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REVIEW ARTICLE

Effect of mirror therapy in the treatment of phantom limb pain in amputees: A systematic review of randomized placebo-controlled trials does not find any evidence of efficacy

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Abstract

Background and Objective: Phantom limb pain (PLP) concerns >50% of amputees and has a negative impact on their rehabilitation, mental health and quality of life. Mirror therapy (MT) is a promising strategy, but its effectiveness remains controversial. We performed a systematic review to: (i) evaluate the effectiveness of MT versus placebo in reducing PLP, and (ii) determine MT effect on disability and quality of life.

Databases and data treatment: We selected randomized-controlled trials in five databases (Medline, Cochrane Library, CINAHL, PEDro and Embase) that included patients with unilateral lower or upper limb amputation and PLP and that compared the effects on PLP of MT versus a placebo technique. The primary outcome was PLP intensity changes and the secondary outcomes were PLP duration, frequency, patients′ disability and quality of life.

Results: Among the five studies included, only one reported a significant difference between the MT group and control group, with a positive MT effect at week 4. Only one study assessed MT effect on disability and found a significant improvement in the MT group at week 10 and month 6.

Conclusions: Our systematic review did not allow concluding that MT reduces PLP and disability in amputees. This lack of strong evidence is probably due to (i) the low methodological quality of the included studies, and (ii) the lack of statistical power. Future trials should include a higher number of patients, increase the number and frequency of MT sessions, have a long-term follow-up and improve the methodological quality.

Significance: Recent meta-analyses concluded that MT is effective for reducing phantom limb pain. Conversely, the present systematic review that included only studies with the best level of evidence did not find any evidence about its effectiveness for this condition. We identified many ways to improve future

randomized-controlled trials on this topic: increasing the number of participants, reducing the intra-group heterogeneity, using a suitable placebo and intensifying the MT sessions and frequency.

1 | INTRODUCTION

Phantom limb pain (PLP), which affects between 49% and 88% of amputees (Nikolajsen & Jensen, 2001), is a neuropathic pain defined as a painful or unpleasant sensation perceived in the territory of the amputated or deafferented limb (Niraj & Niraj, 2014). Patients describe PLP as a strong pain like electric currents, or as a burning, stinging, cramping or stabbing pain (Hsu & Cohen, 2013). PLP often occurs suddenly and lasts from few seconds to several hours, and is mostly felt in the distal part of the phantom limb (fingers or toes). PLP affects negatively rehabilitation, mental health and quality of life (Sinha et al., 2011; van der Schans et al., 2002).

The mechanisms underlying PLP have not been clearly identified and are probably multiple (Flor et al., 2006; Makin et al., 2013). According to the maladaptive cortical plasticity theory, PLP emerges following the progressive occupation of the cortical areas that correspond to the missing limb by adjacent areas. This is due to the absence of sensory afferent signals from the missing limb and spinal dysregulation that increases the transmission of the pain signal (Flor, 2002). Spinal dysregulation contributes to the pro-nociceptive effect due to a cascade mechanism that implicates increased activity of nociceptors in the dorsal horn, degeneration of C-fibres in the lamina II, sprouting of A-fibres, downregulation of GABAergic activity and opioid receptors, expansion of adjacent receptive fields in deafferented zones, and spinal cord hyperexcitability linked to the altered substance P expression by Aß fibres (Flor, 2002; Woolf et al., 1992; Woolf & Mannion, 1999). According to another theory, PLP extent is related to the preserved representation of the phantom limb in the cortex that can be activated and to a reduction of inter-regional functional connectivity in the primary sensorimotor cortex (Makin et al., 2013).

Several pharmacological, surgical or non-pharmacological approaches have been proposed for PLP management. The effectiveness of pharmacological treatments remains low (Alviar et al., 2016). Surgical strategies are effective, but invasive and with a long healing time and loss of function (Dumanian et al., 2019; Herr et al., 2020; Knotkova et al., 2012). Therefore, they are not used as first-line treatment. Among non-pharmacological interventions, mirror therapy (MT), first proposed by Ramachandran (1996), seems to be a promising strategy. MT consists in placing a mirror in the parasagittal plane between the healthy limb and the amputated limb. The image of the healthy limb is reflected in the mirror and the patient perceives the reflection of the healthy limb instead of the amputated limb. By creating a visual representation of the missing limb, MT might restore the cortical (motor and sensory) areas that correspond to the absent limb. By restoring the body image and body schema disturbed by the amputation, MT might reduce PLP (Flor, 2002; Foell et al., 2014; Ramachandran & Altschuler, 2009).

MT effectiveness remains controversial (Barbin et al., 2016; Batsford et al., 2017; Herrador Colmenero et al., 2018; Plumbe et al., 2013; Rothgangel et al., 2011; Thieme et al., 2016, 2018; Xie et al., 2021) because previous reviews and meta-analyses found inconclusive evidence. This could be due to the fact that the studies included in these reviews assessed MT in various pathologies (Rothgangel et al., 2011; Thieme et al., 2016) or in combination with other techniques (Batsford et al., 2017; Herrador Colmenero et al., 2018). Barbin et al. (2016) analysed MT use specifically in amputees with PLP (Barbin et al., 2016). They found only three randomized-controlled trials and concluded that the level of evidence was not adequate, due to the low methodological quality of the included studies and the small sample sizes. Two recent meta-analyses on this question concluded that MT is effective for PLP management (Wang et al., 2021; Xie et al., 2021). One found a positive effect of MT at month 1 of treatment ($I^2 = 0\%$, standardized mean difference = −0.46, 95% CI: −0.79 to 0.13, $p = 0.007$), but not at month 3 or 6 of follow-up (Xie et al., 2021). The other meta-analysis showed that MT reduces pain with a larger effect size ($I^2 = 82\%$; standardized mean difference = −0.81; 95% CI = −1.36 to −0.25; $p = 0.005$) compared with other methods (Wang et al., 2021). However, the conclusion of these meta-analyses are subject of debate due to questionable methodological and statistical choices: the use of fixed-effect analyses (Borenstein et al., 2010), the inclusion of low-powered and poor-quality studies, the strong heterogeneity and the interpretation of non-clinically relevant effects (Moore et al., 2022). Furthermore, no systematic review has evaluated MT impact on the patients' quality of life and disability. Pain reduction is a good indicator of PLP improvement, but changes in disability and well-being also are important (World Health Organization, World Bank, 2011).

Therefore, we performed a systematic review: (i) to evaluate the effectiveness of MT versus placebo in reducing PLP; and (ii) to determine MT effect on disability

and quality of life. To overcome the previously stated limitations, we included only randomized-controlled trials that compared MT versus a placebo in unilateral amputees.

2 | LITERATURE SEARCH METHODS

This systematic review of the literature followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

2.1 | Eligibility criteria

We defined the eligibility criteria to include studies according to the Population, Intervention, Comparison, Outcomes and Study (PICOS) model:

- Population: adult patients with unilateral, lower or upper limb amputation due to any cause and with PLP.
- Intervention: MT to reduce PLP. It has been hypothesized that MT restores the cortical (motor and sensory) areas corresponding to the missing limb through the co-occurrence of visual, proprioceptive information from the intact limb, and motor inputs from both limbs. This input combination is considered to be the active component of MT (Schone et al., 2022). To avoid heterogeneity and to specifically assess the association of these components, we chose MT only as the intervention. We considered that other techniques, such as mental visualization, tactile discrimination and virtual reality, target a similar process (i.e. maladaptive plasticity), but have different active components. Mental visualization does not induce motor commands or sensory inputs. Tactile discrimination enhances sensory stimulation on the stump; however, it does not implicate movements, motor commands and proprioceptive inputs. Virtual reality can act as MT, but virtual reality approaches are heterogenous (e.g. using the residual or the intact limb, moving one or two arms, interacting with exergames or avatars).
- Comparison: any other technique considered as placebo (covered mirror or mirrorless visualization). The covered mirror is classically considered as the best controls for MT (Chan et al., 2007; Finn et al., 2017; Ramadugu et al., 2017; Schone et al., 2022). To test the effect of MT active components, an adequate control is a technique as similar as possible. When using the covered mirror and the mirrorless approaches as placebo, the only difference, compared with MT, is the suppression of the

visual feedback, while the other inputs remain the same.
- Outcomes:
    Primary: PLP intensity (measured with a scale).
    Secondary:
      • PLP duration and frequency
      • Disability and quality of life (measured with questionnaires)
- Study types: randomized-controlled trials published between 1996 (first description of MT) and 01 July 2021.

  Non-inclusion criteria were:

  • Articles without available full text.
  • Articles published in a language other than English or French.
  • Articles comparing the effects of MT with another technique (TENS, motor imagery, phantom exercise, tactile discrimination).

2.2 | Information sources and search strategy

We used Medline, Cochrane Library, CINAHL, PEDro and Embase as information sources and searched them using the index terms and syntax listed in Table 1.

2.3 | Study selection

This step was carried out by two independent reviewers (L.R., N.R.) following the established inclusion and non-inclusion criteria. Duplicates were removed from the list of results. A first selection was made by reading the titles and abstracts to remove articles not meeting the inclusion criteria. The final selection was made by reading the full text of the selected articles. When no agreement could be reached, a third reviewer (M.G.) intervened to reach an agreement.

2.4 | Data extraction

The data extracted were:

- Participants: sample size, age, sex, location and cause of amputation, PLP intensity and time of onset since amputation.
- Intervention: data were extracted based on the French translation of the Template for Intervention Description and Replication (TIDieR) item list.
- Measurements: tools used to measure PLP and the number of measurements performed.

TABLE 1 Index terms and syntax for each database

Database	Index terms and syntax
PubMed	("Amputation"[Mesh] OR "Amputees"[Mesh]) AND ("Phantom Limb/therapy"[Mesh]) AND (mirror* OR mirror therap* OR mirror box).
Cochrane Library	amput* AND (phantom limb OR phantom pain) AND (mirror therapy* OR mirror* OR mirror box)
CINHAL	((MH "Phantom Limb") OR (MH "Phantom Pain")) AND ((MH "Amputation") OR (MH "Amputees")) AND ([MH "Mirror Therapy"] OR mirror* OR mirror therapy* OR mirror box)
PEDro	amput* AND "phantom limb pain" AND mirror* *The "clinical trial" filter was added to limit the search to clinical trials*
Embase	('amputation'/exp OR 'amputee'/exp) AND 'phantom pain'/exp AND ('mirror therapy'/de OR 'mirror'/de) *The filter "Embase" was used to eliminate articles fromPubMed and keep only articles that are indexed only in Embase*

- Intervention effect: we extracted results of intra- and inter-group assessments. We extracted only results that compared the effect of MT versus placebo. We did not consider comparisons with other techniques (mental visualization, virtual reality).

2.5 | Methodological quality of the included studies

We assessed the methodological quality of the retained randomized-controlled trials using the PEDro scale (Brosseau et al., 2015). The PEDro scale includes 11 criteria in order to help the PEDro database users to rapidly identify which clinical studies (i.e. randomized clinical trials and controlled clinical trials) are likely to be internally valid (criteria 2–9) and to have sufficient statistical information to make their results interpretable (criteria 10–11). Criterion 1, which relates to external validity, is not used to calculate the PEDro score. Two reviewers (L.R., N.R.) independently scored the articles, and discussed areas of disagreement. When no agreement could be reached, a third reviewer (M.G.) intervened to reach an agreement.

3 | RESULTS

3.1 | Study selection

The literature search identified 155 articles (flowchart in Figure 1). We excluded 43 articles after the removal of duplicates and 94 after reading the titles and abstracts. The reasons for exclusions are detailed in Figure 1. We did not find one study (text unavailable; Perry, 2013). Following this selection, we examined the full text of 17 articles and

retained five articles (Brodie et al., 2007; Chan et al., 2007; Finn et al., 2017; Ramadugu et al., 2017; Rothgangel et al., 2018).

3.2 | Study methodological quality

We assessed the methodological quality of the five studies with the PEDro scale (Table 2). Their scores ranged from 4 to 8. Three studies had a score >6 and could be considered as having a limited risk of bias (Brodie et al., 2007; Ramadugu et al., 2017; Rothgangel et al., 2018). The other two studies [27,28] had a score <5 and were at higher risk of bias.

3.3 | Study characteristics

Three studies used a parallel group design (Brodie et al., 2007; Finn et al., 2017; Rothgangel et al., 2018) and two a cross-over design (Chan et al., 2007; Ramadugu et al., 2017). In total, 256 patients were included, with sample sizes varying from 15 to 80 patients. Participant characteristics (age, location and cause of amputation, time of PLP onset since amputation, and PLP intensity at inclusion) varied among the studies (Table 3). Conversely, the type of exercise (i.e., the study intervention) and the control intervention (opaque sheet or mirrorless) were similar among studies. However, the duration, number and frequency of MT sessions varied (Table 4). The intervention was performed under the supervision of an examiner in four studies (Brodie et al., 2007; Chan et al., 2007; Finn et al., 2017; Ramadugu et al., 2017). PLP intensity was assessed with different tools: visual analogue scale (VAS; Brodie et al., 2007; Finn et al., 2017; Ramadugu et al., 2017),
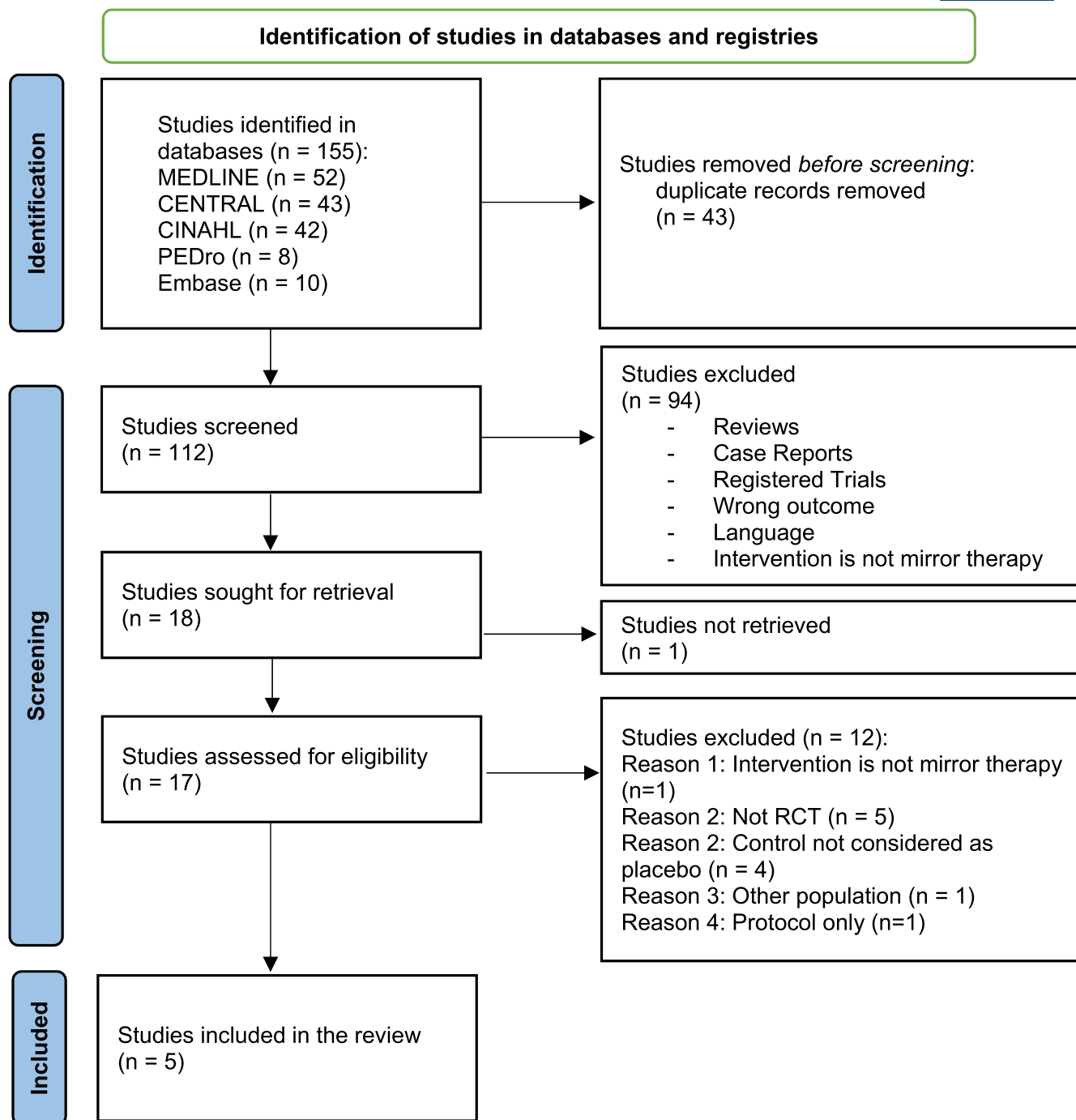
Identification of studies in databases and registries

FIGURE 1 Study selection flowchart according to the PRISMA guidelines. RCT, randomized-controlled trial

numeric rating scale (Rothgangel et al., 2018) and McGill Pain Questionnaire, original (Brodie et al., 2007) or shorter version (Ramadugu et al., 2017). Only one study assessed MT impact on the patients' disability and quality of life (Rothgangel et al., 2018). Disability was assessed with the Patient Specific Functional Scale (PSFS) and the Pain Disability Index (PDI). Quality of life was assessed with the EuroQol 5-Dimensional Questionnaire (EQ-5D-5L) and two numeric rating scales that measure the impact of pain on sleep and mood.

3.4 | Synthesis of the results

The results obtained for each group and the conclusion on the primary outcome of each study are presented in Table 4.

3.4.1 | Primary outcome: PLP intensity

Among the four studies with an intergroup comparison (Brodie et al., 2007; Chan et al., 2007; Ramadugu

TABLE 2 PEDro score of the selected studies

| | Items | | | | | | | | | | | |
First author	1	2	3	4	5	6	7	8	9	10	11	Total score/10
Brodie et al.	1	1	0	1	0	0	0	1	1	1	1	6
Chan et al.	0	1	0	1	0	0	0	1	0	1	0	4
Finn et al.	1	1	0	1	0	0	0	1	1	0	0	4
Ramadugu et al.	1	1	1	1	0	0	1	1	0	1	1	7
Rothgangel et al.	1	1	1	1	0	0	1	1	1	1	1	8

Note: Criterion 1: eligibility criteria were specified; criterion 2: subjects were randomly allocated to groups; criterion 3: allocation was concealed; criterion 4: at baseline, the most important prognostic indicators were similar between groups; criterion 5: blinding of all subjects; criterion 6: blinding of all therapists who administered the therapy; criterion 7: blinding of all assessors who measured at least one key outcome; criterion 8: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; criterion 9: all subjects for whom outcome measures were available received the treatment or control condition, as allocated; criterion 10: the results of between-group statistical comparisons are reported for at least one key outcome; criterion 11: the study provides both point measures and variability measures for at least one key outcome.

et al., 2017; Rothgangel et al., 2018), only one found a significant difference between MT group and control (placebo) group with a positive effect of MT at week 4 of follow-up (Chan et al., 2007). Furthermore, in the study by Rothgangel et al. (2018) a subgroup analysis suggested clinically significant effects of MT on the mean PLP intensity in women and in patients with a motor component (cramps or unnatural phantom limb position) of PLP.

For intra-group comparisons, three studies showed a significant decrease in pain in the MT group after the intervention (Chan et al., 2007; Finn et al., 2017; Ramadugu et al., 2017).

3.4.2 | Secondary outcomes

PLP duration and frequency
The included studies did not find any inter-group difference in PLP duration and frequency at 4 and 6 weeks of MT (Ramadugu et al., 2017; Rothgangel et al., 2018), but PLP duration was significantly reduced at 6 months in the MT group compared with placebo (Rothgangel et al., 2018). For intra-group comparisons, three studies found that PLP duration and frequency were decreased in both (MT and control) groups (Finn et al., 2017; Ramadugu et al., 2017; Rothgangel et al., 2018).

Effect on disability and quality of life
Only the study by Rothgangel et al. assessed MT effect on the patients' disability level and quality of life. According to some PSFS items (daily living activities), disability was significantly reduced in the MT group at week 10 and 6 months (Rothgangel et al., 2018). Conversely, quality of life (EQ-5D–5 L questionnaire) was comparable between groups.

4 | DISCUSSION

Among the five studies included in this systematic review, three found that MT decreased PLP intensity, but mainly in the intra-group comparison. Only Chan et al. (2007) found a specific positive effect of MT on PLP at week 4 compared with the control group, but this study has a low methodological quality score. One study reported an improvement of disability by MT through the reduction of PLP impact on daily living activities (Rothgangel et al., 2018). Thus, our systematic review did not allow concluding that MT reduces PLP intensity, frequency and duration, disability and quality of life.

The lack of strong evidence of MT efficiency in PLP is probably due to (i) the low methodological quality (Table 2), and (ii) the lack of statistical power of the included studies. Several studies included fewer than 10 patients per group (Chan et al., 2007; Finn et al., 2017) although Rothgangel et al. calculated that at least 30 patients per group were needed to detect a 2-point difference, with high effect size (Cohen's d close to 0.8). As they did not detect any effect, the effect size for MT might be smaller (Cohen's d close to 0.5). This would imply that more than 50 patients per group should be recruited to detect an effect with 80% of power. Furthermore, intra-group heterogeneity was high and several factors should have been considered, such as sex, type of prosthesis, ability to move the phantom limb, and presence of a PLP motor component (cramps or unnatural position of the phantom limb; Rothgangel et al., 2018). Future studies should take into account these factors when deciding the inclusion and exclusion criteria.

Our conclusion is similar to that of previous reviews (Aternali & Katz, 2019; Barbin et al., 2016), but differs from that of the two most recent meta-analyses that reported a significant positive effect of MT on PLP (Wang

TABLE 3 Characteristics of the patients included in the selected studies

Author, years	Pathology	Age (years), sex	PLP intensity and/or number of PLP episodes at recruitment	Interval between amputation and inclusion in the study
Brodie et al., 2007	Unilateral lower limb amputees Reason for amputation: congenital (1%), cancer (5%), accident (33%), medical (61%)	$N = 80$; ♂ (79%) Mean age: 55 (20–83)	—	<2 weeks: 65% <1 year: 20% >1 year: 6%
Chan et al. (2007)	Unilateral lower limb amputees Reason for amputation: not specified	$N = 22$	—	—
Finn et al. (2017)	Unilateral upper extremity amputees Reason for amputation: accident (100%)	$N = 15$; ♂ (100%) Mean age: 28.7 (19–68)	Episodes per week: 3	Mean: 4.51 months (0.55–24)
Ramadugu et al. (2017)	Unilateral lower limb (84%) and unilateral upper extremity amputees (16%) Reason for amputation: not specified Non-inclusion criteria: traumatic brain injury or major psychiatric illness	$N = 64$; ♂ (100%) Mean age: NA (17–62)	Intensity (VAS): 30 (10.7)	—
Rothgangel et al. (2018)	Unilateral lower limb amputees Reason for amputation: accident (33%), diabetes (11%), vascular problems (29%), tumour (13%), other (e.g., infection; 13%)	$N = 75$; ♂ (69%) Mean age: 61.1 (NP)	Episodes per week: at least one Intensity (VAS): 5.7	Mean: 3 years

Abbreviations: NA, not available; VAS, visual analogue scale.

TABLE 4 Summary of the characteristics, intervention and outcomes of the selected studies

Author, year, study type	Intervention group	Control intervention	Measurements: Primary outcome secondary outcome(s)
Brodie et al. (2007) RCT—parallel group	Mirror therapy $N = 41$	Covered mirror $N = 39$	• 100-mm VAS • MPQ
Chan et al. (2007) RCT-crossover for the control group	Mirror therapy $N = 6$ (number of participants who completed the study)	Covered mirror $N = 6$ (number of participants who completed the study)	• 100-mm VAS
Finn et al. (2017) RCT–parallel group	Mirror therapy $N = 9$	Covered mirror $N = 3$	• 100-mm VAS • Number of PLP episodes per day • PLP duration
Ramadugu et al. (2017) RCT-crossover for the control group	Mirror therapy $N = 32$	Covered mirror $N = 28$	• 100-mm VAS • SF-MPQ • PLP frequency (Likert scale) • PLP duration (Likert scale)
Rothgangel et al. (2018) RCT—parallel group	Mirror therapy $N = 25$	Mirrorless $N = 24$	• NRS—10 points • PLP frequency (Likert scale) • PLP duration (Likert scale) • NPSI • PSFS • PDI • 11-point NRS on mood and sleep • EQ-5D–5L • 100-mm VAS overall health • Pain self-efficacy questionnaire • Global perceived effect scale

Abbreviations: MPQ, McGill pain questionnaire; NPSI, Neuropathic Pain symptom inventory; NRS, numerical rating scale; PDI, pain disability index.; PSFS, patient-specific functional scale; RCT, randomized-controlled trial; SF-MPQ, Short McGill pain questionnaire; VAS, visual analogue scale.

et al., 2021; Xie et al., 2021). However, the methodological quality of these meta-analyses raises questions. In the meta-analysis by Xie et al. (2021), the risk of bias of the included studies (GRADE method) was not evaluated. Moreover, a fixed effect model was used instead of a random effect model that considers trials as different parameters. The observed statistical effect is questionable because the study that contributed to 54% of the conclusion had a low methodological quality (PEDro score = 2). A sensitivity analysis should have been carried out to assess the effect of removing low-quality studies (Borenstein et al., 2010). In the meta-analysis by Wang et al. (Wang et al., 2021) the conclusion displayed a large heterogeneity ($I^2 > 80\%$), suggesting the need of a subgroup analysis. When this subgroup analysis was carried out, MT effect, compared with a covered mirror, disappeared. However, the authors concluded that MT is an effective technique to reduce PLP in amputees. On the basis of these different points, we disagree with the interpretation and conclusions of these two meta-analyses.

Although evidence is lacking concerning MT effectiveness for PLP, the beneficial effects of MT in other conditions suggest that it may be useful also for PLP. The latest Cochrane review shows a significant effect of MT on motor function (effect size: 0.47 [0.27, 0.67]) following stroke (Thieme et al., 2018), and a meta-analysis found an effect of MT on pain associated with post-stroke complex regional pain syndrome (Duong et al., 2018). In these reviews, the MT intervention modalities were more intense (30-minute sessions, 5 times per week) than those used in the five studies included in this review (Table 4; Thieme et al., 2018). Therefore, increasing the MT session frequency and duration (per week and/or for a longer period) might influence brain plasticity and consequently PLP (Andoh et al., 2017; Flor, 2008; Flor et al., 2006; Kuner & Flor, 2016). It has also been shown that MT effects last for several months after treatment, particularly on motor functions, daily living activities and pain (Sütbeyaz et al., 2007). In agreement, Rothgangel et al. found that MT still modulated pain episode frequency at 6 months of

Procedure	Supervised intervention (yes/no)	Number of sessions and session duration	Fidelity to the programmed intervention
Ten movements with both limbs, each repeated 10 times, with a break between each movement type	Yes	Only one session	—
Movements with both limbs	Yes	15 minutes per day, for 8 weeks (for the control group, covered mirror the first 4 weeks then change to mirror therapy)	At 4 weeks, all patients completed the study
Both limbs perform slow movements with progressive increase in amplitude	Yes	15 minutes per day, 5 days per week for 4 weeks	Due to lack of efficacy of the control treatment, all participants in the control group received the MT intervention after 11 sessions (planned change at 20 sessions initially)
Movements with both limbs	Yes	15 minutes per day, for 4 weeks	All patients in the mirror group completed the study and 86% of participants in the control group completed the study
Intervention group: exercise program adapted to the patient's preferences with both limbs. -Observation of different positions -Motor exercises -Exercises using sensory stimuli (e.g. vibration, heat) - Functional motor exercises with objects	Yes, during the first 4 weeks. Then unsupervised for the next 6 weeks (home)	10 sessions of at least 30 min/each for the first 4 sessions As many sessions as the patient wishes during the following 6 weeks	84% of participants in the intervention group completed the study and 80% of participants in the control group completed the study

follow-up (Rothgangel et al., 2018). This could be due to its stabilizing effect on brain plasticity.

4.1 | Limitations and strengths

This review presents some limitations. First, we limited the search to five databases, and the selected articles had to be in French or English. Second, we did not register our study in the PROSPERO database, although we followed a pre-established protocol (wrote in French) before the start of our study that was approved by the ethics committee. Third, during the literature search, we identified many study protocols to address the research question, but the results of these trials have not been published yet, or they might have been negative, and the authors did not try to publish them (publication bias).

The strengths of this review are: (i) we followed the PRISMA reporting recommendations, (ii) we only included studies with a placebo control group, (iii) we

assessed the methodology quality of the studies with the PEDro scale, and (iv) we interpreted their results in function of the PEDro scores. We also assessed secondary outcomes: pain frequency and duration, disability and quality of life.

5 | CONCLUSION

The results obtained in this systematic review do not allow us to conclude that MT reduces PLP intensity, frequency, duration or disability. Future clinical studies should enrol a larger number of patients to increase the statistical power, use a covered mirror or mirrorless exercises as placebo, intensify MT sessions and frequency (Duong et al., 2018; Thieme et al., 2018), include a long-term follow-up (Rothgangel et al., 2018), reduce intra-group heterogeneity (sex, prosthesis type, ability to move the phantom limb, presence of a PLP motor component), improve their methodological quality (PEDro scale), and

evaluate also other criteria (e.g. duration and frequency of painful episodes, disability and quality of life). Other study designs could be considered, for instance, single-case experimental design (SCED) studies that are adapted to rare diseases with a variety of specific and clinical situations (Ganz & Ayres, 2018; Krasny-Pacini & Evans, 2018; Smith, 2012; Tate et al., 2008).

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. NR and LR extracted data from the trials and evaluated the inclusion and exclusion criteria. NR, LR and MG assessed the methodological quality of the trials. All authors contributed to the interpretation of the data and drafted the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this manuscript.

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