: none"> - 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

Accepted Article

(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 DouleurNeuropathique 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***

the objective diagnostic test

- Charcot-Marie-tooth disease

- pregnancy

	<p>confirm the lesion or disease of the peripheral somatosensory nervous system (such as neurophysiological tests</p>	
<p>Intervention(s)</p>	<p>at least one of the following sensory re-training modalities:</p> <ul style="list-style-type: none"> - proprioception training (vibration, joint position sense or kinesthesia) - point-to-point training - tactile/tactile acuity training - tactile object recognition (e.g. two-point discrimination) training - electrical stimulation and discrimination training - temperature discrimination training - graphesthesia training - localization training - motor imaginary training 	<ul style="list-style-type: none"> - combination of the sensory training with any other treatment as the effects of sensory training cannot be isolated from the effects of the other treatment(s) - massage - brain stimulation techniques (transcranial magnetic stimulation, EEG) - strengthening exercises (theraband)

Accepted Article

	<ul style="list-style-type: none"> - visual imagery training - auditory imagery training - touch imagery training - mirror therapy - spatial organization training - virtual reality 	
<p>Comparison(s)</p>	<ul style="list-style-type: none"> - placebo/sham treatment - no-intervention/ waiting list - other treatment methods used in rehabilitation except sensory re-training: <ul style="list-style-type: none"> - exercise - musculoskeletal manipulations - acupuncture - 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)	
Outcome	cortical reorganization	no description of cortical reorganization as an outcome
Study design and report	<ul style="list-style-type: none"> - randomized controlled trial - non-randomized controlled trial - reported only in English 	<ul style="list-style-type: none"> - uncontrolled studies - non-experimental studies - reported in other languages than English

PNP: Peripheral neuropathic pain, EEG: Electroencephalogram.

Table 2. Evidence-Based Guideline Development (EBRO) Method

Level of evidence

Accepted Article

A1	Systematic reviews and independent A2 studies	meta-analyses based on minimally	2
A2	Randomized controlled trials	(RCTs):	double-blinded;
B	Comparative studies, but lacking the quality criteria of A2	with sound methodology and sufficient sample size	
C	Non-comparative studies	(including cohort studies and case-control studies)	
D	Expert opinion		

Table 3: Evidence Table of Included Studies

Author and Year of Publication and Country	Study Design	Pathology; Sample Size (n); Age (in years Mean \pm SD or Median \pm IQR); Gender (F/M in %); Time Since Disease Onset (in months); Pain Intensity (Mean \pm SD or Median \pm 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 \times 2 factorial clinical 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 <u>tDCS</u> - anodal electrode = over the primary motor cortex contralateral to the amputation side	TMS Single Pulse TMS - 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 <u>affected hemisphere</u> no statistically significant increase with: - Mirror therapy compared to sham therapy (B = 0.2, p = 0.57)

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

	<p>months</p> <p>pain intensity (VAS) = 6.28 ± 1.67</p> <p>Sham Treatment Group n = 27</p> <p>42.96 ± 12.28 years</p> <p>F/M = 37.04% - 62.96</p> <p>time since disease onset (amputation) = 63.88 ± 9.55 months</p> <p>pain intensity (VAS) = 5.89 ± 1.57</p>	<p>weeks period</p> <p>Mirror Therapy Group</p> <p>Treatments</p> <p>a. Mirror Therapy</p> <p>b. Sham tDCS <i>Mirror Therapy</i></p> <ul style="list-style-type: none"> - 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 			<p><u>- Mirror therapy compared to sham therapy</u> (p value not reported)</p> <p>Map Volume Changes <i>affected hemisphere</i> no statistically significant decrease with:</p> <p><u>- Mirror therapy compared to sham therapy</u> (B = -0.31, p = 0.72)</p> <p><i>non-affected hemisphere</i> no statistically significant changes with:</p> <p><u>- Mirror therapy compared to sham therapy</u> (p value not reported)</p> <p>Center of Gravity</p>
--	---	---	--	--	--

		<p><u>Sham tDCS</u></p> <ul style="list-style-type: none"> - 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 <p>tDCS Group</p> <p>Treatments</p> <ol style="list-style-type: none"> a. Transcranial Direct Current Stimulation b. Covered Mirror 			<p>Changes (x angle)</p> <p><u>affected hemisphere</u></p> <p>no statistically significant increase with:</p> <ul style="list-style-type: none"> - <u>Mirror therapy compared to sham therapy</u> <p>(B = 0.03, p = 0.95)</p> <p><u>non-affected hemisphere</u></p> <p>no statistically significant changes with:</p> <ul style="list-style-type: none"> - <u>Mirror therapy compared to sham therapy</u> <p>(p value not reported)</p> <p>Center of Gravity</p> <p>Changes (y angle)</p> <p><u>affected hemisphere</u></p> <p>statistically significant more lateral</p>
--	--	---	--	--	--

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)

		<p>for 10 days</p> <ul style="list-style-type: none">- home exercise = 10 sessions at home over 2 weeks period <p>Sham Treatment Group</p> <p>Treatments</p> <ol style="list-style-type: none">Sham tDCSCovered Mirror Therapy <p><u>Sham tDCS</u></p> <ul style="list-style-type: none">- 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			
--	--	---	--	--	--

			<p>applied at first 30 seconds of the 20 min</p> <p>- frequency = daily session for 10 days</p> <p><u>Covered Mirror Therapy</u></p> <p>- functional task with the covered mirror by imagining movement</p> <p>- duration = 20 minutes</p> <p>- frequency = daily session for 10 days</p> <p>- home exercise = 10 sessions at home over 2 weeks period</p>			
Schaorun et al (2014) ¹ not reported	placebocontrol ledcrossoverstudy	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 <u>affected hemisphere</u> statistically significant decreases with:

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

	<p>30 ± 2.0 years</p> <p>F/M = 43.75% - 56.25%</p> <p>time since disease onset = not reported</p> <p>pain intensity (NRS) = 5.3 ± 0.4</p>	<p>a. tDCS</p> <p>b. Peripheral Electrical Stimulation</p> <p><u>tDCS</u></p> <p>- anodal electrode = motor cortical representation of the back muscles contralateral to the side of worst pain</p> <p>- cathodal electrode = contralateral supraorbital region.</p> <p>- current density=(0-1 mA) and down (1-0 mA) over 10 s at the beginning and end of the 30-min stimulation period</p> <p>- duration = 30 minutes</p> <p>- frequency = one session</p>	<p>- coil type = figure-of-eight coil</p> <p>- muscle = paraspinal muscles</p>	<p>- cortical representation</p> <ul style="list-style-type: none"> ●number of discretepeaks ●center of gravity <p>investigated hemisphere</p> <p>- affected hemisphere</p> <p>investigated brain region</p> <p>- primary motor cortex</p> <p>evaluation time</p> <p>- baseline</p> <p>- immediately after post-intervention</p>	<p>- Peripheral electrical stimulation compared to tDCS</p> <p>(p = 0.024*) (p = 0.73)</p> <p>- Peripheral electrical stimulation compared to sham treatments</p> <p>(p = 0.024*) (p = 0.59)</p> <p>Number of Discrete Peaks</p> <p>Proportion of Individual Maps Containing Two Peaks</p> <p><u>affected hemisphere</u></p> <p>no statistically significant differences with:</p> <p>- Peripheral electrical stimulation compared to tDCS</p>
--	---	--	--	--	--

			<p><u>Peripheral Electrical Stimulation</u></p> <ul style="list-style-type: none"> - biphasic waveform - pulse duration = 0.1 ms -stimulation intensity = 2x3 perceptual threshold - duration = 30 minutes - frequency = one session <p>tDCS Group</p> <p>Treatments</p> <ol style="list-style-type: none"> a. tDCS b. Sham Peripheral Electrical Stimulation <p><u>tDCS</u></p> <ul style="list-style-type: none"> - anodal electrode= motor cortical 			<p>(p value not reported for both of the groups)</p> <p>no statistically significant differences with:</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to sham treatment</u> <p>(p value not reported for both of the groups)</p> <p>One Single Peak affected hemisphere</p> <p>no statistically significant differences with:</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to tDCS</u> <p>(0.0 ± 0.00) (p = 0.42) (p = 0.23)</p> <ul style="list-style-type: none"> - <u>Peripheral electrical</u>
--	--	--	---	--	--	--

			<p>representation of the back muscles contralateral to the side of worst pain</p> <ul style="list-style-type: none"> - 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 <p><i>Sham</i> <i>Peripheral</i></p> <p><u>Electrical Stimulation</u></p> <ul style="list-style-type: none"> - biphasic waveform - pulse duration:0.1 ms - stimulation intensity: 0 			<p><u>stimulation compared to sham treatment</u></p> <p>(0.2 ± 0.2) (p = 0.42) (p = 0.69)</p> <p>Center of Gravity (x angle)</p> <p><u>affected hemisphere</u></p> <p>no statistically significant differences with:</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to tDCS</u> <p>(p value not reported for both of the groups)</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to sham treatment</u> <p>(p value not reported for both of the groups)</p>
--	--	--	--	--	--	---

			<p>mA perceptual threshold</p> <ul style="list-style-type: none"> - duration = 30 minutes - frequency = one session <p>Peripheral Electrical Stimulation Group</p> <p>Treatments</p> <p>a. Peripheral Electrical Stimulation</p> <p>b. Sham tDCS</p> <p><u>Peripheral Electrical Stimulation</u></p> <ul style="list-style-type: none"> - biphasic waveform - pulse duration = 0.1 ms - stimulation intensity = 2x3 perceptual threshold - duration = 30 minutes - frequency = one session 			<p>Center of Gravity (y angle)</p> <p><u>affected hemisphere</u></p> <p>no statistically significant differences with:</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to tDCS</u> <p>(p value not reported for both of the groups)</p> <ul style="list-style-type: none"> - <u>Peripheral electrical stimulation compared to sham treatment</u> <p>(p value not reported for both of the groups)</p>
--	--	--	--	--	--	---

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

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

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

²Only 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.

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

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

<p>(t (18) = 0.77, p value reported as a not significant))</p> <p>Distance of the First and Fifth Finger of the Hand Representation in Primary Somatosensory Cortex</p> <p><i>affected hemisphere</i></p> <p>no statistically significant differences between:</p> <ul style="list-style-type: none">- Graded motor imagery compared to wait – list <p>(p value not reported for both of the groups)</p>					
---	--	--	--	--	--

Teixeira et al (2021) ³ USA	randomized, blinded, sham-controlled, 2 × 2 factorial clinical 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 ± 7.5 months pain intensity (VAS) = 6.2 ± 1.7	tDCS and Mirror Therapy Group Treatments a. tDCS b. Mirror Therapy <u>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 = 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 <u>affected hemisphere</u> no statistically significant differences between: <u>- Mirror therapy compared to tDCS</u> (B = -9.40, p = 0.563) (B = 15.22, p = 0.342) <u>non-affected hemisphere</u> no statistically significant differences between: <u>- Mirror Therapy compared to tDCS</u>
---	--	--	--	---	---	---

³This 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 separately, keeping in mind that the longitudinal changes of intracortical excitability with-in subjects (post-predifference) were not statistically significantly different in this study. However, multivariate models for the change in intracortical inhibition and intracortical facilitation for both hemispheres 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

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

b. Sham tDCS

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

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 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

		<ul style="list-style-type: none">- cathodal electrode = over the contralateral supraorbital area- current density = 2 mA- duration = 20 minutes- frequency = daily session for 10 days <p><u>Covered Mirror Therapy</u></p> <ul style="list-style-type: none">- 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 <p>Sham Treatment Group</p>		
--	--	--	--	--

		<p>Treatments:</p> <ul style="list-style-type: none">a. Sham tDCSb. Covered Mirror Therapy <p><u>Sham tDCS</u></p> <ul style="list-style-type: none">- 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 <p><u>Covered Mirror Therapy</u></p> <ul style="list-style-type: none">- 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: Standard 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 and year	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 and year	confounding	selection of participants	classification of intervention	deviations from intended intervention	missing data	outcome measurement	reported results	overall result	Level of evidence
Schauman 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	Sensory training	Control group	Primary motor cortex Affected hemisphere	Primary motor cortex Non-affected hemisphere	Primary somatosensory cortex 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

<i>Cortical excitability</i>		et al. (2021)	imagery ²⁶	list ²⁶			• facilitation =			
	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	
<i>Cortical representation</i>	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 =				
	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
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.

Accepted Article

FIGURE LEGENDS

Fig 1. The flowchart of the study selection

Accepted Article

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:

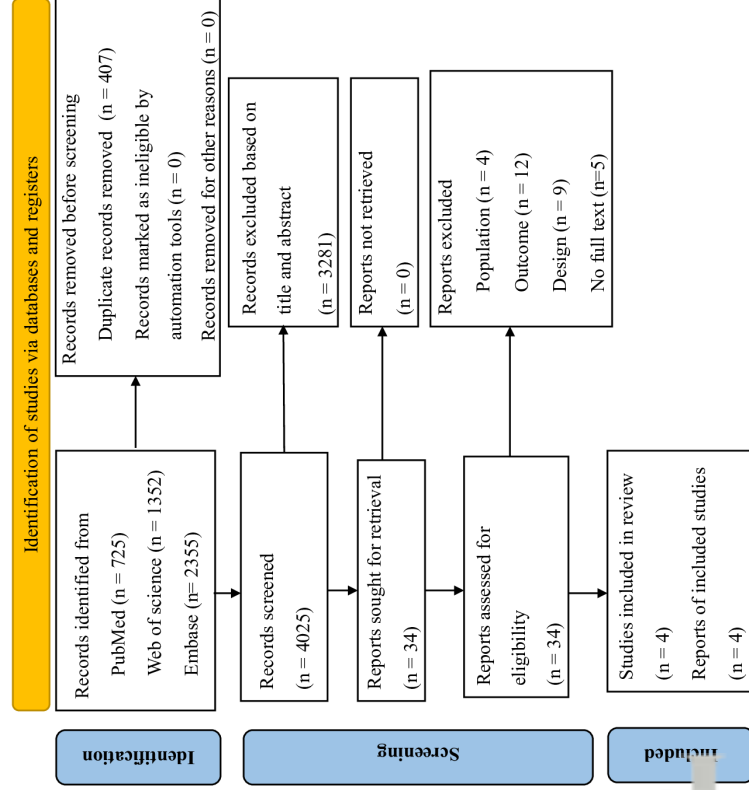
('pain'/exp OR 'pain') AND ('complex regional pain syndromes'/exp OR 'complex regional painsyndromes' OR 'causalgia'/exp OR 'causalgia' OR 'neuralgia'/exp OR 'neuralgia' OR 'phantomlimb'/exp OR 'phantom limb' OR 'amputees'/exp OR 'amputees' OR 'amputation'/exp OR 'amputation' OR 'amputation stumps'/exp 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'h and'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

Accepted Article

((('syndrome'/exp OR syndrome) AND ('shoulder hand' OR (('shoulder'/exp OR shoulder) AND ('hand'/exp OR hand))) OR pronator OR 'killoh nevin' OR 'radial tunnel' OR (radial AND ('tunnel'/exp OR tunnel)) OR struthers 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 OR plexopathy)) OR 'brachial plexitis'/exp OR 'brachial plexitis' OR (brachial AND plexitis) OR 'neuralgic amyotrophy'/exp OR 'neuralgic amyotrophy' OR (neuralgic AND ('amyotrophy'/exp OR amyotrophy)) OR 'neuritis'/exp OR neuritis) NOT ('congenital amputation'/exp OR 'congenital amputation' OR (('congenital'/exp OR congenital) AND ('amputation'/exp OR amputation)) 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'/exp OR 'hearing' OR 'sensory'/exp OR 'sensory' OR 'tactile acuity'/exp OR 'tactile acuity' 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 position sense'/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 OR localization OR 'mirror'/exp OR mirror OR 'lateralization'/exp OR lateralization OR oculomotor OR '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 OR organization OR 'plasticity'/exp OR plasticity OR changes OR alteration OR 'adaptation'/exp OR adaptation OR 'modification'/exp OR modification OR remodeling OR remap* OR reshaping OR 'rearrangement'/exp OR rearrangement OR 'homunculus'/exp OR homunculus)



*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/register).

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

Ezrom, Page M1, Mcenzie 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