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Trajectory of phantom limb pain relief using mirror therapy: Retrospective analysis of two studies

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HIGHLIGHTS

- The degree of PLP at baseline affects when mirror therapy relieves pain.
- Those with low baseline PLP tend to show pain relief by session 7 of treatment.
- Those with medium baseline PLP tend to show pain relief by session 14 of treatment.
- Those with high baseline PLP tend to show pain relief by session 21 of treatment.

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ABSTRACT

Background and purpose: Research indicates that mirror therapy reduces phantom limb pain (PLP). Objectives were to determine when mirror therapy works in those who respond to treatment, the relevance of baseline PLP to when pain relief occurs, and what pain symptoms respond to mirror therapy.
Methods: Data from two independent cohorts with unilateral lower limb amputation were analyzed for this study ($n = 33$). Mirror therapy consisted of 15-min sessions in which amputees performed synchronous movements of the phantom and intact legs/feet. PLP was measured using a visual analogue scale and the Short-Form McGill Pain Questionnaire.
Results: The severity of PLP at the beginning of treatment predicted when pain relief occurred. Those with low baseline PLP experienced a reduction ($p < 0.05$) in PLP by session 7 of treatment, those with medium baseline PLP experienced pain relief by session 14 of treatment, and those with high baseline PLP experienced pain relief by session 21 of treatment. Mirror therapy reduced throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting, and punishing-cruel pain symptoms.
Conclusion: The degree of PLP at baseline predicts when mirror therapy relieves pain.
Implications: This article indicates that the degree of baseline PLP affects when mirror therapy relieves pain: relief occurs by session 7 in patients with low PLP but by session 21 in patients with high PLP. Clinicians should anticipate slower pain relief in patients who begin treatment with high levels of pain.
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1. Introduction

Since its initial documentation over 500 years ago (Ambroise Paré), phantom limb pain (PLP) – pain in a missing limb – has eluded effective treatment [1,2]. Theories of why phantom limb pain occurs include learned paralysis, the neuromatrix, and proprioceptive memory [3–5]. Numerous therapies have failed to reduce pain effectively in randomized clinical trials [2]. One exception is mirror therapy, which appears to be effective and without the side effects that typically accompany pharmaceuticals [6].

Ramachandran and Rogers-Ramachandran first described mirror therapy over 20 years ago [7]. The therapy stemmed from the theory of learned paralysis, which posits that after amputation the brain continues to transmit efferent motor commands to the limb,

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but because the limb is missing no afferent sensory signals return to confirm that the limb successfully moved [3,7]. Over time this mismatch tricks the brain into perceiving the limb as paralyzed, which in turn causes pain. Mirror therapy was developed to reverse this paralysis by creating the illusion that the limb responds to motor commands. In mirror therapy, a mirror is placed between the intact and amputated limb to generate the visual impression of two healthy limbs. The individual then attempts to move both limbs in synchrony while watching the reflection, thus creating visual feedback that the limb is moving in response to motor commands and thereby reversing learned paralysis [3,7]. In their case series, Ramachandran and Rogers-Ramachandran reported that mirror therapy created the illusion of successful movement of the missing limb in 6 of 10 individuals, which for some reduced pain [7]. Subsequent research further supports the efficacy of mirror therapy. A randomized, sham-controlled trial of 22 patients showed that mirror therapy reduced PLP after lower extremity amputation as compared to a covered mirror condition (performing movements in front of a mirror covered by opaque sheet) and mental visualization (imagining movements with the amputated limb) [6]. Furthermore, with the exception of two cases of brief emotional reactions in the mirror group upon seeing the reflected limb, the trial did not detect any adverse side effects of treatment.

In spite of this evidence supporting the efficacy and safety of mirror therapy, in a survey of over 200 individuals with amputation(s) only 34% had tried mirror therapy and of these individuals only 40% reported benefit (unpublished data). One potential reason why research on mirror therapy has yet to translate widely into clinical practice is that the treatment parameters remain undefined; there is no standard treatment protocol for mirror therapy. Moreover, it is unclear who will respond to treatment and how long it takes to see therapeutic benefit. The present paper seeks to elucidate when and how mirror therapy works to inform treatment parameters with the hopes of allowing this therapy to enter standard clinical practice. The key items of interest were the trajectory of pain relief using mirror therapy, time to pain relief, the relevance of baseline pain to treatment response, and what pain qualities (e.g., throbbing, cramping and shooting) respond to mirror therapy.

2. Methods

2.1. Participants

Data from two independent cohorts with unilateral lower limb amputation were analyzed for this study. This study was retrospective, thus sample size was not calculated but rather all relevant data from the two studies were used.

In the first cohort, participants were recruited from Walter Reed Army Medical Center, Washington, DC from March 2006 through January 2007. Inclusion criteria included the presence of phantom limb pain greater than 3/10 on a visual analogue scale at least 3 times a week; exclusion criteria included bilateral lower or bilateral upper limb amputation, known neurological disease or brain damage, history of vertebral disk disease/condition, sciatica, or radiculopathy, known uncontrolled systemic disease, concurrent participation in another investigational drug or study device for phantom limb pain or participation in the 30 days immediately prior to study enrollment, current Axis I or II diagnosis determined by a neurologist or psychiatrist in the 6 months prior to entry into the study. The study was registered on clinicaltrials.gov (NCT00662415) and received approval from the Walter Reed Army Medical Center Institutional Review Board. Informed consent was sought and granted for all research subjects prior to enrollment in the study. The results of this study cohort were previously published and the specific data used for these analyses come only from mirror therapy sessions from the participants [6].

In the second cohort, participants were recruited from 2008 through 2014 from Walter Reed Army Medical Center and Walter Reed National Military Medical Center, Bethesda, MD as well as from the community for a functional magnetic resonance imaging study examining the effects of mirror therapy on brain activation patterns. Inclusion criteria included the presence of phantom limb pain greater than 3/10 on a visual analogue scale at least 3 times a week; exclusion criteria included multiple limb amputation, cause of amputation being diabetes or vascular claudication, pending revision surgeries, presence of embedded metallic shrapnel or other metal not compatible with MRI scanning, presence of traumatic brain injury, known neurological disease or brain damage, or history of vertebral disk disease/condition, sciatica, or radiculopathy, known uncontrolled systemic disease, concurrent participation in another investigational drug or study device for phantom limb pain or participation in the 30 days immediately prior to study enrollment, current Axis I or II diagnosis determined by a neurologist or psychiatrist in the 6 months prior to entry into the study, and pregnancy. The study was registered on clinicaltrials.gov (NCT00623818) and received approval from the respective Institutional Review Boards of Walter Reed and the National Institutes of Health. Informed consent was sought and granted for all research subjects prior to study enrollment. The results of this study have not yet been published.

2.2. Treatment

For both cohorts standard mirror therapy consisted of approximately 4 weeks of therapy sessions for 5 days a week, although treatment length and number of days/week varied depending on scheduling. Therapy sessions consisted of three different exercises, each lasting 5 min to total 15 min of therapy per day. Subjects flexed and extended the ankle (“as if stepping on the gas pedal of a car”), moved the foot from side to side (“windshield wiper”), and rotated the foot in a circle (“as if drawing a circle with your toes”), and for those with above knee amputation, flexion and extension of the leg at the knee (additional 5 min). At the beginning of each therapy session subjects were instructed to move the intact limb slowly to allow the phantom limb to move at the same pace. In addition subjects were instructed to move the phantom only as much as they could if range of movement was limited and to gradually increase the range of motion with each treatment session. Treatment was either conducted independently (participants followed instructions on their own) or directly observed by an investigator.

2.3. Outcome measures

2.3.1. Visual analogue scale

The visual analogue scale (VAS) is widely used in both clinical and research settings to measure pain. The VAS has been shown to be reliable, internally consistent, and sensitive to treatment [8,9]. The VAS in both studies consisted of a 100-mm horizontal line with two endpoints which were labelled “no pain” (far left) and “worst pain someone could ever experience” (far right). Subjects were given the following instructions: “Present Pain Intensity (PPI) – Visual Analogue Scale (VAS). Make a tick mark along the scale below that represents the phantom limb pain experienced over the last 24 hours”.

2.3.2. Short-Form McGill Pain Questionnaire

The Short-Form McGill Pain Questionnaire consists of 15 pain descriptors rated on a scale of 0 (corresponding to none) to 3 (corresponding to severe). The Short-Form McGill Pain Questionnaire