Effectiveness of motor imagery in complex regional pain syndrome: A Systematic Review with Meta-Analysis

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ABSTRACT

Purpose: To determine the effects of MI on pain intensity and disability in individuals with CRPS.

Materials and Methods: A systematic search was conducted in various electronic databases: PubMed, CINAHL, WOS, PEDro, CENTRAL, Scopus. Randomized controlled trials assessing the effects of MI for CRPS were included. The risk of bias was assessed with Cochrane Risk of Bias tool, methodological quality with PEDro scale, and level of evidence with GRADE. Between-groups standardized mean differences (SMD) were calculated.

Results: Six studies were included. The meta-analysis found moderate-quality evidence that MI improves pain intensity and related disability as immediate (pain: SMD -1.07, 95% CI: -1.53 to -0.60; disability: SMD 1.05, 95% CI: 0.59 to 1.51), short-term (pain: SMD -1.28, 95% CI: -2.14 to -0.42; disability: SMD 1.37; 95% CI: 0.16 to 2.58) and long-term effects (pain: SMD -1.18; 95% CI: -1.89 to -0.46; disability: SMD 1.18; 95% CI: 0.46 to 1.89), as compared with a comparison group. The risk of bias of the trials was relatively low, but the imprecision of the results downgraded the level of evidence.

Conclusions: Moderate-quality evidence suggests a positive effect of MI for improving pain intensity and disability immediately after and at short-term in individuals with CRPS.

Keywords: chronic pain; complex regional pain syndrome; motor imagery; physical therapy; systematic review.

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a multifactorial disease, which consists in a group of symptoms that include sensory, vasomotor, sudomotor, trophic, and motor dysfunction in the affected limb [1]. Pain, allodynia, swelling, vasomotor impairment, limited range of motion, and motor dysfunction are frequent [2]. Based on the International Association for the Study of Pain (IASP), CRPS is classified as chronic primary pain [3] and the most prominent factor for the diagnosis based on the Budapest criteria is the presence of 'continuing pain, which is disproportionate to any inciting event' [4]. Its physiopathology, which includes peripheral (i.e., inflammation, peripheral sensitization, and sympatho-afferent coupling) and central mechanisms (i.e., neuroplastic changes as cortical reorganization, altered afferent-efferent feedback, and central autonomic dysregulation), could explained clinical manifestations [5].

CPRS can be classified as Type 1 if no nerve damage occurs, and Type 2 where there is associated underlying nerve damage [6]. A recent revision has enhanced relevance of CPRS as a relatively frequent and very debilitating complication of multiple clinical situations, in which the primary goal of restoring function and participation is usually complicated by this entity [7]. In fact, this painful and incapacitating disorder can emerge after a stroke, a trauma in the extremities, or in some cases, without any known precipitating incident [8]. Even if its development as a complication of a spinal cord injury is less frequent, some cases of bilateral CRPS in central cord syndrome have been described in literature [6, 9-11]. Although

hyperalgesia and allodynia to mechanical stimuli are hallmark signs in subjects with CRPS [4], CRPS is easily overlooked in individuals with complex symptoms (e.g., pain after spinal cord injury) [10]. Thus, a careful evaluation is needed in these persons [11,12].

After an accurate diagnosis, management of CRPS includes pharmaceuticals (ketamine, antidepressants, nonsteroidal anti-inflammatory drugs, opiates, and anticonvulsants), physiotherapy, psychological therapy, sympathetic blockades, and electrical stimulation of the spinal cord [10]. Current principles for the diagnosis and treatment of CRPS consider both physiological and psychological mechanisms [7], and motor imagery (MI) has been proposed as a promising treatment integrating them. MI is a therapeutic approach consisting on mental execution of movement without real movement occurs, i.e., it consists on mental execution of an action is rehearsed without overt peripheral motor output [13]. Although several techniques for cortical representation of movement through cognition and/or perception (e.g., action observation therapy or mirror therapy) have been used in neurorehabilitation, MI is a technique for cortical representation of movement with promising results in CRPS [14,15] and relevant improvements in various chronic pain conditions [13,16,17]. In fact, MI sequentially activate the motor cortical networks, which could influence cortical reorganization through neuroplasticity in order to improve neural organization [14]. Thus, it is hypothesized that this therapy could activate cortical areas leading to cortical reorganization and reduction of pain; however, there is not sufficient evidence to recommend MI over other treatments [14,15] and more research is needed to strengthen the evidence base in this field [7]. In fact, a recent revision [18] has studied the effects of physiotherapy treatments on pain and disability in CRPS, and it has concluded that the evidence is very uncertain. Scarce studies about MI were analyzed

[18]. In addition, no studies investigating the overall effects of MI in terms of immediate, short-term, and long-term effects, applied alone or in combination with other therapies, for the management of CRPS have been included [18]. Due to the promising results of this noninvasive, inexpensive, and accessible therapy for CRPS, in addition to the importance of determining effects of MI, applied alone or in combination with other interventions, in terms of immediate, short-term, and long-term effects for the management of CRPS, a qualitative and quantitative analysis of the current literature is needed.

Therefore, this systematic review and meta-analysis aims to determine the effects of MI on pain intensity and related disability in individuals with CRPS.

MATERIALS AND METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19,20], and the Guidelines of Cochrane Handbook for Systematic Reviews of Interventions [21]. The International Prospective Register of Systematic Reviews (PROSPERO) registry code is CRD42023398815.

Systematic Literature Review

Electronic literature searches for completed published and unpublished studies were conducted on PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science (WOS), Physiotherapy Evidence Database (PEDro), Cochrane Library (CENTRAL), and Scopus databases from inception to February 28, 2023. Neither specific database filters nor language restrictions were applied to databases searches. Studies were included in the review if they were randomized

controlled trials (RCTs) investigating the effectiveness of MI for CRPS. All clinical trials included in this review were obtained from peer-reviewed journals.

The PICO strategy was developed in order to conduct an accurate search strategy:

- Population: Adults (older than 18 years old) with diagnosis of CRPS at any severity level.
- Intervention: MI applied to CRPS. The MI could be applied as a single treatment or in combination with other interventions.
- Comparator: Conventional physical therapy, other intervention, or no treatment.
- Outcomes: The primary outcome measure was pain intensity. Secondary outcome was related disability.

An example of the detailed search strategy is presented in Supplementary Data Table 1.

Study Eligibility Criteria

The RCTs assessing the effectiveness of MI for CRPS were included. Due to the heterogeneity in the terminology, we included the following diagnosis: CRPS, causalgia, reflex sympathetic dystrophy, sudeck atrophy, or algodystrophy. Specific inclusion criteria were: 1) RCT design; 2) adult population (>18 years old) with CRPS; 3) at least one group receiving MI; 4) comparison group received other treatment or no intervention; and 5) the primary outcome of the study should include pain intensity (e.g., as measured with a visual analogue scale (VAS) or numerical pain rating scale (NRS)). Studies were excluded if any of the following criteria were met: pilot studies, published proceeding, case reports, and case series studies.

Screening, selection process, and data extraction

Two reviewers (M.R.-L. and A.C.-G.) independently searched the literature for potentially relevant articles through electronic database search. After the removal of duplicates, titles, and abstracts (where available) were displayed and screened by one reviewer (M.R.-L.) to identify relevant trials. Full-text copies of peer-reviewed relevant papers were retrieved, and their reference lists were screened to identify further relevant studies. The methods of the retrieved papers were extracted and reviewed independently by two reviewers (S.D.-F. and P.M.-C.) using predetermined criteria. Both reviewers were blinded to authors, journals, and results of the studies. Disagreement or ambiguous issues were resolved by consensus after discussion with a third reviewer (A.C.-G.).

For each included study, two reviewers (M.R.-L. and A.C.-G.) independently extracted the relevant data using a standard form. If different data were extracted by the two reviewers, data were crosschecked by both reviewers. If disagreement continued, a third author (S.D.-F.) arbitrated. When information was not available in the published trials, details were requested from the corresponding author.

The following data were extracted from each eligible study and tabulated: study design, participants (sample size, age, diagnosis, characteristics of pain), intervention, outcome measures, and results. The measures used to record outcomes and the timing of measurement were recorded and compared to describe the trials.

Assessment of Methodological Quality and Risk of Bias

The methological quality of included trials was assessed using the Physiotherapy Evidence Database (PEDro) scale (Table 1), which is an 11-item scale designed for rating methodological quality (internal validity and statistical information) of RCTs. Each item, except for Item 1 (eligibility criteria), contributes one point to the total PEDro score (range=0−10 points). Scores of 9–10 were considered “excellent”, 6–8 “good”, 4–5

"fair," and 0–3 "poor" [22,23].

The risk of bias was assessed with the revised Cochrane Risk of Bias (RoB 2) assessment tool. The RoB 2 tool includes the following domains: (1) bias due to randomization process; (2) bias due to deviations from intended intervention; (3) bias due to missing data; (4) bias in outcome measurement; and (5) bias in selection of the reported result. Each item was classified as high-risk, low-risk, or unclear [24].

Two trained raters (M.R.-L. and A.C.-G.) independently assessed methodological quality and risk of bias, and disagreements were resolved by a third rater (P.M.-C.). Scores were based on all information available from both the published version and from communication with the authors.

Level of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the level of evidence [25]. The evidence level was classified as high, moderate, low or very low based on study limitations, indirectness of evidence, unexplained heterogeneity, inconsistency of the results, imprecision of results, and high probability of publication bias [26]. High-quality evidence was considered when the items did not have serious risk; moderate quality was scored if one item had serious risk; low quality was ranked if two items included serious risk or one item showed very serious risk; or very low quality was scored when three or more items demostrated serious risk or two or more showed very serious risk [25-27]. This assessment was also independently performed by two authors (M.R.-L. and A.C.-G.) and a third one (P.M.-C.) participated if disagreement occurred.

Data Synthesis and Analysis

Data analysis was performed with the Review Manager statistical software (RevMan

version 5.4, London; Cochrane, London, UK). Data synthesis was presented by groups according to comparative groups, such as control or other intervention, and by follow-up (immediate: up to 24 hours; short-term: from 24 hours to 3 months; long-term: more than 3 months). We also analyzed multiple comparisons between 1, MI alone vs. other treatment or control; or, 2, MI plus other intervention vs. other treatment or control.

The effects were investigated by calculating the standardized mean differences (SMDs) with the 95% confidence interval (CI) for the baseline–to–post-intervention change scores. For this purpose, sample size, means and standard deviations (SDs) were extracted. When the trial reported standard errors, they were converted to SDs. Mean and SDs were estimated from graphs when needed. In case of a missing SD of the difference, this was imputed from other data reported in the study by using other measures reported following the principles described in the Cochrane Handbook [21].

A random-effects model was used to determine the effect sizes (SMD). An effect size (SMD) of 0.8 or greater was considered large, an effect size between 0.5 and 0.8 was considered moderate, and an effect size between 0.2 and 0.5 was considered small [28]. *p*-values < 0.05 were considered statistically significant.

When two subgroups included the same intervention, the sample size was adjusted by dividing the sample size for avoiding duplication in the overall effect according to the Cochrane Handbook [18,29].

The I^2 statistic was applied to determine the heterogeneity between the included trials. The following interpretation according to the Cochrane group was used: 0–40% represented no relevant/important heterogeneity; 30–60% suggested moderate heterogeneity; 50–90% represented substantial heterogeneity; and 75–100% suggested considerable heterogeneity [21]. If heterogeneity was considered significant ($I^2 > 70$), sensitivity analysis was conducted.

RESULTS

Study selection

A total of 488 studies were identified through databases, which amounted to 204 potentially relevant articles after removal of duplicates. Following inspection of the titles and abstracts, 182 were excluded. Further analysis of the full text from the remaining 22 studies resulted in 6 clinical trials fulfilling the inclusion criteria and were considered eligible for data analysis. Therefore, six studies [14,30-34] were included in the qualitative and quantitative synthesis. The PRISMA flow chart for study selection is detailed in *Figure 1*.

Study characteristics

The characteristics of the included trials are summarized in *Table 2*. A total sample size of 174 participants (43.7% women, age range: 18-70 years) was included. The diagnoses included CRPS type 1 [14,30-34] or CRPS type 2 [31,34].

Four studies applied MI alone [14,30,32,33], while two trials [31,34] used MI combined with other therapies, such as virtual reality [31] or conventional treatment [34].

The comparison groups were heterogeneous across trials and included movement observation [31], conventional treatment [14,30,32,34] (e.g., pharmacological treatment, contrast baths, exercise [34], and mirror therapy [33].

Most studies conducted a treatment program during 4-6 weeks [14,30,32-34]; however, Hwang et al. [31] conducted a single treatment session.

The pain intensity was assessed using Visual Analogue Scale (VAS) [14,30] and Numerical Rating Scale (NRS) [31-34], including NRS of the Neuropathic Pain Scale (NPS) [14,32]. Related disability was assessed in three trials [14,30,33], where two used

NRS [14,33] and the third [30] the Michigan Hand Questionnaire (MHQ).

All studies measured the immediate effects [14,30-34]. Three trials also measured short-term or long-term effects [14,32,33].

Methodological Quality

The methodological quality and reporting of the eligible trials is presented in *Table 1*. The total PEDro scores ranged from 5 to 7 (mean: 6; standard deviation: 0.98) out of a maxium of 10 points. All trials satisfied the items related to random allocation of participants, between-group statistical comparisons, and point and variability measures. The unsatisfied items were blinded therapists and blinded subjects. Among 6 eligible trials, just one didn´t show blinded assessors [31], groups similar at baseline [14], or fewer than 15% dropouts [34].

Risk of bias

The details of the risk of bias assessment of the included RCTs are described in *Figure 2*. Two studies [30,32] showed an overall low risk of bias. However, four studies [14,31,33,34] presented some concerns regarding randomization process and intended interventions which should be considered on data interpretation.

Effects of MI on pain intensity in CRPS

The meta-analysis found that MI exhibited an overall significant effect (SMD -1.08; 95% CI: -1.39 to -0.76; n = 209; Z = 6.72; $P < 0.00001$) for reducing pain intensity versus a comparison group, with nonrelevant heterogeneity ($I^2 = 8\%$) between the trials *(Figure 3)*. A significant immediate effect was observed after MI (SMD -1.07; 95% CI: -1.53 to -0.60; n = 146; Z = 4.47; $P < 0.00001$), with moderate heterogeneity ($I^2 = 38\%$) between the studies. MI also showed a significant short-term effect (SMD -1.28; 95%

CI: -2.14 to -0.42; n = 27; Z = 2.92; *P* = 0.004) and long-term effect (SMD -1.18; 95% CI: -1.89 to -0.46; n = 36; Z = 3.23; *P*=0.001) for decreasing pain intensity versus a comparison group, with nonrelevant heterogeneity (I^2 = 0%) between trials measuring short-term effect; however, analysis of long-term effect was based on just one trial [14] *(Figure 3).*

The application of MI alone showed a significant effect (SMD -1.06, 95% CI -1.41 to -0.72; n = 152; Z = 5.98; *P* < 0.00001**)** on pain intensity when compared to other interventions, with nonrelevant heterogeneity (I^2 = 0%) between the studies *(Figure 4).* A significant immediate effect was observed after MI applied alone (SMD -0.97, 95% CI -1.47 to -0.47; n = 89; Z = 3.81; *P* = 0.00001), with nonrelevant heterogeneity (I^2 = 15%) between the trials. MI applied alone also showed a significant short-term effect (SMD -1.28, 95% CI -2.14 to -0.42; n = 27; Z = 2.92; *P* = 0.004) and long-term effect (SMD -1.18; 95% CI: -1.89 to -0.46; n = 36; Z = 3.23; *P*=0.001) for decreasing pain intensity when compared to other interventions, with nonrelevant heterogeneity (I^2 = 0%) between studies measuring short-term effect; however, analysis of long-term effect was based on just one trial [14] *(Figure 4).*

When comparing MI plus other intervention to other therapy, there was a significant effect (SMD -0.98, 95% CI -1.83 to -0.12; n = 83; Z = 2.24; *P* =0.03**)** for decreasing pain intensity but with substantial heterogeneity (I^2 = 68%) between the trials *(Figure 5).*

Effects of MI on related disability in CRPS

The meta-analysis revealed that MI exhibited an overall significant effect (SMD 1.11; 95% CI: 0.75 to 1.48; n = 136; Z = 5.95; *P* < 0.00001) for improving related disability versus a comparison group, with nonrelevant heterogeneity (I^2 = 0%) between the trials *(Figure 6).* A significant immediate effect was observed after MI (SMD 1.05; 95% CI:

0.59 to 1.51; n = 86; Z = 4.51; $P < 0.00001$), with nonrelevant heterogeneity ($I^2 = 0\%$) between the studies. MI also showed significant short-term (SMD 1.37; 95% CI: 0.16 to 2.58; n = 14; Z = 2.22; $P = 0.03$) and long-term effects (SMD 1.18; 95% CI: 0.46 to 1.89; n = 36; Z = 3.23; P=0.001) for improving related disability versus a comparison group; however, analysis of short-term and long-term effects were based on just one trial each (*Figure 6).*

Quality of Evidence (GRADE)

The risk of bias, inconsistency of the results, indirectness of evidence, imprecision of results, and publication bias for determining the level of evidence according to GRADE assessment are detailed in *Table 3*. The level of quality of evidence was rated as moderate, since the serious imprecision downgraded the evidence level of MI to moderate.

DISCUSSION

This systematic review and meta-analysis examined the effectiveness of MI for the management of CRPS. To our knowledge, this is the first meta-analysis summarizing the overall effects of MI, applied alone or in combination with other treatments, against a comparative intervention on pain and disability in individuals with CRPS. In addition, the present meta-analysis is the first investigating the immediate, short-term, and long-term effects of MI in CRPS. The main findings showed moderate evidence suggesting a positive immediate effect of MI for decreasing pain intensity and related disability compared with a comparative intervention. In addition, we also found moderate evidence suggesting significant improvements in pain and disability in short- and long-

term using MI compared with other comparative groups. In general, included trials showed good quality and low risk of bias, but some concerns related to risk of bias should be considered on data interpretation.

Previous systematic reviews [15,18,35,36] found inconclusive evidence with regard to the effects of MI due to the small number of trials published and low quality of included studies. Three systematic reviews [15,18,36] only included three published randomized controlled trials [14,32,33] comparing MI, particularly graded motor imagery (GMI, *see description in footnote in Table 2*), versus comparison group for the management of CRPS, whereas Żyluk and Puchalski [35] only included two published randomized controlled trials [14,32]. In addition, Smart et al. [18] concluded very low evidence supporting GMI for improving pain and disability in individuals with CRPS type 1. Only two randomized controlled trials [14,32] investigating MI were included in the meta-analysis [18], as well as in the present meta-analysis.

The present meta-analysis is the first investigating the immediate, short-term, and long-term effects of MI, applied alone or in combination with other interventions, against a comparative treatment for the management of CRPS. We found moderate quality evidence supporting a large positive effect of MI for improving pain and disability in the short and long term, in addition to a positive immediate effect, as compared with a comparative intervention. Our results at short term are similar to those previously reported by Smart et al. [18]. Futhermore, the findings of this meta-analysis are consistent with the previous systematic reviews that reflected that GMI could improve pain and function/disability in CRPS type 1 [15,35,36], including poststroke CRPS-1 [36].

Previous studies [37-39] also showed similar results, except for Johnson et al. [40] that found improvements on disability and failed to improve pain due to used

protocol. Furthermore, associations between these improvements and changes in activation of several cortical and subcortical areas were found [38,39,41]. Walz et al. [41] showed the effects of MI on cortical representation of affected extremity during manual grasping task [15]. The functional magnetic resonance imaging found reduced contralateral activation of S1 and S2 (areas of discriminative pain processing) and maintained activation of the anterior insula and anterior cingulate cortex (areas of affective pain processing) [15,38]. Therefore, MI could preserve the integrity of the cortical somatosensory representation of body parts affected by CRPS and regulate cortical reorganization mechanisms involved in CRPS painful symptoms [42]. Thus, the effects of MI could be based on activation of cortical motor networks and improvement in their organization, which alleviate pain and improve function/disability [15]. Furthermore, the increase in putamen activation could also explain improvements in function/disability since basal ganglia contributes to complex motor performance and individuals with CRPS show a remarkable pattern of dystonic symptoms and tremor related to basal ganglia function [38].

The present findings and previous results suggest that MI could potentially be effective for treating pain and improving disability in individuals with CRPS, since it could ameliorate maladaptive somatosensory and motor cortex reorganization (cortical reorganization) [14,32,35]. In addition, MI, applied alone or in combination with other interventions, could have superior effects on pain relief compared with other treatments. Nevertheless, although MI could show improvements in pain and disability as compared with a comparative intervention in the long term, these comparisons were based on just one trial. Thus, there is not enough literature to determine the effects of MI on pain and disability at long term in individuals with CRPS.

Although the current meta-analysis include comprehensive literature search, methodological rigor, data extraction, rigorous statistical analysis, and the inclusion of randomized controlled trials with good quality in the quantitative analysis, there are some limitations. First, the number of included trials was small (n=6). However, good methodological quality of studies supports the results observed. Secondly, just one trial included long-term effects with a limited follow-up period. Thus, it may not have been sufficient to determine the long-term effects. Finally, the imprecision of some trials limit the generalization of the results. Therefore, the obtained results should be interpreted with caution. Future well-designed randomized controlled trials with larger sample sizes examining the effects of MI, alone or in combination with other interventions, particularly at long-term follow-up periods, are needed.

Conclusions

This systematic review and meta-analysis found moderate evidence supporting that MI, applied alone or in combination with other interventions, can be effective for improving pain intensity and related disability when compared with a control group immediately after and at short-term follow-up in people with CRPS. Although MI, applied alone or in combination with other therapies, have demonstrated more effectiveness than other interventions on pain and disability at long-term, these findings should be considered with caution due to moderate evidence level and small number of studies investigating the long-term effect. The risk of bias of the clinical trials included was relatively low, but the imprecision of the results downgraded the level of evidence. Thus, further large-scale, adequately powered, high-quality randomized controlled trials are needed to provide more trustworthy evidence in this area.

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TABLES

Table 1. PEDro scores of included studies (n=6).

Study	PEDro score items											Total
	1*	2	3	4	5	6	7	8	9	10	11	0-10
Dilek et al. [30]	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Hwang et al. [31]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10
Moseley [32]	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Moseley [33]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Moseley [14]	Y	Y	N	N	N	N	Y	Y	N	Y	Y	5/10
Sarkar et al. [34]	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5/10

1: Eligibility criteria were specified; 2: Subjects were randomly allocated to groups; 3: Allocation was concealed; 4: The groups were similar at baseline regarding the most important prognostic indicators; 5: There was blinding of all subjects; 6: There was blinding of all therapists who administered the therapy; 7: There was blinding of all assessors who measured at least one key outcome; 8: Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome

was analyzed by “intention to treat”; 10: The results of between-group statistical comparisons are reported for at least one key outcome; 11: The study provides both point measures and measures of variability for at least one key outcome. Y=Yes; N=No.

* Eligibility criteria item does not contribute to total score since it is related to external validity.

Table 2. Summary of included trials (n=6).

Study	Design	Population	Intervention	Outcome measures	Results
Dilek et al. [30]	RCT	n = 36 (G1=17; G2=19) CRPS type 1 Age *(yr)* = 49.8 (SD 10.1) Duration of pain *(mth)*: not specified	G1=GMI G2=traditional rehabilitation program *Intervention duration: 8 wk	Pain: VAS Disabilitty: MHQ *Follow-up=0,8 wk	After intervention, significant improvements in pain (pain at rest, pain during) were found in all groups ($p<0.05$). Improvements in pain and disability were greater for G1 than those for G2 ($p<0.05$).
Hwang et al. [31]	RCT	n = 39 (G1=13; G2=13; G3=13) CRPS types 1 and 2 Age *(yr)* = 40.8 (SD 2.4) Duration of pain *(mth)*=56.3 (SD 15.0)	G1=MI,VR G2=Movement observation G3=MI *Intervention duration: 1 session	Pain: NRS *Follow-up=pre- and post-treatment	No significant improvements in pain were found ($p>0.05$).

Moseley [32]	RCT	n = 13 (G1=7; G2=6) CRPS type 1 Age *(yr)* = 36.5 (SD 14.5) Duration of pain *(mth)*=58 (SD 18.5)	G1=GMI G2=Conventional medical treatment *Intervention duration: 6 wk	Pain: NPS (NRS) *Follow-up=0,2,4,6,12 wk	Significant reduction in pain during intervention, at 6 and 12 weeks were found in G1 ($p<0.01$).
Moseley [33]	RCT	n = 20 (G1=7; G2=6; G3=7) CRPS type 1 Age *(yr)* = 34 (SD 7.7) Duration of pain *(mth)*=14 (SD 5.3)	G1=GMI G2=IM,RL,IM G3=RL,MT,RL *Intervention duration: 6 wk	Pain: NPS (NRS) Disability: NRS *Follow-up=0,4,6,18 wk	At 6 and 18 weeks, improvements in pain and disability were greater for G1 than it was for G2 or G3 ($p<0.05$).
Moseley [14]	RCT	n = 36 (G1=17; G2=19) CRPS type 1 Age *(yr)*: not specified	G1=GMI G2=conventional medical and physiotherapy treatments *Intervention duration: 6 wk	Pain: VAS Disability: NRS *Follow-up=0,6,24 wk	At 6 and 24 weeks, improvements in pain and disability were greater for G1 than it was for G2 ($p<0.05$).

		Duration of pain *(mth)*: not specified			
Sarkar et al. [34]	RCT	n = 30 (G1=10; G2=10; G3=10) CRPS types 1 and 2 Age *(yr)*: 18 - 70 Duration of pain *(mth)*<12	G1=pharmacological treatment, contrast baths G2=pharmacological treatment, contrast baths, exercise G3=MI, pharmacological treatment, contrast baths, exercise *Intervention duration: 4 wk	Pain: NRS *Follow-up=0,1,2,4 wk	Significant improvements in pain (pain at rest, pain on movement) were found in all groups ($p<0.05$). Improvements in pain were greater for G3 than those for G1 and G2. At 4 wk, significant pain reduction were maintained in G3 ($p<0.05$).

GMI=Graded Motor Imagery*; IM=Imagined hand movements; MHQ=Michigan Hand Questionnaire; MI=Motor imagery; MT=mirror therapy; NPS = Neuropathic Pain Scale; NRS=Numerical Rating scale; RCT=Randomized Controlled Trial; RL= Recognition of hand laterality; VAS = Visual Analogue Scale; VR=virtual reality. *GMI includes three progressive stages: (1) left/right judgment training, (2) imagined movements, and (3) mirror therapy.

Table 3. GRADE evidence profile for the effects of motor imagery on complex regional pain syndrome.

Number of Studies	Risk of Bias	Inconsistency	Indirectness of Evidence	Imprecision	Publication Bias	Quality of Evidence	SMD [95% CI]
Effects of motor imagery on pain intensity (immediate effects) (n = 6)	No	Not serious (I^2=38%)	No	Serious	No	⊕⊕⊕◯ Moderate	-1.07 [-1.53, -0.60]*
Effects of motor imagery on pain intensity in the short term (n = 2)	No	Not serious (I^2=0%)	No	Serious	No	⊕⊕⊕◯ Moderate	-1.28 [-2.14, -0.42]*
Effects of motor imagery on pain intensity in the long term (n = 1)	No	-	No	Serious	No	⊕⊕⊕◯ Moderate	-1.18 [-1.89, -0.46]*
Effects of motor imagery on related disability (immediate effects) (n = 3)	No	Not serious (I^2=0%)	No	Serious	No	⊕⊕⊕◯ Moderate	1.05 [0.59, 1.51]*
Effects of motor imagery on related disability in the short term (n = 1)	No	-	No	Serious	No	⊕⊕⊕◯ Moderate	1.37 [0.16, 2.58]*

Effects of motor imagery on related disability in the long term (n = 1)	No	-	No	Serious	No	⊕⊕⊕◯ Moderate	1.18 [0.46, 1.89]*

Risk of bias: No: Most information is from results at low risk of bias; Serious: Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect; Very Serious: Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect. Inconsistency: Serious: I^2 > 40%; Very Serious: I^2 > 80%. Indirectness of Evidence: No indirectness of evidence was found in any study. Imprecision (based on sample size): Serious: n < 250 subjects; Very Serious: n < 250 and the estimated effect is little or absent. Publication bias (based on funnel plots): No publication bias was observed based on funnel plots (not shown because the lower number of studies < 10). * p < 0.05.

FIGURES

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart.

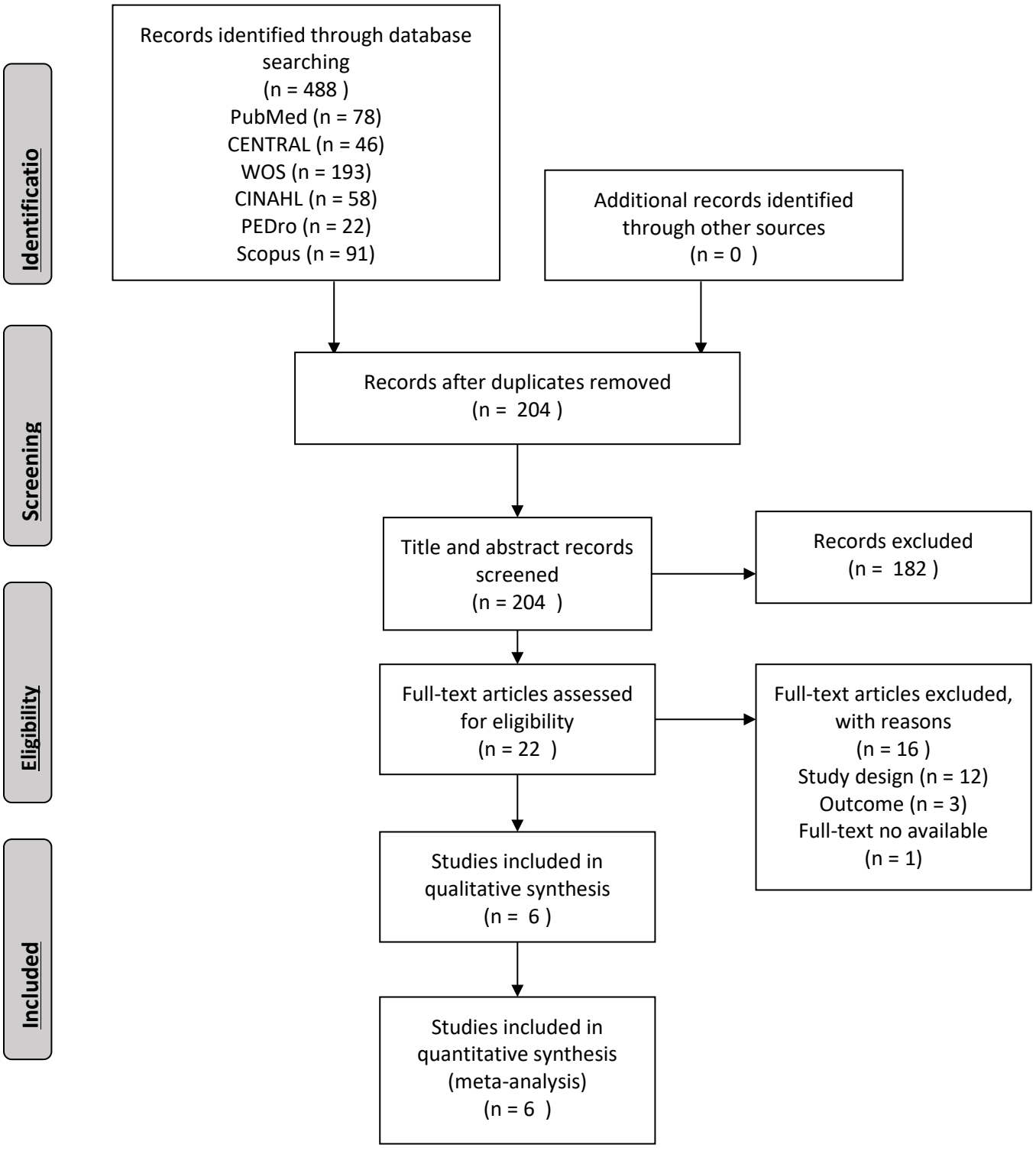
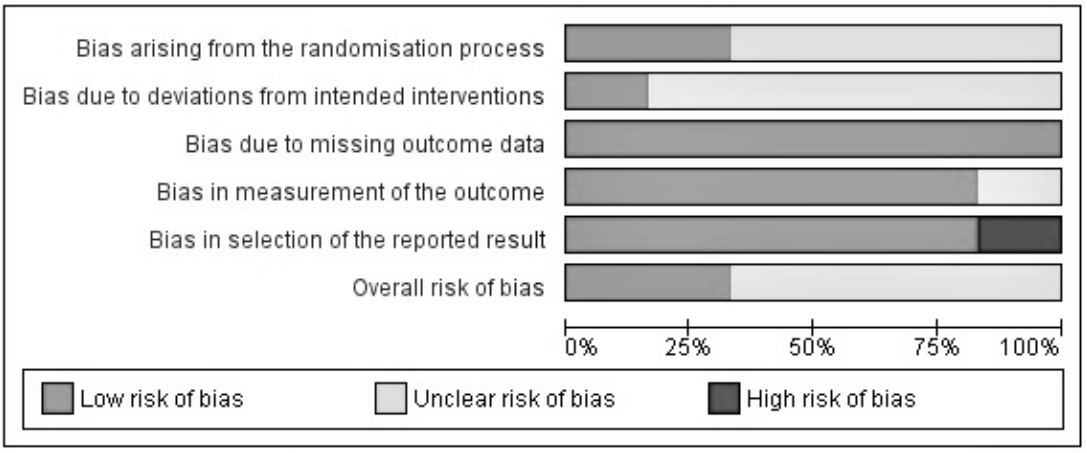


Figure 2. Plots of risk of bias of the included studies.



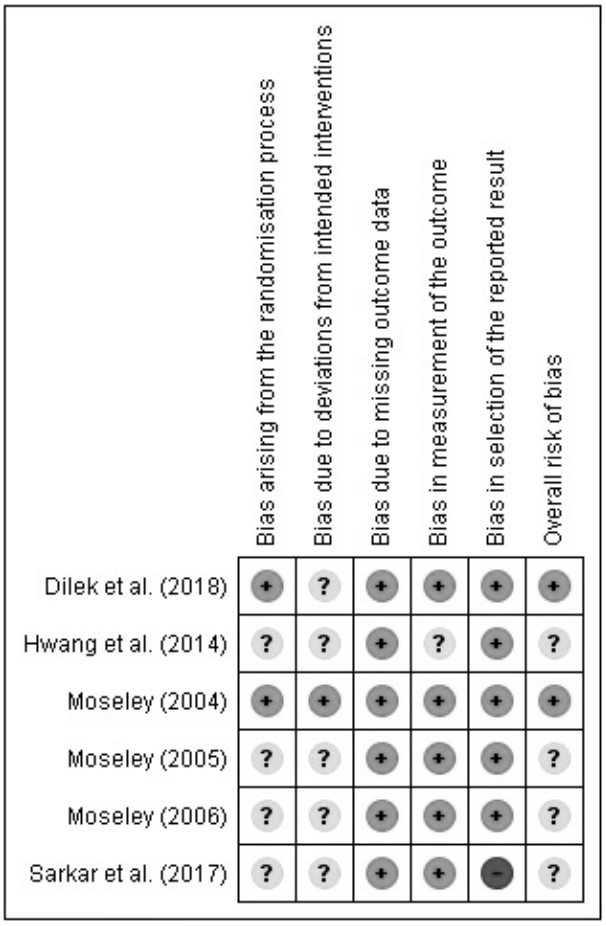


Figure 3. Comparison (standardized mean difference) between the effects of motor imagery and a comparative group on pain intensity (immediate, short-term and long-term effects).

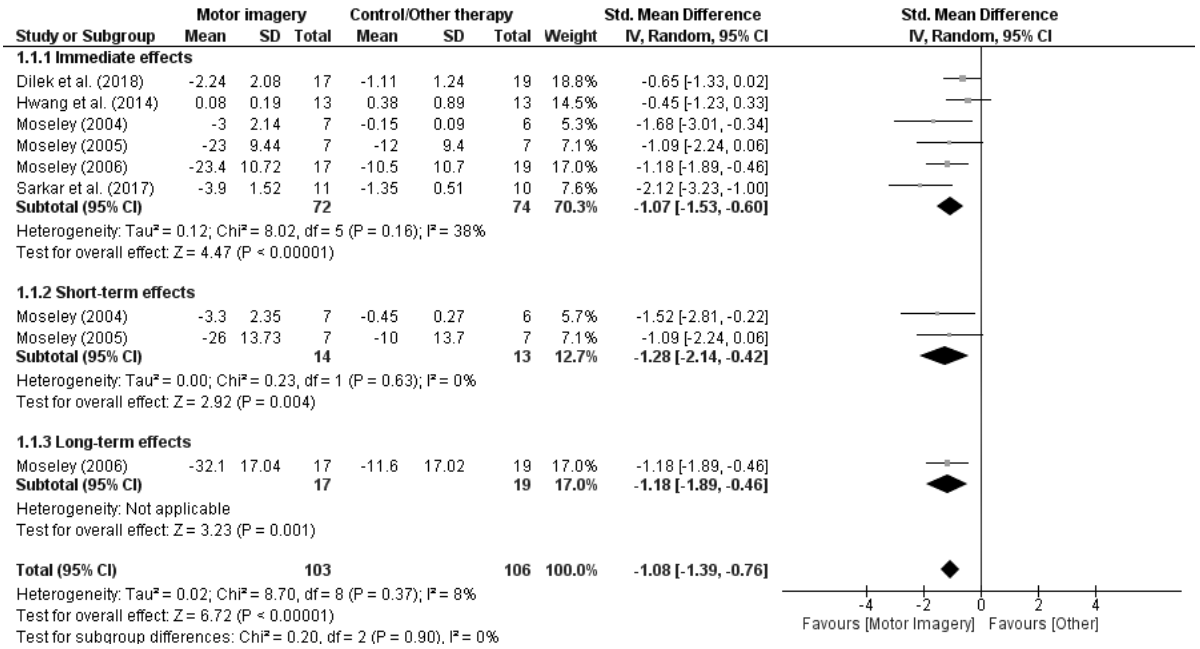


Figure 4. Comparison (standardized mean difference) between the effects of motor imagery alone versus a comparative group on pain intensity (immediate, short-term and long-term effects).

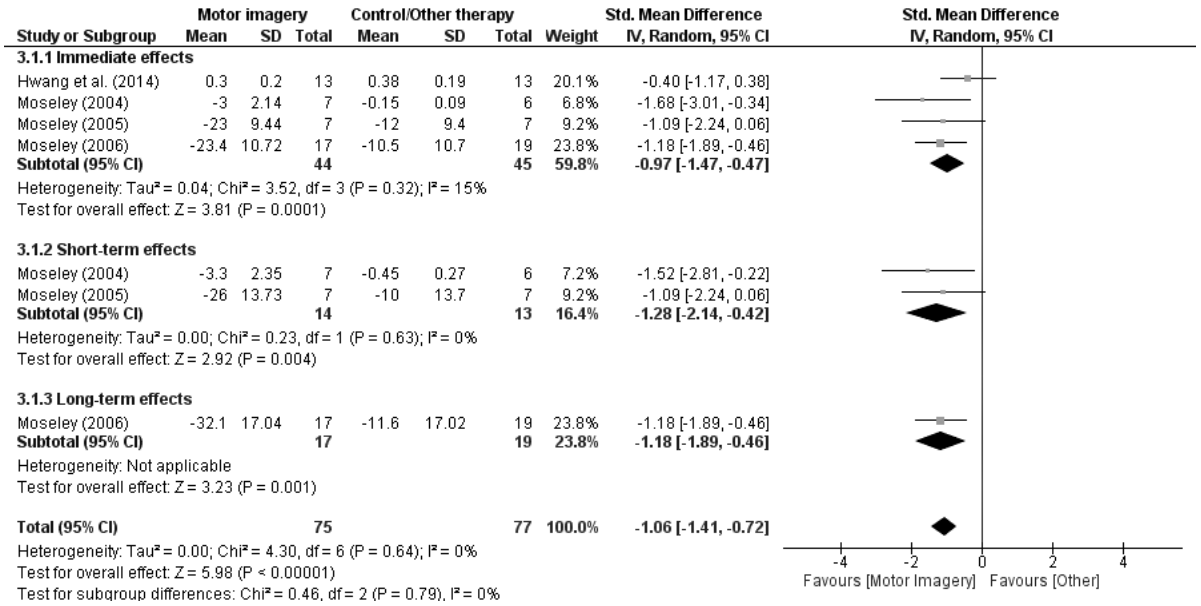


Figure 5. Comparison (standardized mean difference) between the effects of motor imagery plus other intervention versus a comparative group on pain intensity (immediate effects).

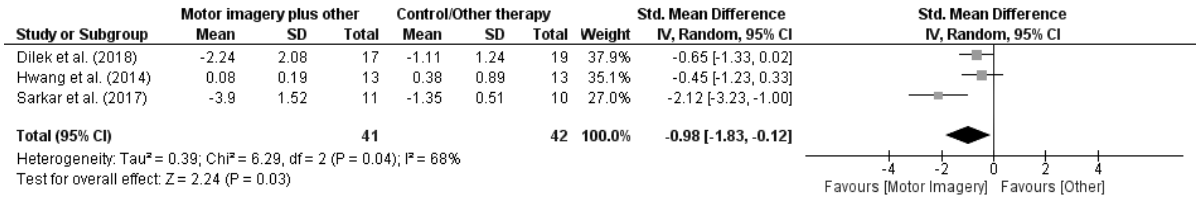


Figure 6. Comparison (standardized mean difference) between the effects of motor imagery and a comparative group on related disability (immediate, short-term and long-term effects).