

Clinical pain research

## 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](http://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](http://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

has been shown to produce similar scores as the standard McGill Pain Questionnaire and be sensitive to treatment [10].

#### 2.4. Effective versus ineffective treatment

Mirror therapy was deemed effective versus ineffective depending upon the decline in pain as measured by the VAS. For those with high (>60 mm on the VAS) or medium (31–60 mm on the VAS) PLP at baseline, effective treatment was defined as a decline of at least 20 mm, which corresponds to the two point reduction specified by Farrar et al. [11]. For those with low (<30 mm on the VAS) PLP at baseline, effective treatment was defined as a decrease of 50% over the course of treatment, a cut-off which is common in pharmaceutical trials since its recommendation by Moore et al. [12].

#### 2.5. Analyses

##### 2.5.1. Trajectory of pain relief with mirror therapy

The average pain trajectory across all patients was analyzed using polynomial regression of VAS scores versus treatment sessions. A logit transformation was used to fit the data given the lower limit of 0. Only participants for whom mirror therapy was effective (see definition under Section 2.4) were included in this analysis, as the question of interest was when pain relief occurred in cases of effective mirror therapy. In addition, a one-way ANOVA was conducted comparing the initial pain level to pain levels on sessions 2, 3, 4, and 5 of treatment to determine whether there is a PLP increase when beginning treatment. This was examined as anecdotally some patients have complained of increased PLP after starting mirror therapy.

##### 2.5.2. Relevance of baseline pain level to treatment response

Data was divided into 3 categories according to baseline phantom limb pain as measured by the VAS: low (VAS score under 30 mm), medium (VAS score from 31 to 60 mm), and high (VAS score over 60 mm). A polynomial regression of VAS or McGill scores versus treatment sessions was used to look at the trajectory of pain relief for those with effective treatment (see definition under Section 2.4). A logit transformation was used to fit the data given the lower limit of 0 for both scales.

##### 2.5.3. Time to pain relief

The data for effective treatment was then analyzed using a one-way ANOVA looking at sessions 1, 7, 14, and 21. These time points were chosen as the trajectory of pain relief indicated these to be the inflection points in treatment response. A Dunnett multiple comparisons test was used to compare pain levels on session 1 to pain levels on session 7, 14, and 21. We conducted independent analyses for each category of baseline pain (high, medium, and low).

##### 2.5.4. PLP symptoms

The different pain qualities measured by the McGill questionnaire were examined individually to evaluate their specific responses to treatment. The average responses were analyzed using a quadratic regression. All subject data (i.e., those for whom mirror therapy was effective and those for whom it was ineffective) were included in this analysis.

##### 2.5.5. Sensitivity analyses

Subjects with missing data were excluded from analyses requiring that data. To account for the possibility of bias due to missing data, sensitivity analyses were performed treating the VAS response for all subjects as observations in an intention to treat (ITT) model with a last observation carried forward (LOCF) approach to account for patients who did not complete all planned treatment sessions.

**Table 1**  
Demographics.

| Age | Gender | Site of amputation         | Time since amputation (years) |
|-----|--------|----------------------------|-------------------------------|
| 21  | M      | Left Transfemoral          | 0.3                           |
| 25  | M      | Right transtibial          | 1                             |
| 34  | M      | Left transtibial           | 0.2                           |
| 33  | M      | Left transfemoral          | 0.1                           |
| 20  | M      | Right transfemoral         | 0.2                           |
| 20  | M      | Right transtibial          | 0.1                           |
| 25  | M      | Right transtibial          | 1                             |
| 38  | M      | Left transtibial           | 0.4                           |
| 23  | M      | Left transtibial           | 0.1                           |
| 19  | M      | Left transtibial           | 0.1                           |
| 21  | M      | Left transtibial           | 0.1                           |
| 31  | M      | Right transfemoral         | 0.05                          |
| 39  | M      | Left transfemoral          | 1.7                           |
| 31  | M      | Left transtibial           | 0.1                           |
| 22  | M      | Right transtibial          | 0.2                           |
| 53  | M      | Right transfemoral         | 0.2                           |
| 20  | M      | Right transfemoral         | 1                             |
| 22  | M      | Right transtibial          | 0.1                           |
| 30  | M      | Left transfemoral          | 0.2                           |
| 29  | M      | Left transfemoral          | 0.1                           |
| 20  | M      | Right transfemoral         | 0.2                           |
| 59  | F      | Left transtibial           | 3                             |
| 21  | M      | Left transtibial           | 0.1                           |
| 52  | M      | Left transfemoral          | 2                             |
| 47  | M      | Right transtibial          | 21                            |
| 75  | F      | Right transfemoral         | 5                             |
| 36  | F      | Left transfemoral          | 0.25                          |
| 60  | M      | Right transfemoral         | 15                            |
| 45  | F      | Right transtibial          | 1                             |
| 39  | M      | Right transfemoral         | 0.5                           |
| 30  | M      | Right knee disarticulation | 1                             |

### 3. Results

#### 3.1. Participants

Demographics are presented in Table 1. The participants for this study were predominately male (87.5%). The mean age for all study participants was 33.5 years (range: 19–60 years) and the mean time since amputation was 1.8 years (range: 0.05–21 years). In the first cohort, 32 subjects were screened, 22 of which were randomly assigned to one of three treatment groups (mirror, mental visualization, and covered mirror). The 10 subjects who were screened but not assigned to a treatment group declined to take part in the study due to lack of interest or inability to complete 1 month of treatment. Four subjects (3 from the mirror treatment group, 1 from the covered mirror treatment group) left the study during the first week due to inability to complete 1 month of treatment. Data from all subjects who received mirror therapy (21 subjects) were analyzed for this study. In the second cohort, 19 individuals with amputation were recruited; four of which were deemed ineligible based on the physical examination and follow-up information and two of which lost interest in the study prior to enrollment. One participant did not complete the study due to a personal issue. Additionally, data from two subjects were not used; the first subject did not submit the outcome measures of interest for this study and the second had an upper extremity amputation. Data from the remaining 10 subjects were analyzed for this study.

Study participants were not followed after termination of treatment, but the average number of treatment sessions was 19.3 (range: 3–40). One subject was missing data on the Short-Form McGill Pain Questionnaire; data on both variables was available for all other participants. There were two summary measures – the Short-Form McGill Pain Questionnaire and the VAS – measured over time.

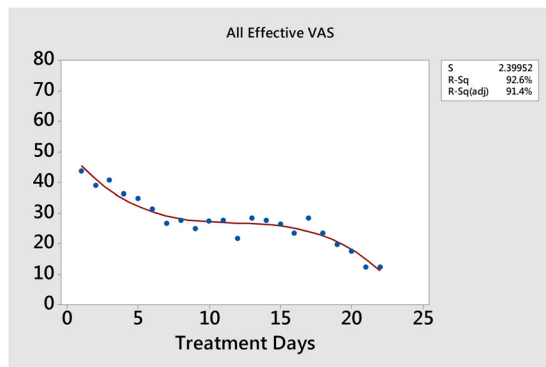


Fig. 1. Model of phantom limb pain as measured by the VAS over time.

### 3.2. Trajectory of pain relief with mirror therapy

In this combined cohort, mirror therapy was deemed effective for 27 of 31 (87%) subjects. The polynomial regression of VAS versus treatment sessions in these subjects showed a statistically significant decrease in pain over time ( $p < 0.0001$ ). To allow for the bounded nature of the VAS scale, i.e., there is a lower limit of 0, a logit transformation was used to properly fit the data. As seen in Fig. 1, the average pain level of the group decreases substantially over the first 7 treatment sessions, plateaus from sessions 7 to 14, then again declines from session 14 onward. There was no statistically significant increase in pain upon commencement of treatment. A one-way ANOVA with Dunnett's comparisons comparing the initial pain level to treatment 2, 3, 4 and 5 showed no significant difference ( $p = 0.761$ ).

### 3.3. Relevance of baseline pain level to treatment response

A one-way ANOVA with Dunnett's comparisons was used to compare the difference of the initial treatment pain levels to treatment sessions 7, 14, and 21. The polynomial regression of VAS versus treatment sessions indicated three different trajectories of pain relief for the categories of baseline phantom limb pain severities of low (VAS score under 30), medium (VAS score from 30 to 60), and high (VAS score over 60).

The low and medium initial VAS groups showed basically a continuous decrease (Figs. 2 and 3). The high initial VAS group showed an initial improvement, a levelling off, and then a final improvement (Fig. 4). Inspection of the individual patient trajectories showed that some of these patients improved rapidly, while others had an induction period of up to 15 sessions before therapy was effective. Consequently, the initial drop in the aggregate trajectory is related to those patients who improved immediately,

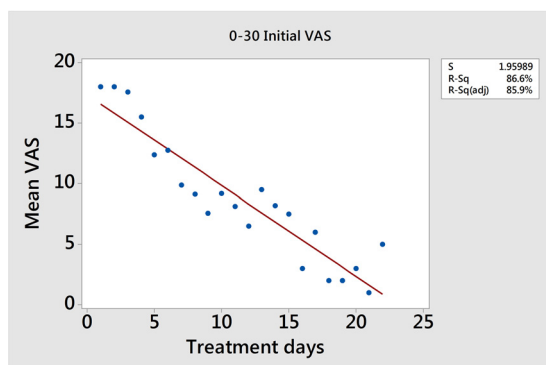


Fig. 2. Trajectory of pain relief for low baseline pain group.

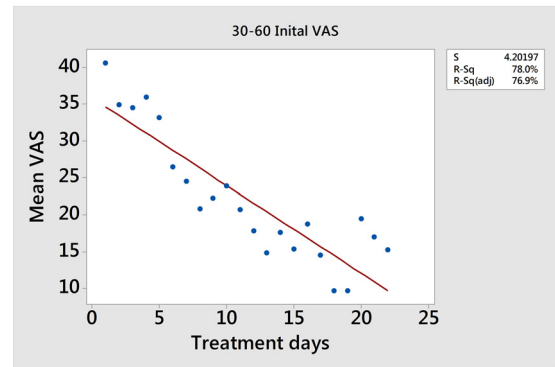


Fig. 3. Trajectory of pain relief for medium baseline pain group.

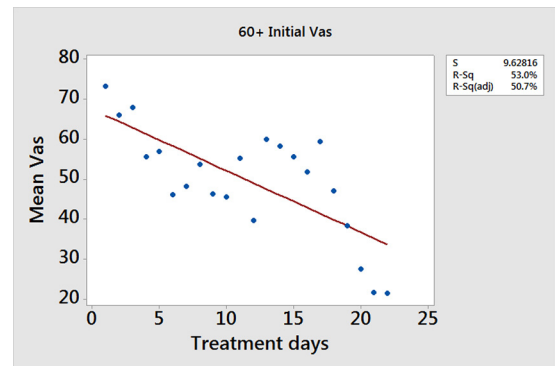


Fig. 4. Trajectory of pain relief for high baseline pain group.

while the final drop is from those who maintained high levels of pain through session 15.

### 3.4. Time to pain relief

The Dunnett comparisons showed different findings for the low, medium, and high baseline pain groups. The low baseline pain group showed a significant difference in pain from sessions 1 to 7 ( $n = 8$  distinct data measurements), sessions 1–14 ( $n = 6$  distinct data measurements), and sessions 1–21 ( $n = 4$  distinct data measurements; see Fig. 5). That is to say, for those with low initial PLP severity for whom treatment was effective, pain significantly dropped by session 7 of treatment. The medium baseline pain group showed a significant difference in pain from sessions 1 to 14 ( $n = 5$  distinct data measurements) and sessions 1–21 ( $n = 4$  distinct data measurements), but not from sessions 1 to 7 ( $n = 7$  distinct data measurements; see Fig. 6). This indicates that for those with

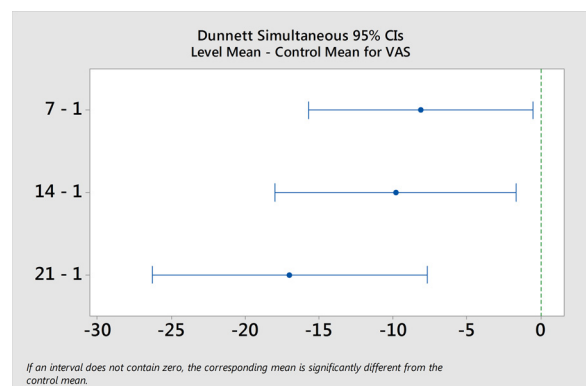


Fig. 5. Dunnett comparison for low baseline pain group.



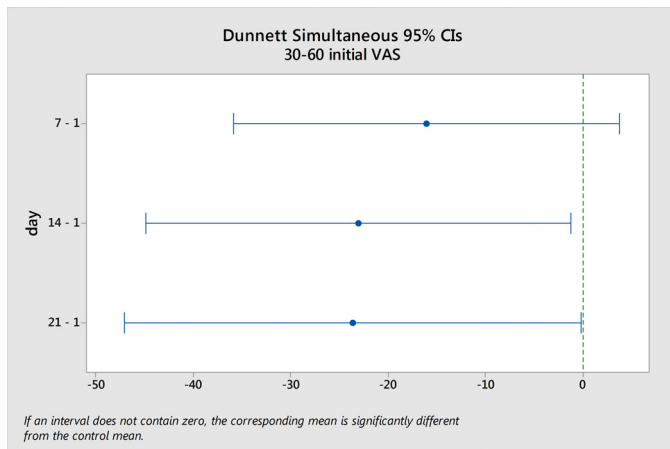


Fig. 6. Dunnett comparison for medium baseline pain group.

medium initial PLP for whom treatment was effective, pain significantly dropped by session 14 of treatment. The high baseline pain group showed a significant difference in pain from sessions 1 to 21 ( $n = 3$  distinct data measurements), but not from sessions 1 to 7 ( $n = 7$  distinct data measurements) or sessions 1–14 ( $n = 6$  distinct data measurements; see Fig. 7). For those for with high initial PLP for whom treatment was effective, pain significantly dropped by session 21 of treatment.

### 3.5. PLP symptoms

The quadratic regression looking at the responses of different pain qualities to treatment showed that some qualities showed a significant effect of treatment while others did not. Endorsement of the pain descriptors of throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting, and punishing-cruel significantly decreased over the course of treatment ( $p < 0.05$ ), whereas endorsement of the descriptors gnawing, hot/burning, heavy, sickening, fearful did not (Table 2).

### 3.6. Sensitivity analysis

To evaluate the potential bias introduced by attrition, a sensitivity analysis was performed treating the VAS response for all subjects as observations in an intention to treat (ITT) model with a last observation carried forward (LOCF) approach to account for patients who did not complete all planned treatment sessions. This

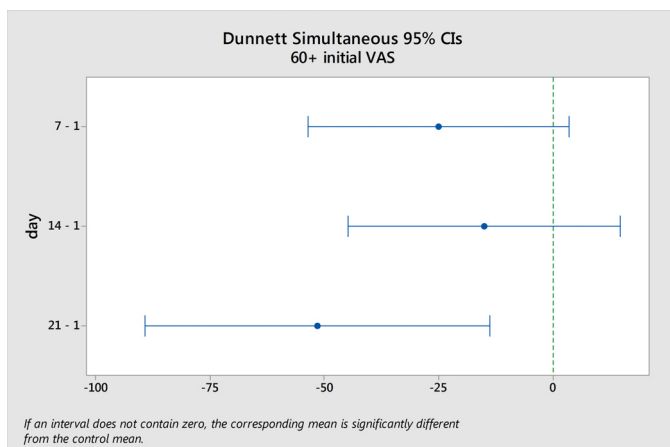


Fig. 7. Dunnett comparison for high baseline pain group.

Table 2

Reduction in pain in each of the McGill pain characteristics.

| Pain quality      | p value for quadratic regression |
|-------------------|----------------------------------|
| Throbbing         | <0.001*                          |
| Shooting          | <0.001*                          |
| Stabbing          | 0.0053*                          |
| Sharp             | <0.001*                          |
| Cramping          | 0.002*                           |
| Gnawing           | 0.0851                           |
| Hot/burning       | 0.4226                           |
| Aching            | 0.0342*                          |
| Heavy             | 0.5186                           |
| Tender            | 0.0004*                          |
| Splitting         | 0.0053*                          |
| Tiring/exhausting | 0.0192                           |
| Sickening         | 0.7701                           |
| Fearful           | 0.0626                           |
| Punishing-cruel   | 0.0426*                          |

\*  $p < 0.05$  is considered significant at the 95% confidence level.

analysis showed minor differences in the model, and no differences in the overall conclusions. Similarly, a sensitivity analysis of the response from patients with effective treatment showed no deleterious data effects from attrition.

## 4. Discussion

This paper is the first to closely examine mirror therapy to determine when, after initiating treatment, an effect is seen and what pain sub-types this treatment works for. The first major finding is that PLP tends to decline rapidly during the first week of mirror therapy, plateau from sessions 7 to 14, and then declines from session 14 onward. However, this trajectory is influenced by the severity of PLP experienced at baseline. Those with low and medium levels of PLP at the beginning of treatment show essentially a continuous decline. There appears to be a dichotomy in the trajectory of pain relief for those initiating treatment with high levels of PLP. Some improve rapidly while others experience what appears to be an induction period of up to 15 sessions before a therapeutic effect is seen. Second, pain dropped by session 7 of treatment for those with low levels of PLP ( $p < 0.05$ ), by session 14 for those with medium levels of PLP ( $p < 0.05$ ), and by session 21 for those with high levels of PLP ( $p < 0.05$ ). Finally, the study examined whether mirror therapy reduced certain pain qualities more than others, demonstrating that the pain qualities of throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting, and punishing-cruel significantly ( $p < 0.05$ ) decreased over treatment, whereas endorsement of the descriptors gnawing, hot/burning, heavy, sickening, and fearful did not.

Selecting a treatment for PLP can be difficult given the number of treatment options available and how differently persons with major limb amputations can respond to the same treatment [2]. As such, determining early indicators of whether a therapy will work has the potential to tailor treatment to provide pain relief as quickly as possible or to avoid abandoning treatment before a point of efficacy can be expected. Mirror therapy appears to be a treatment that has a high efficacy rate combined with low cost and minimal side effects compared to other treatments for PLP [2,6]. However, as mirror therapy is not universally effective, it is important to recognize as soon as possible if it will ultimately prove ineffective for an individual, so that the healthcare provider can identify an alternate treatment. Our findings demonstrate that initial PLP severity affects how quickly mirror therapy can lead to pain reduction and may explain why some studies [13,14] did not report the same success rates reported by Chan et al. [6]. Most importantly, some patients with higher initial levels of PLP may take longer to respond

to treatment than those with lower pain severity. Although anecdotally some of our patients reported transient increases in PLP after starting mirror therapy, upon detailed analysis we failed to find a statistically significant increase.

This study also examined how different pain qualities responded to mirror therapy. The pain qualities of throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting and punishing-cruel responded to mirror therapy whereas there was not evidence that the other qualities did. Further work is necessary to examine why mirror therapy may affect certain sensations of pain and not others. One possibility would be that there are different mechanisms underlying phantom limb pain [2], that pain qualities correspond to different mechanisms [15], and that mirror therapy is thus only targeting certain pain generators and therefore only muting certain pain qualities. However, this is speculative given that pain qualities have yet to be linked to underlying pathophysiology.

Further research is necessary to substantiate and extend these findings. The first cohort was followed for up to 4 months per protocol after treatment ended although some study volunteers were seen incidentally up to 2 years later during routine longitudinal clinical evaluations. For those participants for whom PLP had decreased after 1 month of mirror therapy, all except 2 subjects reported that their PLP had resolved. The other 2 subjects reported that their PLP had returned following 2 months and that they had again used mirror therapy for 4 weeks with permanent resolution of PLP thereafter. Much longer follow-up is necessary to determine the long-term efficacy of mirror therapy, as well as the long-term efficacy of most other treatments for PLP. Together, examining predictors of treatment response and the mechanism of action of mirror therapy could contribute to developing a revised mechanism-based classification of PLP [2].

This study has several limitations. First, this is a post hoc analysis of a combined data set which constitutes a larger sample size than originally reported by Chan et al. [6]. Second, some participants did not complete the anticipated total number of 20 treatment sessions which could limit statistical power. However, the sensitivity analysis indicates that attrition did not bias study results. Third, since treatment was 5 days per week, data were analyzed by treatment sessions rather than day-to-day changes. Fourth, the participants consisted of a convenience sample that likely differs from the overall population of persons with amputation. Participants in the first cohort are primarily active duty military and thus tend to be younger, more physically active, and male. Participants from both cohorts lived in the Washington, DC metropolitan area; thus the sample is not nationally representative. Fifth, it is possible that some of the change in PLP seen over the course of the study was due to natural fluctuation in PLP [16] after amputation rather than mirror therapy. Lastly, to fully evaluate the utility of mirror therapy for treating PLP, a prospective comparison of this treatment with other treatments is necessary.

To conclude, this study is the first to examine mirror therapy in terms of when a treatment effect is seen and what pain qualities it treats. Results suggest that the majority of pain relief tends to occur over the first seven sessions of treatment, although initial PLP severity affects how quickly the response is seen, which has important practical implications for personalized treatment implementation.

Additional research is necessary to confirm the importance of baseline pain levels and other characteristics as predictors of treatment response and to identify the mechanism of action of mirror therapy.

## Ethical issues

See Section 2.1.

## Conflicts of interest

The authors have no affiliations with or involvement in any organization or entity with financial interest or nonfinancial interest in the subject matter discussed in this manuscript.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Navy or the Department of Defense.

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