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Mirror Therapy for the Alleviation of Phantom Limb Pain following Amputation: A Literature Review

Abstract

Introduction: Phantom Limb pain (PLP) affects up to 85% of all patients following an amputation, causing debilitating effects on their quality of life. Mirror Therapy (MT) has been reported to have potential success for the alleviation of PLP. Current understanding of PLP and the efficacy of MT for its alleviation are still unclear, therefore guidelines for treatment protocols are lacking. This literature review assesses the current best evidence for using MT to alleviate PLP of patients with amputation.

Method: The authors systematically searched the academic databases Medline, Amed, CINAHL and Google Scholar, using key search terms with inclusion and exclusion criteria to identify relevant articles on the use of MT in populations of patients suffering PLP after unilateral limb amputation.

Findings: Seven primary papers were identified and appraised. All the articles reported significant PLP alleviation after using MT with a trend for achieving phantom limb movement (PLM) prior to pain relief.

Conclusions: Mirror Therapy is a promising intervention for PLP. Regular MT sessions are required to maintain treatment effect. Causes of PLP and pathways to its alleviation may be multifactorial; therefore further well-conducted RCTs are required to identify best practice.

Key words: Amputation, Phantom limb pain, Mirror Therapy, Rehabilitation.

Introduction

In the UK approximately 5-600 amputations due to numerous causes occur each year such as; vascular changes, diabetes, trauma, cancer or infection (NHS Choices, 2012). The sensation of a phantom limb (PL) (or feeling that an amputated body part is still present) is a common complication post amputation. While the mere presence of a PL may be tolerable, 50-85% of patients may also experience ongoing phantom limb pain (PLP) (Weeks et al., 2010) with or without the ability to move the PL. In addition, PLP may have a significant negative impact on a persons quality of life (Foell et al., 2011).

The causes of PLP are still unclear and potentially multifactorial involving peripheral, spinal, and supra-spinal structures (Hsu & Cohen., 2013), as a result effective interventions are difficult to prescribe (Knotkova et al., 2012). No specific guidelines are available to clinicians (Viswanathan et al., 2010). Treatment options for PLP consist of; pharmacological interventions such as analgesics; and non-pharmacologic treatments i.e. transcutaneous nerve stimulation (TENS) (Subedi & Grossberg., 2011). The efficacy of pharmacotherapy in PLP has been determined by extrapolating from positive findings of other neuropathic conditions (Knotkova et al., 2012), with the majority showing to be ineffective for PLP (Flor., 2002). Spinal cord and regional anaesthesia (based on spinal or peripheral causes) have only yielded modest efficacy (Hsu & Cohen., 2013). A Cochrane review recently identified a lack of evidence for the effectiveness of TENS for PLP (Mulvey et al., 2010).

One emerging treatment producing perceived positive effects for PLP is Mirror Therapy (MT). By placing a mirror parasagittally between the arms or legs and viewing the reflected movements of the intact limb whilst attempting simultaneous movements with the phantom, the intention is that the patient perceives the reflection to be their amputated limb which possibly addresses incongruence between proprioceptive and visual inputs caused by cortical reorganisation (CR) (Weeks et al., 2010). Ramachandran et al. (1992) hypothesised that sensorimotor CR explains the reason why PL sensations (PLS) can be induced by stimulation of peripheral receptors in unrelated body parts whose cortical representations are (as per the homunculus (fig 1)) adjacent to one another. They suggested that the areas representing the PL within the primary motor and sensory cortices which no longer receive adequate afferent input are invaded by adjacent regions, thereby creating a painful response within the PL.

Figure 1 here

The use of MT to alleviate PLP was first undertaken by Ramachandran (1993) involving a patient with an upper limb amputation with continuous PLP for the previous 11 years, with no clear protocol they reported almost instant pain relief. Ramachandran & Rogers-Ramachandran (1996) demonstrated that visual feedback from a perceived intact limb would allow patients greater PL control, enabling them to voluntarily release paralysis/clenching spasms caused by what they termed “learned paralysis” and “learned pain” through functional neglect prior to amputation. A similar effect was reported by another 8 out of 10 heterogeneous patients using a variety of protocols and methods, with increased use enhancing effect. MacLachlan et al’s (2004) study participant also experienced a significant reduction of PLP and an increased sense of control of the PL. However, MT was replaced by mental visualisation part way into the study; therefor it is difficult to know whether MT was the primary cause of the PLP alleviation. Yet MV has been shown to alleviate PLP as more recent yet exiguous RCTs (Tsao et al., 2007; Chan et al., 2007) exclusively used patients post amputation, and indicated that 15 mins of daily MT was highly effective in treating PLP with a 100% reduction for the MT group, and a 50% reduction within a MV group (Tsao et al 2007). Chan et al. (2007) also showed a significant 100% PLP alleviation in their MT group.

The theory that CR occurs after amputation and contributes to PLP has been observed by studies utilising functional magnetic resonance imaging (fMRI), observing that its reversion back to a normal/pre-amputation state coincides with PLP alleviation (Birbaumer et al., 1997;Flor et al., 2006). Diers et al. (2010) concluded that viewing mirrored movements evoked significantly more bilateral sensorimotor activation in non-PLP patients than those with PLP, and the severity of PLP was negatively correlated with the degree of reorganisation. This reversion of cortical activity alongside PLP reduction concurs with Siedal et al. (2011), who found significant reduction in PLP after 12 sessions of MT, this review aims to explore and discuss the best available evidence to assess the efficacy of MT and its potential mechanism in the alleviation of PLP.

Method

Search strategy

Studies were identified using Google Scholar, Amed, CINAHL, and Medline, plus a hand search of relevant articles. The literature search included the period from January 2003 to December 2013. The following search terms were used in combination; ‘phantom pain’; ‘PLP’; ‘phantom limb’; ‘phantom limb pain’; ‘mirror’; ‘mirror treatment’; ‘mirror therapy’; and ‘virtual limb’.

Screening

Each article was screened against the inclusion criteria; studies not meeting these criteria were excluded. The inclusion criteria were;

- Published in the English language.
- Published between Jan 2003 and Dec 2013.
- Participants were aged >18 with a unilateral amputation of any level and suffering from PLP (not including controls).
- Participants were allocated an intervention including MT (not virtual reality).
- Pain was measured by the visual analogue scale (VAS).

A total of 137 articles were retrieved, 7 of these met the inclusion criteria and were eligible for appraisal. A PRISMA (Moher et al. 2009) flow chart of study selection can be seen in appendix 1 and an overview of the appraised studies seen in appendix 2.

Figure 3 here

Quality appraisal

An assessment of methodological quality of these 7 articles was conducted using the Scottish Intercollegiate Guidelines Network (SIGN) tool for the controlled trials of Mosely (2006) and Brodie et al. (2007). The Centre for Evidence Based Management (CEBMa) critical appraisal tool for case studies was used for the remaining level 4 articles. A table showing the appraisal criteria and scores for SIGN and CEBMa for each article can be seen in appendix 3 and 4. A data extraction table is included (table 2) showing an appreciation for the samples and protocols used, as well as identification of results, adverse effects and drop-outs.

Table 1 here

Findings

Pain

Each of the 7 critically appraised articles reported improved PLP after MT. After a single treatment Brodie et al. (2007) reported a significant decrease of the McGill pain questionnaire (MPQ) (Melzack & Torgerson., 1971) total score ($p < 0.05$), for pre/post MT. Their MV control group also had a significant reduction of PLP. Even though both conditions showed significant improvement the pre/post VAS difference was much larger for MT (17 Vs 4). Mosely (2006) reported a significant effect for treatment group ($p = 0.002$) with the mean reduction of the visual analogue scale (VAS) within the treatment group and control groups being 23.4mm and 10.5mm respectively. This effect continued to 6 month follow-up with mean VAS scores of 32.1 mm and 11.6 mm respectively. The results of Sumatani et al. (2008) showed a significant alleviation of pre vs post treatment PLP VAS (6.6 vs 4.2) ($p < 0.002$). They also reported that deep vs superficial pain descriptors differed significantly post treatment in favour of deep pain. Foell et al. (2013) reported a significant decrease ($p = 0.005$) in pain rating at the end of the intervention period, week 2 (28.26) vs. week 7 (20.6), with a total mean decrease in PLP of 27%. The case study of Clerici et al. (2012), reported benefit after undergoing MT for 30 mins per day which was still present at 6 months. They also reported a significant decrease in PLP ($p < 0.005$) by analysing the VAS scores of weeks 1-6 vs. 20-26. Darnall & Li (2012) showed a significant reduction in PLP at month 1 ($p = 0.0002$) when MT was delivered for 25 mins daily, and at month 2 ($p=0.002$) with a mean percentage reduction of 15.5%. The earlier case study of Darnall (2009) had a complete resolution (100%) of PLP after 12 weeks particularly when switching from 20 to 30 mins per day, yet the PLP would return should he have missed 1-2 days of MT. All studies which reported a follow-up of effect after ceasing MT showed insignificant increases in pain scales.

Prediction of Treatment Effect

Telescopic distortions of the PL were reported by 8 of 13 participants in Foell et al. (2013). The intensity of the telescope was negatively correlated with treatment effect (increased telescope intensity = less pain alleviation). The positive results of pain alleviation in this study were due almost exclusively to those without a telescopic distortion. Darnall & Li (2012) observed that treatment effect was significantly improved in patients with over 16 years education (≥4 years of university education). They further reported a trend for those with low mood to drop out of the study. Within Sumitani et al. (2008) those with willed visuomotor imagery abilities (WVA) of the PL pre-treatment benefitted from greater PLP alleviation post MT than those without WVA. Additionally, deep pain descriptors reduced significantly post MT for those with WVA ($p < 0.0004$), but not for superficial pain descriptors ($p = 0.34$), nor for those without WVA. Suggestions of Brodie et al. (2007) may support this by positing that because MT elicits more phantom limb movement (PLM) than controls, those with an increased ability to move the PL may be more likely to experience a reduction in PLP via MT.

Mechanism of Effect

Foell et al. (2013) reported that treatment effects were associated with CR. For those who experienced a decrease of PLP, peak activity within the contralateral somatosensory cortex began to recreate its presumed normal location prior to amputation, but no connection with the motor cortex was found. Furthermore, pain alleviation was associated with decreased cortical activity within the inferior parietal cortex (IPC), an area known to influence the feeling of agency (the experience of ownership) and pain generation. Although MRI was not conducted in the other studies, this mechanism of CR is considered within the discussions of Brodie et al. (2007) and Mosely (2006).

Recommendations

Due to the heterogeneity of the sample, further large and more homogenous RCTs are required to help explain the mechanisms of pain alleviation from GMI/MT (Mosely., 2006). Additional larger studies are needed to identify follow-up effectiveness, and whether multiple sessions are more beneficial; and if so in what way. (Brodie et al., 2007). Darnal & Li (2012) called for a larger, better powered RCT’s to test true efficacy of self-delivered MT. They also recommended that treatments for those with lower mood should be bolstered with additional psychological support. Foell et al. (2013) suggested that a large study which utilises a control group and the division of groups according to telescoping severity may yield more compelling results. They also recommend that the virtual limb must be congruent with the PL if benefit is to be gained.

Discussion

The articles appraised within this review appear to be in agreement with the previous primary research which suggests MT is effective in the alleviation of PLP (Ramachandran & Rogers-Ramachandran., 1996: Maclachlan et al., 2004; Tsao et al., 2007; and Chan et al., 2007). However, due to their heterogeneity it is difficult to ascertain who with PLP would benefit most from MT, and how the MT should be delivered. These studies suggest that perhaps MT is not protocol, intensity, frequency or subject dependant as the pain alleviation identified was found using various protocols amongst heterogeneous groups, perhaps what is more important is the ability to produce PLM or gain a sense of control/ownership whilst using MT, as this coincided with studies (Clerici et al., 2012; Sumatani et al., 2008; Brodie et al., 2007; Mosely., 2006) which reported PLP alleviation. The MT group of Brodie et al. (2007) were twice as effective as the control MV group at creating PLM and gained more PLA than controls. Also, 10/14 patients who were only "aware" of a PL pre MT within Sumatani et al. (2008) reported vivid voluntary movement post MT. Whether this voluntary PLM was present prior to gaining PLP alleviation was not reported. The results which reported PLM supports previous research in regards to "learned paralysis" with MT/MV allowing the patient to move the PL out of painful distorted positions (Ramachandran & Roger-Ramachandran.., 1996), and that PL exercise (Sherman., 1980) can modify the PLP experience.

There may be a suggestion that perhaps visual feedback through MT is not such an important factor in PLM and subsequent PLP alleviation as this has been achieved in its absence. PLM and subsequent PLP alleviation was experienced by patients with vivid as well as sparse MV abilities (Brodie et al., 2003). And after a single treatment of MV the control group of Brodie et al. (2007) had significant PLP alleviation. Although it is thought that MV only partially activates the same cortical pathways as MT, therefore we should not expect MV to be as effective as actual visual feedback (Ramachandran & Altschular., 2010). Mosely (2006) states that using MV prior to MT within the GMI protocol allows for rehabilitation of the pre-motor cortex prior to the primary cortex, and showed significant results post intervention and at 6 month follow-up. The patients of Sumatani et al (2008) did not undertake a MV element prior to MT but those who benefitted most from MT were already able to utilise WVA and therefor concurs with previous studies. There may be value in a combined approach, yet without a long term follow-up in MT studies postulation of the necessity for MV prior to MT is not possible. Studies which utilised the two methods (MV and MT) (Maclachan et al., 2003; Mosely., 2006; Darnall., 2009; Chan et al., 2007) indicate that the addition of visual feedback may create a much more concentrated effect, which may be a critical component in PLP alleviation as it dominates proprioceptive/sensory feedback thus dampening down conflicting afferent signals (Weeks et al., 2010). Interestingly, in Chan et al (2007), 3/6 participants in the covered mirror group and 4/6 in their

MV group reported an increase in PLP yet after cross over to MT, PLP decreased in 8/9 participants (see figure 2).

Figure 2 here

Agency of a PL may be crucial in the creation of volitional movements (Tsakiris, 2010). The finding of Foell et al. (2013) that those with a "telescoped" PL were less able to relieve their PLP suggests that the incongruent mirror image of the PL did not allow adequate agency. As mentioned, those with increased ability to produce voluntary PLM may experience more PLP alleviation. Therefore if agency of telescopic PL cannot be experienced using a mirror, perhaps virtual reality protocols may be more useful with these patients allowing greater flexibility (Foell et al., 2011) and a more realistic visual PL interpretation, increasing their potential to gain agency and PLM. Additionally, only the patients reporting predominantly deep pain descriptors with WVA of Sumatani et al (2008) benefitted significantly from MT. Muscle spindles within the deep tissue have been shown to contribute more to joint position sense than that of superficial skin receptors (Macefield et al. 1990) therefor the combination of afferent inputs from vision and joint position sense (either by MV or PLM) **should** benefit sensorimotor congruency more than that of visual feedback alone.

Results from the fMRI imaging of Foell et al. (2013) agrees with past research that visual feedback via MT has the potential to reverse sensorimotor CR after amputation and subsequently reduce PLP (Flor et al., 2006; MacIver et al., 2008; Diers et al., 2010; Siedel et al., 2011). However, there are differences within all of these studies regarding the precise cortical regions involved. The finding of Foell et al. (2013) that activation of the IPC reduced alongside PLP reduction is interesting as this area is said to be related to body image, proprioception and pain generation (Harris., 1999) which links to the previous suggestion that an inability to gain agency limits MT effectiveness. Yet Siedal et al. 2011) showed significant activity was identified not in the primary sensorimotor cortices but instead the reduction of PLP was associated with increased prefrontal activity (which is associated with the "Mirror Neuron" system (Rizzolatti & Craighero, 2004)). The apparent differences with cortical involvements may suggest that; PLP experiences are diverse and individual to the patient; or that the speed and ability of cortical re-learning is individual, and studies which have tried to observe changes have not been of sufficient length to identify consistent patterns.

The mechanisms for PLP alleviation may be more multifactorial than previously thought and not attributed to a single cause or cortical area. Additionally, full reorganisation of neural cortices is said to take from a few weeks (Merzenich., 1984) to a few months (Smirnakis et al., 2005). So this may not solely explain the immediate pain relief found by Ramachandran & Rogers-Ramachandran (1996) or the fact that the first week VAS of Foell et al. (2013) and Clerici et al. (2012) showed improvement, and the participants of Brodie et al. (2007) and Sumatani et al. (2008) found benefit after a single intervention. This may suggest the interaction of “Mirror Neurons” (MN) which are activated when we observe the actions of others and allow patients to experience touch/physical response due to the lack of inhibition to MN by absent touch receptors (Ramachandran & Brang, 2009), thereby blocking protopathic pain (Chan et al., 2007; Subedi & Grossberg., 2011). These have been identified in the supplementary motor, premotor, somatosensory, and IPC (Rizzolatti & Craighero., 2004) which can be activated by MT (MacIver et al., 2008; Diers et al., 2010; Siedel et al., 2011; Foell et al., 2013). Perhaps MN are activated once agency is achieved and visual feedback is returned, immediately relieving on-going PLP as well as modulating longer term reorganisation. The existence of MN is a recent theory and direct evidence of their recruitment using MT is lacking (Rothgangel et al., 2011).

The trend for PLP to slowly return during follow-ups (Mosely., 2006; Foell et al., 2013) suggests that MT may need to become a long term intervention. It is possible that the extent of CR is related to the duration of symptoms (Subedi & Grossberg., 2011), therefore frequency/intensity of MT before pain attenuation is experienced may be patient specific. CR certainly seems to be an important factor of MT; however, based on the present review, firm conclusions cannot be drawn regarding its sole contribution in PLP production or alleviation.

Limitations

It was thought that the search term “Mirror Therapy” would identify all studies utilising this intervention, yet many studies refer to “Visual Feedback” or “Mirror Visual Feedback Therapy” therefore it is possible that some articles were missed. Only two articles would be classified as being of high levels of evidence, yet they still include significant limitations in regards to the topic of this review, one testing a single intervention without follow-up (Brodie et al., 2007), (Mosely., 2006) included a multifaceted intervention, and included participants with alternative pathologies, as did Sumatani et al. (2008). Although all conditions create PLP their mechanisms are obviously fundamentally different and therefore their significant positive results on pathological pain reduction may lack validity & reliability. Virtual reality studies were excluded due to its potential cost and availability, yet since the mechanisms of action would be similar to MT they may have provided useful information.

Conclusion

This review suggests that MT is a promising and low-cost treatment for PLP which may attenuate pain if agency and subsequent PLM is achieved. If present, treatments need to take the amount of telescoping into account and advise patients on its regular use to maintain treatment effects. However, after nearly 20 years the evidence regarding MT for PLP can still only be described as weak as the majority is anecdotal, and RCTs have either been too short, included multifaceted protocols, heterogeneous patient groups, or have not been reported thoroughly enough to fully identify their methods. Since no recommendations for PLP alleviation are offered in the British Association of Chartered Physiotherapists in Amputee Rehabilitation (BACPAR) 2006 or 2012 guidelines (Broomhead et al., 2006; 2012) future large, homogenous RCTs with extended follow-ups to measure quality/intensity of pain over time as well as in-depth qualitative accounts of participant experiences are needed in order to; compare effectiveness of MT, MV, pharmacotherapy or a combined approach; identify which unilateral limb loss patients may respond more favourably than others; and to develop a standardised protocol to allow the production of a well informed and evidence based guideline.

Key Points

- Mirror therapy is a promising treatment for the alleviation of phantom limb pain.
- All of the reviewed papers reported PLP relief after MT.
- Treatment effects are associated with cortical re-organisation.
- Regular and frequent use of mirror therapy enhances treatment effect.
- Increased agency and an ability to produce PLM enhanced treatment effect.
- Telescoping needs to be taken into account in order to achieve an acceptable level of agency.
- Future well powered RCTs are needed to identify follow-up effectiveness, and any benefits of multiple MT sessions.

Conflict of interest

The authors of this review have no competing/conflicting interests.

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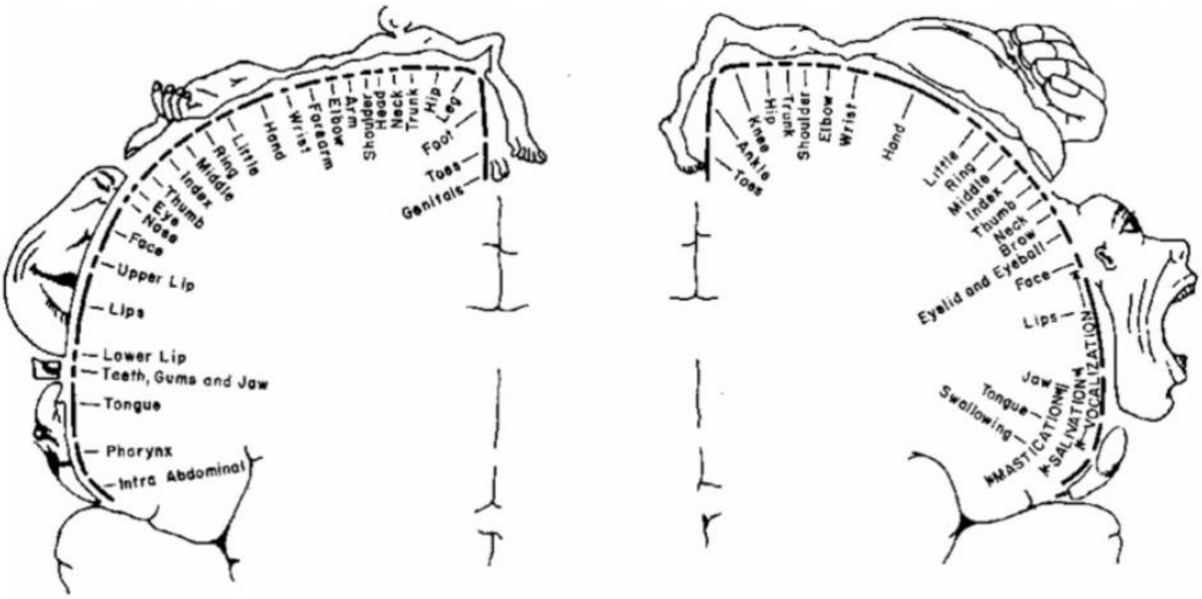


Figure 1. Penfield & Rasmussens (1990) homunculus. Shows the motor and sensory location of specific body parts represented within the somatosensory cortex.

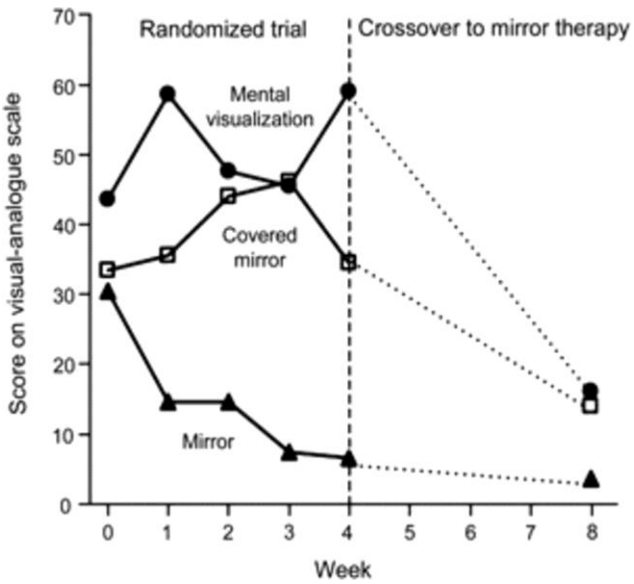
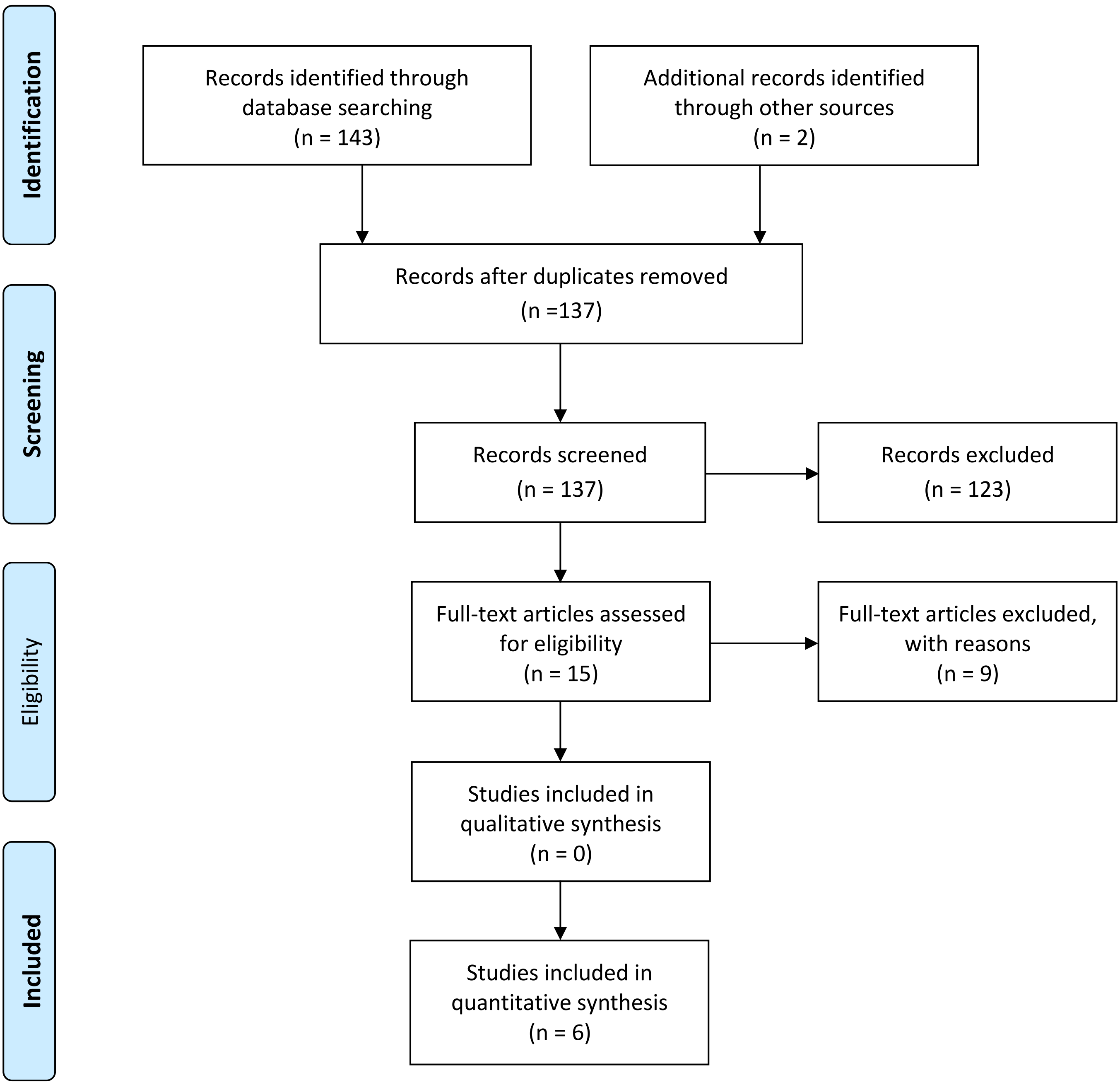


Figure 2. From Chan et al (2007) showing the effects of mirror therapy, covered mirror, & mental visualisation during their 4 week trial and after crossover.

Appendix 1

PRISMA 2009 Flow Diagram



Data extraction table

Author & year	Number of MT Participants	No With PLP	No with PLP ATT	Mean Age	Control	Frequency/duration of intervention	Duration of intervention	Pre-MT PLP intensity (VAS/NRS)	Post-MT PLP intensity (VAS/NRS)	F/up-MT PLP intensity (VAS/NRS)	Follow up period	Adverse events	Drop outs
Brodie et al (2007)	41 (6f)	35	7	55	39 (11f)	Once (10 x 10 movements)	1 day	57 (±24.2)	40 (±41.00)	N/A	N/A	None reported	0
Mosely (2006)	51 (32f), *9 (5f) amps*	51	51	41 (38 amps)	25 *(4 amps)*	Every waking hour (approx. 9 x per day).	6 weeks (2 weeks MT)	57 (±18.5)	33.6	24.9	6 months	None reported	1
Sumitani et al (2008)	22 (6f), 11 amps	22	22	48.4	N/A	1 x 10 mins per day	Participant discretion. Mean = 20.4 weeks	6.6 (±1.7)	4.2 (±2.8)	N/A	N/A	None reported	0
Foell et al (2013)	13 (4f)	13	13	50.6	N/A	1 x 15 mins per day	4 weeks	28.3	20.6	23.44	2 weeks	None reported	0
Darnall & Li (2012)	31 (13f)	31	31	61 (med)	N/A	1 x 25 mins per day	2 months	6 (1-10 scale)	5	N/A	N/A	4 = ↑PLP 1 = ↑ low mood	8
Darnall (2009)	1 (m)	1	1	35	N/A	3 x 20-30 mins per week	3 months	4 (1-10 scale)	0	N/A	N/A	None reported	0
Clerici et al (2011)	1 (m)	1	1	41	N/A	1 x 30 mins per day	6 months	3.6 (1-10 scale)	1.8	N/A	N/A	None reported	0

Table 1. Data extraction of the sample, protocol and results from the appraised papers. MT – Mirror Therapy; PLP – Phantom limb Pain; ATT-At Time of Testing; Amp – Amputee; VAS-Visual Analogue Scale.

Literature review table of final studies

Title	Design	Methods	Sample	Results/Findings	Strengths	Weaknesses
Brodie, E.E., Whyte, A. and Niven, A. (2007) Analgesia through the looking glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement. European Journal of Pain, 11, pp. 428-436.	Randomised control trial.	80 Lower limb amputees were assessed for PLP, PLS, PLM & PLA. Randomised into MT or control (obscured mirror) groups. Both groups carried out 1 session of 10 x 10 movements of their intact limb & PL together. PLP, PLS recorded pre/post intervention using MPQ & VAS.	Mirror = 41 (6f) Control = 39 (11f) Mean age = 55 Mean yrs since amp = 9	Sig MPQ effects for time in both groups P<0.05, but failed to reach 80% power. Analysis of VAS not reported yet MT mean pre/post = 57/40 Vs Control = 33/29 Sig main effect for PLM in MT P=<0.001	A RCT Large sample Only used lower limb amps therefore was more homogenous than an upper and lower limb sample.	Only used a single intervention. Potential for placebo effect. Few participants who reported experiencing PLP prior to testing had PLP at time of testing.
Mosely, L. (2006) Graded motor imagery for pathologic pain. A randomized controlled trial. Neurology, 67, pp. 2129-2134.	Randomised control trial.	51 participants (CRPS, BPAI, & Amps) randomly allocated to GMI or control groups and assessed for VAS pre/post intervention. GMI = weeks 1-2 = limb laterality recognition, weeks 3-4 = imagined movements, weeks	51 = Total 37 = CRPS 5 = BPAI 9 Amps Mean age = 41	Main effect for treatment group post intervention showed sig reduction in VAS scores P=0.002. Main effect for treatment group 6 months post intervention sig reduction in VAS scores P = <0.001	A RCT Sample was subject to a large amount of treatment (although, 9 interventions per day is probably an unrealistic frequency for a home program).	GMI is a multifaceted intervention which includes limb laterality and mental visualisation prior to MT. Only a small proportion of amputees within sample and their results were not analysed separately.

		5-6 = mirror therapy. Each stage was performed once every waking hour.				
Foell, J., Bekrater-Bodmann, R., Diers, M., Flor, H. (2013) Mirror therapy for phantom limb pain: Brain changes and the role of body representation. <u>**European Journal of Pain**</u>**, 10, pp 1532-2149.**	Case series	4 weeks 15 mins per day home MT. Hand & lip movements performed during FMRI to measure brain changes pre/post MT. VAS reported daily	13 (4f) upper limb amputees with chronic PLP. 11 measured with FMRI. Mean age = 50.6 Mean yrs since amp = 21	27% reduction in PLP (sig). Effects predicted by presence of telescope (telescope = reduced effect). Pain reduction = decreased activation in inferior pariental cortex over the course of MT.	Used a standard protocol of MT exercises and frequency for each participant. The use of fMRI to observe and measure peak activity locations Baseline VAS assessed from average of 2 weeks pre intervention. Mirror supplied (therefore standardised) by researchers.	Level 4 study. Small sample. Use of self-report exercise diaries. No control/comparison groups. Unimpaired hemispheres used as a control.
Sumitani, M., Miyauchi, C., McCabe, C.S., Shibata, M., Maeda, L., Saito, Y., Tashiro,T., Mashimo, T. (2008) Mirror visual feedback	Case series	1 x 10 mins of MT every day. Duration of treatment was individually determined by each participant. Pre/post evaluation of pain	11 = Amps 7 = Brachial plexus avulsion 2 = Partial Spinal cord injury 2 = Peripheral nerve injury Mean age = 48.4	NRS significantly decreased across all participants (pre 6.6 vs post 4.2; *P*< 0.002). MT induced greater MV ability for those describing deep	Self-delivered MT therefore reduces risk of a “Hawthorn” effect. Uses pain descriptors alongside NRS.	Level 4 study No control group. Duration of treatment determined by individual participants. Heterogeneous

alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. Rheumatology, 47, pp. 1038–1043		descriptors/qualities; PLA, pain intensity (NRS)		pain. Those with willed MV reported significantly greater reductions in PLP (P< 0.001), whereas those without willed MV ability did not (P = 0.5).	Identifies participants with superficial vs deep pain.	sample disabilities. Continuation of pharmacological and physical therapy.
Darnall, B,D., Li, H. (2012) Home-based self-delivered mirror therapy for phantom pain: a pilot study', Journal Of Rehabilitation Medicine: Official Journal Of The UEMS European Board Of Physical And Rehabilitation Medicine, 44, 3, pp. 254-260.	Case series	Participants self-treated with MT for 25 mins daily for 8 weeks. Completed and posted back outcome questionnaires at 4 and 8 weeks.	31 (13f) unilateral upper/lower limb amputees. Median age = 61	Median pain reduction of 15.5% from baseline to month 2. Sig pain reduction for the most educated participants. 4 reported worse PLP. 6 reported no change. 16 reported reduced PLP.	Large sample for a case series. Comprehensive reporting of demographic information. Self-delivered MT therefore reduces risk of a “Hawthorn” effect.	Level 4 study. Limited inclusion/exclusion criteria. Participants were paid $10 to complete questionnaires, and $10 to purchase a mirror. Self-reporting home exercise diaries/questionnaires.
Darnall, B.D. (2009) Self-delivered home based mirror therapy for lower limb phantom	Case study	Self-delivered unstructured MT 3 x per week for 20-30 mins, for 12 weeks.	35 yr old male. Above knee amputation.	VAS reduced to 0-10 from 4-10 at baseline. Case study was able	Suggests that the frequency/intensity of MT is more important than a structured exercise	Single person case study. Self-purchased mirror, meaning that its

pain. <u>American Journal of Physical Medicine & Rehabilitation,</u> 88, pp. 78-81.		VAS measured pre/post intervention.	Surgical amputation after trauma. PLP for 3 years.	to taper off his usual analgesics. Improvements were sustained 4 months post treatment with regular MT.	protocol. Self-delivered MT therefore reduces risk of a "Hawthorn" effect.	appropriateness for the intervention cannot be accounted for. Unstructured exercise protocol Also used relaxation treatment each day. Psychologically compromised (depression). Self-report diaries.
Clerici, A.C., Spreafico, F., Cavalotti, G., Consoli, A., Veneroni, L., Sala, A., Massimino, M. (2013) Mirror therapy for phantom limb pain in an adolescent cancer survivor. <u>Tumori</u>, 98, pp. e27-e30.	Case study	6 months self-delivered, unstructured MT. 30 mins per day. Exercises consisted of looking at, touching, caressing, scratching and moving his intact leg. Recorded daily self-report diary,VAS, and Zung depression test.	41 year old male. Surgical AKA at age 17 due to childhood osteosarcoma. PLP for 8 years	Significant reductions in PLP (first 6 weeks vs last 6 weeks) $P=\leq 0.05$. No evidence of significant depression via Zung test. Subjective enjoyment and stress relief.	Long term (6 months) implementation of MT. Weekly VAS/Zung recording.	Single person case study. Part of a multi-faceted approach including analgesics, exercise, psychological and physiotherapy support. No report of statistical procedures.

Appendix 2. Literature review table of all included studies including protocol, sample details, results, strengths and weaknesses. MT – Mirror Therapy; PL - Phantom Limb; PLA - Phantom Limb Awareness; PLP – Phantom Limb Pain; PLM – Phantom Limb Movement; PLS – Phantom Limb Sensation; Amp – Amputee; VAS-Visual Analogue Scale; MPQ – McGill Pain Questionnaire; AKA – Above Knee Amputation

SIGN RCT Checklist	Brodie, Whyte, & Niven 2007	Mosely 2006
Appropriate & clearly focussed question?	What effect does viewing a 'virtual limb' plus attempting to move a phantom limb have on PLP, sensation and movement?	Is Graded Motor Imagery equally effective for PLP as it is for CRPS
Assignments of subjects to treatment groups are randomised?	Yes	Yes
Adequate concealment used?	No report of concealment	No
Subjects & investigators are kept blind to treatment allocation?	No report of blinding	No. Single blinding only.
Treatment & control groups are similar at the start of the trial?	Yes	Yes
The only difference between groups is the treatment under investigation?	Yes	Yes
All relevant outcomes are measured in a standard, valid and reliable way?	Yes. McGill Pain Questionnaire. VAS.	Yes. McGill Pain Questionnaire. VAS.
What percentage of the individuals in each arm of the study dropped out before the study was completed?	No drop-outs.	No drop-outs
All the groups are analysed in the groups to which they were randomly allocated (intention to treat)?	No	No
Where the study is carried out at more than one site, results are comparable for all sites.	N/A	Can't say
Score?	**6/9**	**6/10**

Appendix 3. Table of SIGN appraisal criteria and scores for the RCTs included within this review.

<u>CEBMa Checklist</u>	Darnall & Li 2012	Darnall 2009	Clerici et al 2011	Foell et al 2013	Sumitani et al 2008
Clearly focussed question/issue?	Yes. To determine if home based PLP patients would self-treat with MT and whether this would attenuate pain.	Yes. Will home based, patient delivered MT be as effective for pain relief as structured supervised MT.	No. The discussion of advantages of using MT.	Yes. 1. Does MT attenuate PLP? 2. Do brain changes occur during MT treatment? 3. Are there any predictors of treatment success?	Yes. Is the alleviation of PLP via MT dependent on pain description (Superficial vs deep).
Is the study design appropriate for answering the research question?	Yes. But since efficacy has already been observed in previous pilot/case studies, a controlled trial may be more appropriate.	Yes, for a preliminary study. But does not allow for strict data collection.	Yes, for a preliminary study.	Yes. They were unable to include a control group due to small sample size.	Yes, for a preliminary report.
Are both the setting & the settings representative with regard to the population to which the findings will be referred?	Yes. Home based amputees.	Yes. Home based amputees.	Yes. Home based MT/amputees.	Yes. Home based amputees.	Yes. Home based amputees.
Is the researchers perspective clearly described and taken into account?	Yes	Yes	Yes	Yes	Yes
Are the methods for collecting data clearly described?	Yes. Self-report diaries, VAS.	Yes. Brief pain inventory.	No. Vaguely reports VAS for pain and control.	Yes. Daily pain rating (VAS). fMRI scans pre/post intervention.	No
Are the methods for analysing the data likely to be valid and reliable?	Yes. SAS statistical software used.	Yes. Pre/post VAS scores displayed.	Yes. Weekly VAS/Zung reported.	Yes. Description of statistical analysis included.	Yes. Description of statistical analysis included.

Was the analysis repeated by more than one researcher to ensure reliability?	Can't say	No	Can't say/No	Can't say	Can't say.
Are the results credible, and if so, are they relevant for practice?	No. Too much potential for bias, i.e. incentives, self-report diaries.	No. Too much potential for placebo and bias from other ongoing therapies. 1 person sample.	No. Participant was undergoing other treatments alongside MT.	Can't say. Potential for bias. Small sample.	Can't say. Potential for bias from other ongoing therapies. Treatment delivery was not standardised.
Are the conclusions drawn justified by the results?	Yes	No. Limitations of on-going therapies not reported.	Yes. Takes multifaceted treatment into account.	Yes	Yes
Are the findings transferable to other settings?	Yes.	No. Only home based amputees	No.	Yes	Yes
Score?	**8/10**	**6/10**	**6/10**	**8/10**	**7/10**

Appendix 4. Table of the CEBMa appraisal criteria for the case studies/case series within this review.

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